PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, June 17th, 2025
5:00pm – 7:00pm

Alameda Alliance for Health
1240 South Loop Road
Alameda, CA 94502

Location: Microsoft Teams
Meeting ID: 221 781 496 127
Password: C6Vhnr

YOU MAY SUBMIT COMMENTS ON ANY AGENDA ITEM OR ON ANY ITEM NOT ON THE AGENDA, IN WRITING VIA MAIL TO "ATTN: ALLIANCE PHARMACEUTICAL AND THERAPEUTICS COMMITTEE" 1240 SOUTH LOOP ROAD, ALAMEDA, CA 94502; OR THROUGH E-COMMENT AT bochoa@alamedaalliance.org . YOU MAY WATCH THE MEETING LIVE BY LOGGING IN VIA COMPUTER AT THE FOLLOWING LINK: Microsoft Teams Meeting OR MAY LISTEN TO THE MEETING BY CALLING IN TO THE FOLLOWING TELEPHONE NUMBER: +1 510-210-0967,694519784# IF YOU USE THE LINK AND PARTICIPATE VIA COMPUTER, YOU MAY, THROUGH THE USE OF THE CHAT FUNCTION, REQUEST AN OPPORTUNITY TO SPEAK ON ANY AGENDIZED ITEM, INCLUDING GENERAL PUBLIC COMMENT. YOUR REQUEST TO SPEAK MUST BE RECEIVED BEFORE THE ITEM IS CALLED ON THE AGENDA. IF YOU PARTICIPATE BY TELEPHONE, YOU MAY SUBMIT ANY COMMENTS VIA THE E-COMMENT EMAIL ADDRESS DESCRIBED ABOVE OR PROVIDE COMMENT DURING THE MEETING AT THE END OF EACH TOPIC.

PLEASE NOTE: THE ALAMEDA ALLIANCE FOR HEALTH IS MAKING EVERY EFFORT TO FOLLOW THE SPIRIT AND INTENT OF THE BROWN ACT AND OTHER APPLICABLE LAWS REGULATING THE CONDUCT OF PUBLIC MEETINGS, IN ORDER TO MAXIMIZE TRANSPARENCY AND PUBLIC ACCESS. DURING EACH AGENDA ITEM, YOU WILL BE PROVIDED A REASONABLE AMOUNT OF TIME TO PROVIDE PUBLIC COMMENT. THE COMMMITTEE WOULD APPRECIATE, HOWEVER, IF COMMUNICATIONS OF PUBLIC COMMENTS RELATED TO ITEMS ON THE AGENDA, OR ITEMS NOT ON THE AGENDA, ARE PROVIDED PRIOR TO THE COMMENCEMENT OF THE MEETING.

AGENDA

ITEM	DESCRIPTION	TIME	VOTE
I)	**Call to order** *Donna Carey, MD, Chief Medical Officer – Alameda Alliance* • Agenda Overview	2 min	-
II)	**Informational Updates** *Donna Carey, MD, Chief Medical Officer – Alameda Alliance* *Luke Lim, RPh, Senior Pharmacy Director – Alameda Alliance* • New Senior Director of Pharmacy – Luke Lim • P&T Stipend	15 min	-
III)	**Pharmacy Utilization Reports (Quarter 1, 2025)** *Luke Lim, RPh, Senior Pharmacy Director – Alameda Alliance* • Top 50 Drugs by Cost • Top 50 PA Reviewed Drugs	2 min	-
	ADJOURN TO CLOSED SESSION *(Pursuant to California Government Code Title 5, §54954.5(h))* ***Discussion will Concern:*** *Review and Recommendations to changes to the AAH Formulary and utilization management for selected drug classes* ***Estimated Date of Public Disclosure: 06/17/2025*** *(formulary changes only; no trade secrets will be disclosed)*		

IV) E-Voting Material/Consent Agenda

The following items have been sent to the voting committee for review via E-voting

Luke Lim, RPh, Senior Pharmacy Director – Alameda Alliance
Benita Ochoa, CPhT, Lead Pharmacy Technician – Alameda Alliance
(All matters listed on the Consent Calendar are to be approved with one motion unless a member of the P&T Committee removes an item for separate action. Any consent calendar item for which separate action is requested shall be heard as the next Agenda item in closed session.)

Monographs/Class Reviews	Changes
Anticonvulsants Class Review	• No changes
Contraceptives, Foams and Devices Class Review	• No changes
Parkinson's Disease Agents Class Review	• No changes
Potassium Removing Agents Class Review	• No changes
Potassium Supplements Class Review	• No changes
Luxturna Monograph	• No changes
Provenge Monograph	• No changes
Ridaura Monograph	• No changes
Sucraid Monograph	• No changes
Medication Request Guidelines	**Changes**
Formulary, step therapy required *For drugs without specific criteria	• No changes
Non-formulary and prior authorization required oral liquid formulations	• No changes
Medications for Attention Deficit Hyperactivity Disorder (ADHD) and	• No changes
Roflumilast (Daliresp)	• No changes
febuxostat (Uloric)	• No changes
Levalbuterol (Xopenex/Xopenex HFA)	• No changes
Lidocaine Patch	• No changes
Fenofibrates	• No changes
Nutritional formulas, infant formulas	• No changes
Lipotropics	• No changes
Long acting opioids	• No changes
Serotonin Receptor Agonists (Triptans)	• No changes
Pregabalin (Lyrica and Lyrica CR)	• No changes
Sedative Hypnotics	• No changes, minor correction in the criteria statement

10 min EV

Hepatitis C Medications	• No changes
Phosphate Binders	• No changes
Xolair (omalizumab) for Asthma, Urticaria, and IgE-Mediated Food Allergy	• No changes
Short acting opioid containing products	• No changes
Alprazolam (Xanax)	• No changes
Diuretics	• No changes
Rectiv (nitroglycerin) ointment	• No changes
Acute Migraine Treatments	• No changes
Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors	• No changes
Gonadotropin Releasing Hormone Antagonists	• No changes
Hereditary Angioedema (HAE)	• No changes
Lupkynis	• No changes
Radicava ORS (edaravone)	• No changes
Daybue (trofinetide)	• No changes
Filspari	• No changes
Joenja	• No changes
Skyclarys (omaveloxolone)	• No changes
Vyjuvek	• No changes
Filsuvez	• No changes, minor addition that the tube is for single use for clarity
Wegovy	• No changes
Rezdiffra	• No changes
Physician Administered Drug (PAD) Guidelines	**Changes**
SMN2 Splicing Modifiers for the Treatment of Spinal Muscular Atrophy (SMA)	• No changes
Naglazyme	• No changes
Leqembi	• No changes
Radicava (edaravone)	• No changes
Vyjuvek	• No changes
Generalized Pustular Psoriasis (GPP) Agents	• No changes
Amtagvi	• No changes
Lenmeldy	• No changes

Interim Formulary Updates	
See p. 275 in packet	
Summary of Physician Administered Drug (PAD) Updates	
See p. 276 in packet	
Pharmacy Policy & Procedure Updates	
• RX-001 Pharmaceutical Operating Processes Summary	• Removed lost, stolen language AB 118
• RX-003 Exception Review Process	• Removed lost, stolen language AB 118
• RX-004 Formulary Management	• AB 118 exclusions & SB 729
DSNP Policy & Procedures (7 NEW)	
• RX-D-012 Medicare Part D Fraud, Waste and Abuse (FWA)	• RX-D-021 Medicare Part D Best Available Evidence (BAE)
• RX-D-013 Explanation of Benefits (EOB) Oversight and Monitoring	• RX-D-022 Medicare Part D Complaint Tracking Module (CTM)
• RX-D-019 Medicare Prescription Payment Plan (M3P) Process, Monitoring and Oversight	• RX-D-025 Appointment of Representative (AOR)
• RX-D-020 Part D Delegation Oversight Auditing (PBM)	•
ED Oversight	
• 1 finding: tadalafil (Cialis) 20mg tablet – pending SIU review	
90 Day Maintenance List updates	
• None	
P&T Meeting Minutes	
• P&T Meeting Minutes Q1 March 18, 2025	

V) New Business

Iryna Makukh, PharmD, Pharmacist – PerformRx

New MRG

1. Tryngolza
2. Crenessity
3. H. Pylori Treatment Medications
4. MEK inhibitors for Neurofibromatosis Type 1 (NF1)

New PAD

1. Kebilidi
2. Agents for graft versus host disease
3. Fertility Agents
4. Tryngolza

VI) Class Reviews, Monographs, and Recommendations

Iryna Makukh, PharmD, Pharmacist – PerformRx

45 min V

1. Alzheimer's Disease Agents Class Review
2. Stelara biosimilars review

VII) Medication Request Guidelines
Rahel Negash, PharmD, Pharmacist – Alameda Alliance

1. Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention
2. Hepatitis B Drugs
3. Injectable Atypical Antipsychotic Medications
4. Opioid Use Disorder (OUD) Agents
5. Sleep Disorder Therapy
6. Transthyretin-mediated Amyloidosis Agents
7. Eohilia
8. Spravato
9. Hemlibra (emicizumab-kxwh)
10. Anti-Obesity Medications
11. Erectile Dysfunction Medications
12. Vaginal Progesterone
13. Fertility Agents
14. Complement Inhibitors for the Treatment of Paroxysmal Nocturnal Hemoglobinuria (PNH)
15. Complement Inhibitors for the Treatment of Myasthenia Gravis

VIII) Physician Administered Drug (PAD) Policies — 10 min — V
Iryna Makukh, PharmD, Pharmacist – PerformRx

1. Anti-CD19 CAR-T Immunotherapies
2. Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention
3. Complement Inhibitors
4. Myasthenia Gravis Agents
5. Bleeding Disorder Products

IX) Informational Updates on New Developments in Pharmacy — 2 min — V
Iryna Makukh, PharmD, Pharmacist – PerformRx

- New Product Review

X) Old Business — 2 min — -

- None

RECONVENE IN OPEN SESSION

XI) Public Comment

XII) Adjournment

PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, June 17th, 2025
5:00pm – 7:00pm

ACTION / FOLLOW-UP ITEMS		
ITEM	**DUE DATE**	**RESPONSIBLE**

FUTURE P&T MEETINGS	
NEXT MEETING	**2025 P&T MEETINGS**
September 16, 2025	December 16, 2025

The Alameda Alliance for Health Pharmacy & Therapeutics Committee welcomes you to its meetings and your interest is appreciated. If you wish to speak on a matter on the agenda, you will have the opportunity to do so in the order determined by the Chair. If you wish to speak on a matter not on the agenda, please wait until the Chair asks for public comments at the end of the regular agenda. Please be brief and limit your comments to the specific subject under discussion.

Note: Only matters within the jurisdiction of the Alameda Alliance for Health Pharmacy & Therapeutics Committee may be addressed. If necessary, the Chair may limit the total time to be devoted to public comment on any item, and the time allotted to individual speakers, to ensure sufficient time for the consideration of all matters on the agenda.

This meeting is wheelchair accessible. Please contact Rahel Negash at 510-747-6108 rnegash@alamedaalliance.org at least 72 hours before the meeting to request agenda materials in an alternative format, or any other reasonable disability-related accommodations or services that may be necessary for you to participate in and enjoy the benefits of the meeting.

636 IHSS Top 50 Drugs by Cost for 1st Quarter 2025

- The top 50 drugs accounted for **1,268 claims** for **649 members** and cost **$1,463,967**, which is a decrease of $125,484 in spend from the previous quarter.
- Biktarvy remains at number one, claims having gone up by 2, and there are two additional members since the previous quarter.
- Ozempic is at numbers 2, 3 and 5, with 274 total claims for 127 members. There was an increase of 2 claims and a decrease of 10 members from the previous quarter.
- Vemlidy is down to number 4 with 54 claims for 23 members. There was a decrease of 1 claim for 23 members from the previous quarter. This medication is managed via the Hepatitis B MRG, which requires trial and failure of, intolerance to, or reason not to use, entecavir.
- Verzenio is up at number 6 with 3 claims for 1 member. There was an increase of one claim for one member from the previous quarter. This medication is managed via the Oncology MRG.

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
1	201625	Biktarvy Oral Tablet 50-200-25 MG	34	14	$145,079.30
2	221271	Ozempic (0.25 or 0.5 MG/DOSE) Subcutaneous Solution Pen-injector 2 MG/3ML	101	50	$95,207.25
3	218338	Ozempic (2 MG/DOSE) Subcutaneous Solution Pen-injector 8 MG/3ML	95	36	$90,096.06
4	195609	Vemlidy Oral Tablet 25 MG	54	23	$86,663.94
5	209911	Ozempic (1 MG/DOSE) Subcutaneous Solution Pen-injector 4 MG/3ML	78	41	$73,769.41
6	199758	Verzenio Oral Tablet 100 MG	3	1	$47,222.25
7	214809	Skyrizi Pen Subcutaneous Solution Auto-injector 150 MG/ML	2	2	$43,990.72
8	177191	Eliquis Oral Tablet 5 MG	73	31	$40,008.62
9	215133	Wegovy Subcutaneous Solution Auto-injector 2.4 MG/0.75ML	30	12	$38,821.20
10	223809	Cosentyx UnoReady Subcutaneous Solution Auto-injector 300 MG/2ML	5	2	$37,270.20
11	215662	Rezurock Oral Tablet 200 MG	1	1	$35,696.02
12	198848	Nerlynx Oral Tablet 40 MG	4	1	$33,678.88
13	207961	Rybelsus Oral Tablet 7 MG	35	16	$33,039.15

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
14	215132	Wegovy Subcutaneous Solution Auto-injector 1 MG/0.5ML	24	13	$31,218.45
15	163343	Dasatinib Oral Tablet 80 MG	2	1	$31,181.24
16	182336	Farxiga Oral Tablet 10 MG	53	30	$29,744.32
17	184849	Jardiance Oral Tablet 25 MG	51	20	$29,300.25
18	218737	Radicava ORS Oral Suspension 105 MG/5ML	2	1	$29,284.24
19	190802	Genvoya Oral Tablet 150-150-200-10 MG	7	3	$28,440.78
20	208474	Vumerity Oral Capsule Delayed Release 231 MG	3	1	$26,770.89
21	207962	Rybelsus Oral Tablet 14 MG	27	12	$25,548.51
22	201117	Steglatro Oral Tablet 15 MG	73	28	$24,094.05
23	215135	Wegovy Subcutaneous Solution Auto-injector 0.25 MG/0.5ML	18	13	$23,237.47
24	197146	Cosentyx Sensoready (300 MG) Subcutaneous Solution Auto-injector 150 MG/ML	3	1	$22,263.68
25	219135	Skyrizi Subcutaneous Solution Cartridge 360 MG/2.4ML	1	1	$21,995.36
26	229056	Dupixent Subcutaneous Solution Auto-injector 300 MG/2ML	5	3	$19,677.10
27	229051	Trulicity Subcutaneous Solution Auto-injector 1.5 MG/0.5ML	20	8	$18,763.86
28	192096	Odefsey Oral Tablet 200-25-25 MG	5	2	$18,414.01
29	193035	Ocaliva Oral Tablet 10 MG	2	1	$18,349.18
30	215134	Wegovy Subcutaneous Solution Auto-injector 0.5 MG/0.5ML	14	11	$18,196.75
31	229087	Cimzia-Starter Subcutaneous Prefilled Syringe Kit 200 MG/ML	1	1	$17,788.32
32	184848	Jardiance Oral Tablet 10 MG	29	15	$17,763.41
33	182335	Farxiga Oral Tablet 5 MG	29	16	$16,298.80

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
34	122702	Januvia Oral Tablet 100 MG	49	22	$14,806.89
35	201116	Steglatro Oral Tablet 5 MG	33	16	$13,971.04
36	203127	Symtuza Oral Tablet 800-150-200-10 MG	3	1	$13,566.66
37	202548	Humira (2 Syringe) Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	1	1	$13,442.57
38	212379	Cabenuva Intramuscular Suspension Extended Release 600 & 900 MG/3ML	2	1	$13,232.78
39	170142	Xarelto Oral Tablet 20 MG	23	8	$12,769.71
40	197463	Dupixent Subcutaneous Solution Prefilled Syringe 300 MG/2ML	3	1	$11,863.18
41	226896	Cimzia (2 Syringe) Subcutaneous Prefilled Syringe Kit 200 MG/ML	2	1	$11,848.88
42	204204	Shingrix Intramuscular Suspension Reconstituted 50 MCG/0.5ML	49	48	$11,147.48
43	120539	Lenalidomide Oral Capsule 15 MG	1	1	$10,830.01
44	171646	Eliquis Oral Tablet 2.5 MG	21	9	$10,598.79
45	229071	Mounjaro Subcutaneous Solution Auto-injector 2.5 MG/0.5ML	10	5	$10,245.49
46	80828	cycloSPORINE Ophthalmic Emulsion 0.05 %	21	12	$9,963.23
47	229073	Mounjaro Subcutaneous Solution Auto-injector 15 MG/0.5ML	9	4	$9,365.91
48	225119	Zepbound Subcutaneous Solution Auto-injector 5 MG/0.5ML	9	5	$9,254.31
49	215136	Wegovy Subcutaneous Solution Auto-injector 1.7 MG/0.75ML	7	5	$9,179.38
50	127437	FreeStyle Lite Test In Vitro Strip	141	98	$9,007.01
TOTAL			**1,268**	**649**	**$1,463,966.99**

Medi-Cal Top 50 Drugs by Cost for 1st Quarter 2025

- The top 50 drugs accounted for 28,126 claims for 24,001 members and cost $60,407,283 which is an increase of $2,289,907 in spend from 4Q2024.
- The drug mix has changed from 4Q2024 because during that quarter the top 50 drugs accounted for 42,049 claims for 36,406 members and cost $58,117,376.51. 1Q2025 represents 66.8% of the claims volume and 65% of the member count and yet $2.2M increased spending.
- Biktarvy remains at the number 1 spot with 969 claims for 725 members. An increase of 80 claims but 2 less members from last quarter. I am unsure if we have days supply per claim but we should hope these are 90-100 day supplies.
- Jardiance is in positions #2 and #3, Jardiance 25mg tab with 2092 claims for 1928 members and Jardiance 10mg with 2108 claims for 1869 members. This increased utilization reflects the expanded indication for Jardiance (Type 2 diabetes, prophylaxis heart failure in diabetes and non diabetes patients and reduction of risk of GFR decline in ESRD patients). 169 more members are using Jardiance 25mg relative to the previous quarter and 121 more members are using Jardiance 10mg relative to the previous quarter.
- Ozempic moves to #4 with 2085 claims for 1625 members. This reflects a decrease of 33 claims and increase of 24 members from 4Q2024.
- Skyrizi remains #5 spot with 110 claims for 104 members, compared to 102 claims for 94 members during 4Q2024.
- Wegovy, a GLP-1 drug indicated for weight-loss and risk-reduction of cardiovascular events is at #6 and over $2M in spending. DHCS has proposed excluding this drug from the 2026 Medi-Cal Rx, citing a need to reduce prescription spending.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	44426	BIKTARVY 50-200-25 MG TABLET	969	725	$6,735,385.32
2	36723	JARDIANCE 25 MG TABLET	2092	1928	$2,912,203.94
3	36716	JARDIANCE 10 MG TABLET	2108	1869	$2,754,727.06
4	53536	OZEMPIC 0.25-0.5 MG/DOSE PEN	2085	1625	$2,578,111.31
5	49591	SKYRIZI 150 MG/ML PEN	110	104	$2,526,635.84
6	49754	WEGOVY 2.4 MG/0.75 ML PEN	1004	721	$2,042,506.52
7	43506	HUMIRA(CF) PEN 40 MG/0.4 ML	130	98	$1,978,934.79
8	48208	OZEMPIC 1 MG/DOSE (4 MG/3 ML)	1281	1030	$1,893,135.22
9	49748	WEGOVY 0.25 MG/0.5 ML PEN	1238	1112	$1,831,678.25

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
10	52125	OZEMPIC 2 MG/DOSE (8 MG/3 ML)	1137	867	$1,758,485.28
11	48277	DUPIXENT 300 MG/2 ML PEN	210	173	$1,703,132.71
12	49749	WEGOVY 0.5 MG/0.5 ML PEN	996	846	$1,510,993.60
13	42624	VEMLIDY 25 MG TABLET	508	394	$1,507,057.42
14	27418	INVEGA SUSTENNA 234 MG/1.5 ML	240	160	$1,442,933.73
15	49752	WEGOVY 1 MG/0.5 ML PEN	863	713	$1,407,157.38
16	49099	CABENUVA ER 600 MG-900 MG SUSP	165	144	$1,300,435.14
17	33935	ELIQUIS 5 MG TABLET	1134	906	$1,260,632.61
18	49753	WEGOVY 1.7 MG/0.75 ML PEN	654	514	$1,115,554.00
19	28159	STELARA 90 MG/ML SYRINGE	33	27	$1,096,598.41
20	47136	TRIKAFTA 100-50-75 MG/150 MG	20	16	$1,010,805.24
21	34394	FARXIGA 10 MG TABLET	720	644	$1,003,853.06
22	40133	TAGRISSO 80 MG TABLET	34	26	$1,003,446.66
23	49468	COSENTYX UNOREADY 300 MG PEN	44	35	$974,413.36
24	47586	TEPEZZA 500 MG VIAL	5	4	$945,799.02
25	97724	ENBREL 50 MG/ML SURECLICK	67	54	$881,655.88
26	40953	DESCOVY 200-25 MG TABLET	263	203	$846,727.79
27	46965	RYBELSUS 7 MG TABLET	414	380	$830,395.00
28	46966	RYBELSUS 14 MG TABLET	369	331	$814,693.32
29	44014	HUMIRA(CF) PEN 80 MG/0.8 ML	20	18	$791,543.42
30	49487	APRETUDE ER 600 MG/3 ML VIAL	152	134	$778,448.11

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
31	43968	SYMTUZA 800-150-200-10 MG TAB	103	76	$775,875.16
32	98637	BASAGLAR 100 UNIT/ML KWIKPEN	1483	1243	$733,657.43
33	25200	FREESTYLE LITE TEST STRIP	4074	3876	$687,714.84
34	94200	DEXCOM G7 SENSOR	610	546	$670,258.38
35	97400	JANUVIA 100 MG TABLET	815	748	$658,903.69
36	37682	ABILIFY MAINTENA ER 400 MG SYR	125	94	$658,553.50
37	48456	EVRYSDI 60 MG/80 ML(0.75MG/ML)	10	7	$617,406.46
38	38702	INVEGA TRINZA 819 MG/2.63 ML	58	58	$609,804.64
39	43699	MAVYRET 100-40 MG TABLET	29	26	$550,366.53
40	37789	COSENTYX SNRDY 300MG DOSE-2PEN	32	26	$537,200.25
41	40092	GENVOYA TABLET	67	56	$532,086.70
42	54456	FERRIPROX 1,000 MG TAB(2X/DAY)	10	9	$499,510.31
43	54988	ZEPBOUND 2.5 MG/0.5 ML PEN	411	366	$492,963.63
44	43924	ENBREL 50 MG/ML MINI CARTRIDGE	26	21	$472,940.87
45	97005	HUMIRA PEN 40 MG/0.8 ML	37	31	$465,176.38
46	54989	ZEPBOUND 5 MG/0.5 ML PEN	363	311	$463,901.07
47	43222	DUPIXENT 300 MG/2 ML SYRINGE	59	48	$453,227.26
48	30819	XARELTO 20 MG TABLET	389	336	$433,294.03
49	37633	ODEFSEY TABLET	65	49	$429,455.48
50	46964	RYBELSUS 3 MG TABLET	295	273	$426,907.23
TOTAL			**28,126**	**24,001**	**$60,407,283.23**

636 IHSS Top 50 Prior Authorization Requests by Volume - 1st Quarter 2025

- Top 50 PA requests = 261. There were 378 total PA requests for quarter 1.
  - 74 requests (28%) were approved. This approval rate is lower by 11% than it was observed last quarter.
  - 187 requests (72%) were denied or partially approved.
- Wegovy is at numbers 1, 7, 11, 12 and 42 with 61 total requests and 10 approvals (16%).
  - Wegovy to reduce excess body weight requires a diagnosis of obesity or BMI ≥27 and at least one weight-related comorbidity (diabetes, hypertension, hyperlipidemia) or history of heart attack, despite diet and exercise, and trial and failure or inability to use Qsymia and Contrave.
  - Wegovy to reduce the risk of major adverse cardiovascular events requires a documentation that the patient is obese or has BMI ≥27, has an established cardiovascular disease (prior myocardial infarction, stroke or symptomatic peripheral arterial disease), patient is on standard of care treatment for CVD and does not have diabetes.
- Lidocaine 5% patch is at number 2 with 25 requests and 5 approvals (20%).
  - Lidocaine requires a diagnosis of neuropathic pain and a trial and failure of gabapentin or pregabalin and one other formulary alternative (e.g., duloxetine, venlafaxine, amitriptyline) used for neuropathic pain or morphine MME $\underline{\geq}$ 50/day for 3 months.
- Jardiance is at numbers 3 & 6 with 33 total requests and 7 approvals (21%).
  - Jardiance requires trial and failure of one of the following: metformin, branded/generic drug containing metformin, branded angiotensin receptor/neprilysin inhibitor (ARNi), generic angiotensin-converting enzyme inhibitor (ACEi), generic angiotensin receptor blocker (ARB), generic mineralocorticoid receptor antagonist (MRA), or generic beta blocker AND documentation of trial and failure, intolerance, contraindication or inability to use one preferred formulary step therapy medication.
- Zepbound is at numbers 4 & 9 with 19 total requests and 2 approvals (11%).
  - Zepbound to reduce excess body weight requires a diagnosis of obesity or BMI ≥27 and at least one weight-related comorbidity (diabetes, hypertension, hyperlipidemia) or history of heart attack, despite diet and exercise, and trial and failure or inability to use Qsymia and Contrave.
  - Zepbound for moderate to severe obstructive sleep apnea requires trial and failure regarding lifestyle changes and behavioral modifications to reach BMI <30 kg/m^2 and trial and failure or inability to use PAP therapy.
- Vemlidy is at number 5 with 11 requests. There were 8 approvals (73%).
  - Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets.

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
1	WEGOVY Soln Auto-inj 0.25MG/0.5ML	39	8	20.51%	28	71.79%	3	7.69%
2	LIDOCAINE Patch 5%	25	5	20.00%	18	72.00%	2	8.00%
3	JARDIANCE Tablet 10MG	23	3	13.04%	16	69.57%	4	17.39%
4	ZEPBOUND Soln Auto-inj 2.5MG/0.5ML	13	2	15.38%	11	84.62%	0	0.00%
5	VEMLIDY Tablet 25MG	11	8	72.73%	0	0.00%	3	27.27%
6	JARDIANCE Tablet 25MG	10	4	40.00%	4	40.00%	2	20.00%
7	WEGOVY Soln Auto-inj 0.5MG/0.5ML	8	0	0.00%	6	75.00%	2	25.00%
8	CONTRAVE Tablet ER 12HR 8;90MG	7	3	42.86%	3	42.86%	1	14.29%
9	ZEPBOUND Soln Auto-inj 5MG/0.5ML	6	0	0.00%	4	66.67%	2	33.33%
10	OZEMPIC (0.25 OR 0.5 MG/DOSE) Soln Pen-inj 2MG/3ML	6	5	83.33%	1	16.67%	0	0.00%
11	WEGOVY Soln Auto-inj 2.4MG/0.75ML	6	1	16.67%	3	50.00%	2	33.33%
12	WEGOVY Soln Auto-inj 1MG/0.5ML	6	1	16.67%	5	83.33%	0	0.00%
13	TACROLIMUS Ointment 0.1%	6	3	50.00%	1	16.67%	2	33.33%
14	DUPIXENT Soln Auto-inj 300MG/2ML	5	3	60.00%	2	40.00%	0	0.00%
15	ZORYVE Cream 0.15%	4	0	0.00%	4	100.00%	0	0.00%
16	OZEMPIC (1 MG/DOSE) Soln Pen-inj 4MG/3ML	4	2	50.00%	0	0.00%	2	50.00%
17	EZETIMIBE Tablet 10MG	4	3	75.00%	1	25.00%	0	0.00%
18	PHENTERMINE HCL Tablet 37.5MG	4	3	75.00%	1	25.00%	0	0.00%
19	CYCLOSPORINE Emulsion 0.05%	3	2	66.67%	0	0.00%	1	33.33%
20	LIRAGLUTIDE Soln Pen-inj 18MG/3ML	3	0	0.00%	2	66.67%	1	33.33%
21	RANOLAZINE ER Tablet ER 12HR 500MG	3	0	0.00%	3	100.00%	0	0.00%
22	TRETINOIN Cream 0.05%	3	1	33.33%	2	66.67%	0	0.00%
23	HUMIRA (2 PEN) Auto-inj Kit 80MG/0.8ML	3	1	33.33%	2	66.67%	0	0.00%
24	LINZESS Capsule 72MCG	3	1	33.33%	2	66.67%	0	0.00%
25	XIIDRA Solution 5%	3	2	66.67%	1	33.33%	0	0.00%
26	LINZESS Capsule 145MCG	3	2	66.67%	1	33.33%	0	0.00%
27	MOUNJARO Soln Auto-inj 2.5MG/0.5ML	3	1	33.33%	2	66.67%	0	0.00%
28	ZORYVE Foam 0.3%	3	3	100.00%	0	0.00%	0	0.00%
29	FLUTICASONE-SALMETEROL Aerosol 115;21MCG/ACT	2	1	50.00%	1	50.00%	0	0.00%
30	BELBUCA Film 75MCG	2	1	50.00%	1	50.00%	0	0.00%
31	TYMLOS Soln Pen-inj 3120MCG/1.56ML	2	0	0.00%	2	100.00%	0	0.00%
32	TRELEGY ELLIPTA Aero Pow Br Act 100;62.5;25MCG/ACT	2	0	0.00%	2	100.00%	0	0.00%
33	EMGALITY Soln Auto-inj 120MG/ML	2	1	50.00%	0	0.00%	1	50.00%
34	SKYRIZI PEN Soln Auto-inj 150MG/ML	2	0	0.00%	2	100.00%	0	0.00%
35	ADDERALL XR Capsule ER 24HR 5MG	2	1	50.00%	1	50.00%	0	0.00%

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
36	TRELEGY ELLIPTA Aero Pow Br Act 200;62.5;25MCG/ACT	2	0	0.00%	2	100.00%	0	0.00%
37	NOVAREL For Solution 5000UNIT	2	0	0.00%	2	100.00%	0	0.00%
38	OZEMPIC (2 MG/DOSE) Soln Pen-inj 8MG/3ML	2	1	50.00%	1	50.00%	0	0.00%
39	MIRABEGRON ER Tablet ER 24HR 25MG	2	0	0.00%	2	100.00%	0	0.00%
40	CANDESARTAN CILEXETIL Tablet 16MG	2	1	50.00%	1	50.00%	0	0.00%
41	VIMPAT Tablet 100MG	2	0	0.00%	1	50.00%	1	50.00%
42	WEGOVY Soln Auto-inj 1.7MG/0.75ML	2	0	0.00%	2	100.00%	0	0.00%
43	XIFAXAN Tablet 550MG	2	0	0.00%	0	0.00%	2	100.00%
44	RYBELSUS Tablet 3MG	2	1	50.00%	1	50.00%	0	0.00%
45	DULERA Aerosol 200;5MCG/ACT	2	0	0.00%	2	100.00%	0	0.00%
46	CETROTIDE Kit 0.25MG	2	0	0.00%	2	100.00%	0	0.00%
47	QSYMIA Capsule ER 24HR 3.75;23MG	2	0	0.00%	2	100.00%	0	0.00%
48	MENOPUR For Solution 75UNIT	2	0	0.00%	2	100.00%	0	0.00%
49	QSYMIA Capsule ER 24HR 7.5;46MG	2	0	0.00%	2	100.00%	0	0.00%
50	NEMLUVIO Auto-injector 30MG	2	0	0.00%	1	50.00%	1	50.00%
TOTAL		**261**	**74**	**28%**	**155**	**59%**	**32**	**12%**

Medi-Cal Top 50 Claims by Volume for 1st Quarter 2025

- The top 50 drugs accounted for 223,447 claims for 200,737 members at a cost of $4,849,619.33. This is a decrease of 11,493 claims (5.4%) from 1Q2025 and decrease cost of $298,478 (-5.8%).
- Diclofenac 1% gel has risen to #1 with 10,513 claims (17.2%) for 8962 members (16.2%). This product rose from 5th to 1st place over the last 3 consecutive quarters.
- Ibuprofen 600mg tab remains at #2 with 10,405 claims for 9456 members. This compares to 1Q2025 with 9,573 claims for 8,656 members. This is an increase of 832 claims (8.7%)
- Albuterol was #1 in claims utilization during 1Q2025 but has fallen to #6 with 8215 claims (-33.3%) for 6843 members (-32.2%). This is a numerical decrease of 4108 claims.
- APAP 500mg caplets is at #3 with 9168 claims and 8188 members.
- Fluticasone has risen from #5 to #4 with 9008 (11.5%) claims for 8157 (13.1%) members.
- No drug for a chronic condition appears until #8, atorvastatin 20mg tablet.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	45680	DICLOFENAC SODIUM 1% GEL	10513	8962	$304,782.05
2	35742	IBUPROFEN 600 MG TABLET	10405	9456	$146,884.75
3	16965	ACETAMINOPHEN 500 MG CAPLET	9168	8188	$120,554.66
4	62263	FLUTICASONE PROP 50 MCG SPRAY	9008	8157	$198,503.52
5	00161	ASPIRIN EC 81 MG TABLET	8946	8215	$99,143.81
6	22913	ALBUTEROL HFA 90 MCG INHALER	8215	6843	$284,546.49
7	49291	CETIRIZINE HCL 10 MG TABLET	6877	6273	$107,178.25
8	43721	ATORVASTATIN 20 MG TABLET	6034	5632	$91,409.62
9	60563	LORATADINE 10 MG TABLET	6033	5395	$93,650.11
10	02683	AMLODIPINE BESYLATE 5 MG TAB	5828	5227	$102,570.61
11	43722	ATORVASTATIN 40 MG TABLET	5825	5319	$97,753.00
12	22913	VENTOLIN HFA 90 MCG INHALER	5777	5006	$314,871.89
13	02682	AMLODIPINE BESYLATE 10 MG TAB	5304	4732	$95,670.29

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
14	10857	METFORMIN HCL 1,000 MG TABLET	5117	4661	$85,311.79
15	86212	POLYETHYLENE GLYCOL 3350 POWD	4758	4343	$120,516.97
16	46430	FAMOTIDINE 20 MG TABLET	4584	4031	$67,308.28
17	10810	METFORMIN HCL 500 MG TABLET	4527	3972	$69,469.04
18	20045	ONDANSETRON ODT 4 MG TABLET	4462	4093	$64,607.60
19	04348	OMEPRAZOLE DR 20 MG CAPSULE	4304	3732	$66,667.26
20	00781	GABAPENTIN 300 MG CAPSULE	4271	3481	$79,659.08
21	94422	VITAMIN D2 1.25MG(50,000 UNIT)	4219	3862	$62,177.76
22	25200	FREESTYLE LITE TEST STRIP	4074	3876	$687,714.84
23	00223	VITAMIN D3 25 MCG TABLET	4030	3799	$49,078.82
24	16965	ACETAMINOPHEN 500 MG TABLET	4007	3686	$37,145.21
25	29840	BENZONATATE 100 MG CAPSULE	3891	3571	$54,208.05
26	99882	VITAMIN D3 50 MCG SOFTGEL	3777	3609	$46,779.18
27	40120	PANTOPRAZOLE SOD DR 40 MG TAB	3695	3121	$58,096.76
28	43720	ATORVASTATIN 10 MG TABLET	3650	3369	$54,295.20
29	39661	AMOXICILLIN 500 MG CAPSULE	3281	3091	$44,693.89
30	09101	DOCUSATE SODIUM 100 MG SOFTGEL	3211	2884	$40,906.50
31	97503	FERROUS GLUCONATE 324 MG TAB	3105	2823	$43,067.91
32	14851	LOSARTAN POTASSIUM 50 MG TAB	3028	2727	$58,077.98
33	16964	ACETAMINOPHEN 325 MG TABLET	2998	2834	$29,351.12

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
34	94781	FOLIC ACID 1 MG TABLET	2986	2540	$49,572.04
35	35741	IBUPROFEN 400 MG TABLET	2977	2823	$40,113.98
36	35930	CHILDREN IBUPROFEN 100 MG/5 ML	2948	2741	$55,733.06
37	35793	NAPROXEN 500 MG TABLET	2943	2635	$47,279.40
38	48191	TAMSULOSIN HCL 0.4 MG CAPSULE	2880	2509	$48,762.56
39	35744	IBUPROFEN 800 MG TABLET	2867	2522	$43,797.56
40	35930	IBUPROFEN 100 MG/5 ML SUSP	2816	2652	$47,160.64
41	14850	LOSARTAN POTASSIUM 25 MG TAB	2799	2514	$50,238.23
42	16391	TRAZODONE 50 MG TABLET	2776	2179	$44,969.09
43	50272	LIDOCAINE 5% PATCH	2758	2438	$218,417.63
44	29189	SYSTANE BALANCE 0.6% EYE DROP	2609	2449	$88,572.03
45	13943	HYDROXYZINE HCL 25 MG TABLET	2572	2006	$41,644.01
46	94200	FREESTYLE 28G LANCETS	2567	2504	$46,009.43
47	94444	MONTELUKAST SOD 10 MG TABLET	2545	2289	$43,144.02
48	30370	CLOTRIMAZOLE 1% TOPICAL CREAM	2538	2359	$40,204.11
49	43032	METRONIDAZOLE 500 MG TABLET	2482	2298	$32,494.22
50	39802	CEPHALEXIN 500 MG CAPSULE	2462	2309	$34,855.03
TOTAL			**223,447**	**200,737**	**$4,849,619.33**

Anticonvulsants

Executive Summary

Class Overview

Anticonvulsants or AEDs are a class of drugs used primarily to treat epilepsy but also other conditions such as migraine, neuropathies, and mental health disorders (e.g. bipolar disorder). Epilepsy is a disorder of the brain characterized by predisposition to seizures; a seizure is a clinical manifestation of abnormal electrical discharges of neurons primarily located in the cerebral cortex. Epilepsy encompasses multiple seizure types and syndromes with diverse etiologies. The first step in treatment is accurate diagnosis and classification of the seizure type using the ILAE; this classification system is used for both adults and children.

There is a broad range of drug therapy treatment options for epilepsy, however, many newer agents carry narrow indications. Testing new treatment options for use as monotherapy represents an ethical dilemma as there is a considerable risk for morbidity and mortality without treatment and given that there are effective therapies available. A novel approach to evaluating effectiveness of newer agents as monotherapy is the historical-control treatment discontinuation trial design. Results of such studies may soon yield expanded indications for existing products. Choice of initial monotherapy should largely be individualized in collaboration with the patient taking into account effectiveness, side effects, comorbidities and cost.

There are a multitude of guidelines published both in the United States and abroad as well as international guidelines from the WHO and the ILAE. This review includes six US guidelines and one US practice parameter from the American Academy of Neurology (AAN) and/or the American Epilepsy Society. Additionally, one set of recommendations from a North American Consensus panel published in Pediatric Neurology and related to the treatment of Dravet Syndrome is included. Finally, recommendations from the ILAE related to the treatment of infantile seizures are included.

Libervant (diazepam) buccal film was approved in April 2024 is the first and only orally-administered rescue product for the treatment of seizure clusters in patients ages 2 to 5. Additionally, Xcopri (cenobamate) tablets can now be crushed and mixed with water and either administered by mouth as an oral suspension or administered via a nasogastric tube. With the 2023 approval of generic diazepam rectal gel, all brand Diastat and Diastat AcuDial gels are no longer available. Brand Gabitril is now discontinued while generic tigabine HCL is available in all strengths and brand Roweepra (levetiracetam) is only available in 500 mg oral tablets. Brand Nembutol and Tranxene T-Tabs are now discontinued with the availability of generic pentobarbital and clorazepate, respectively.

Utilization Findings

There were 349 claims for 251 members, for a total cost of $10,671.59 and an average cost per claim of $30.58. The most highly utilized medication was gabapentin capsules, with 164 claims, followed by gabapentin tablets with 47 claims. There were 5 prior authorization requests with 3 approvals (60%).

Recommendations

- No changes

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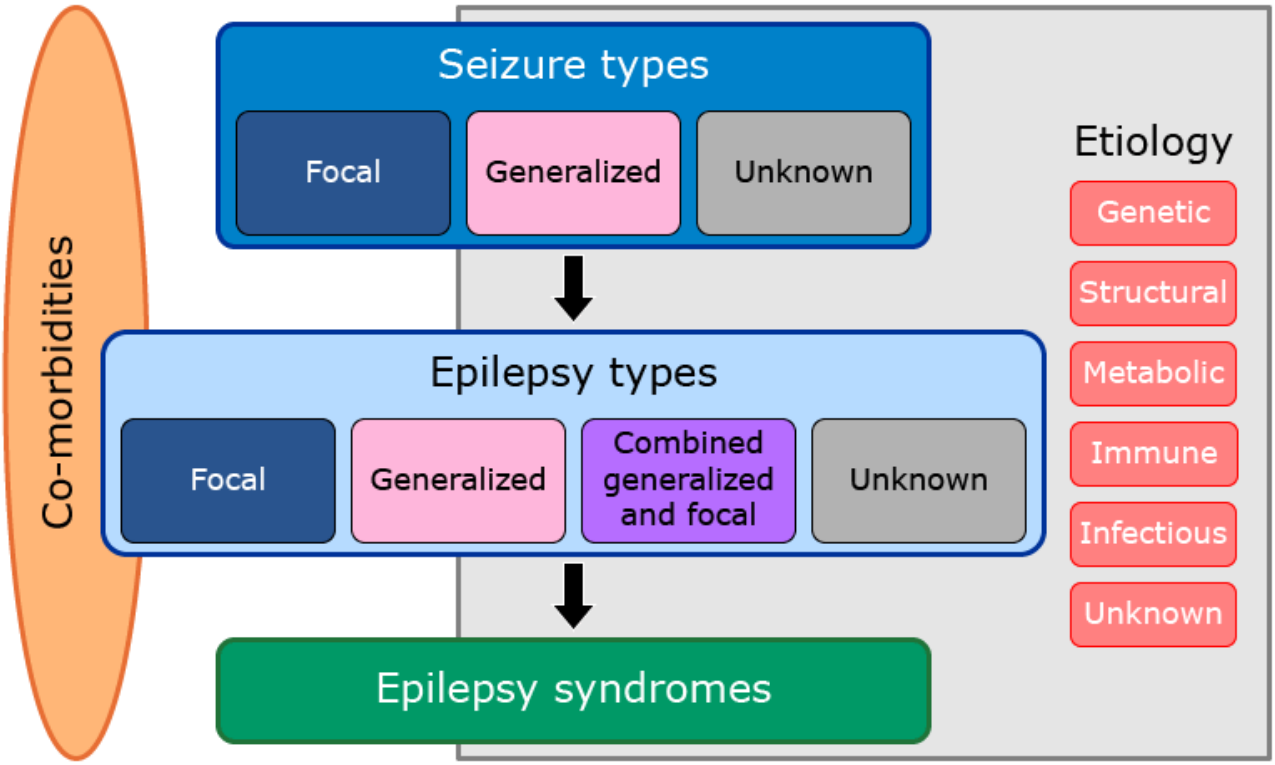
Clinical Summary

AEDs are a class of drugs used primarily to treat epilepsy but also other conditions such as migraine, neuropathies, and mental health disorders (e.g. bipolar disorder). Epilepsy is a brain disorder characterized by predisposition to seizures; a seizure is a clinical manifestation of abnormal electrical discharges of neurons primarily located in the cerebral cortex. Epilepsy encompasses multiple seizure types and syndromes with diverse etiologies. The first step in treatment is accurate diagnosis and classification of the seizure type using the ILAE; this classification system is used for both adults and children. The ILAE framework is comprised of four diagnostic levels: Level 1 – Seizure Type, Level 2 – Epilepsy Based on Seizure Type, Level 3 – Epilepsy Syndrome and Level 4 – Epilepsy with Etiology.

ILAE framework for seizure and epilepsy classification



From: Scheffer IE, Berkovic S, Capovila G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017. DOI: 10.1111/epi.13709. http://onlinelibrary.wiley.com/wol1/doi/10.1111/epi.13709/abstract. Copyright © 2017 The International League Against Epilepsy. Reproduced with permission of John Wiley & Sons Inc. This image has been provided by or is owned by Wiley. Further permission is needed before it can be downloaded to PowerPoint, printed, shared or emailed. Please contact Wiley's permissions department either via email: permissions@wiley.com or use the RightsLink service by clicking on the 'Request Permission' link accompanying this article on Wiley Online Library (http://onlinelibrary.wiley.com).

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There is a broad range of drug therapy treatment options for epilepsy, however, many newer agents carry narrow indications as add-on therapy in treatment-resistant cases. Testing new treatment options for use as monotherapy represents an ethical dilemma as there is a considerable risk for morbidity and mortality without treatment and given that there are effective therapies available. A novel approach to evaluating effectiveness of newer agents as monotherapy is the historical-control treatment discontinuation trial design. Results of such studies may soon yield expanded indications for existing products. Choice of initial monotherapy should largely be individualized in collaboration with the patient taking into account effectiveness, side effects, comorbidities and cost.

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Indications, Dosing and Administration

Medication	Indications	Dosing/Administration
Miscellaneous		
Briviact® (brivaracetam)	Focal (partial) onset seizures • Adjunctive • Monotherapy	Adult Oral, IV: – 50 mg BID (range 25 mg – 100 mg BID based on individual patient response and tolerability) Pediatric Oral*: POS (monotherapy or adjunctive therapy): – Children ≥4 years and Adolescents <16 years: 11 to <20 kg: 0.5 to 1.25 mg/kg BID; may increase up to a maximum of 2.5 mg/kg BID 20 to <50 kg: 0.5 to 1 mg/kg BID; may increase up to a maximum of 2 mg/kg BID ≥50 kg: 25 to 50 mg BID; may increase up to a maximum of 100 mg BID – Adolescents ≥16 years: Refer to adult dosing. *Safety and effectiveness of IV formulation have not been established in pediatric patients < 16 years
Levetiracetam (Keppra®) Spritam® (levetiracetam)	Focal (partial) onset: • IR tablets/oral solution/tablets for oral suspension: in adults and children ≥ 1 month (Keppra) or ≥ 4 years and > 20 kg (Spritam) • ER tablets: adults and adolescents ≥ 12 years • IV: in adults and children ≥ 1 month Generalized onset: Juvenile myoclonic epilepsy: • IR tablets/oral solution/tablets for oral suspension: Adjunctive therapy in adults and adolescents ≥ 12 years • IV: Adjunctive therapy in adults and adolescents ≥ 12 years Primary GTC seizures: • IR tablets/oral solution/tablets for oral suspension: Adjunctive therapy in adults and children ≥ 6 years • IV: Adjunctive therapy in adults and children ≥ 6 years	Adult Focal (partial) onset seizures: – ER: 1,000 mg QD; increase every 2 weeks by 1,000 mg/day* Maximum dose: 3,000 mg QD Focal (partial) onset seizures and generalized onset seizures: – IR tablets/oral solution/tablets for oral suspension: 500 mg BID; increase every 2 weeks by 500 mg/dose* Maximum recommended dose: 1,500 mg BID – IV: 500 mg BID; increase every 2 weeks by 500 mg/dose Maximum dose: 1,500 mg BID *Note: Oral loading doses of 1,500 - 2,000 mg IR have been well tolerated and may be useful for more rapidly achieving serum concentrations associated with seizure control; however, necessity has not been established Pediatric Focal (partial) onset: – IR tablets/oral solution: *Infants 1 month to <6 months*: 7 mg/kg/dose BID; increase every 2 weeks by 7 mg/kg/dose to a recommended dose of 21 mg/kg/dose BID *Infants and children 6 months to <4 years*: 10 mg/kg/dose BID; increase every 2 weeks by 10 mg/kg/dose to a recommended dose of 25 mg/kg/dose BID *Children and Adolescents 4 to <16 years*: ○ Oral solution: 10 mg/kg/dose BID; increase every 2 weeks by 10 mg/kg/dose to a recommended dose of 30 mg/kg/dose BID Maximum dose: 3,000 mg/day

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Medication	Indications	Dosing/Administration
		○ Tablets: 20 to 40 kg: 250 mg BID, increase every 2 weeks by 250 mg BID to the maximum recommended dose of 750 mg BID >40 kg: 500 mg BID, increase every 2 weeks by 500 mg BID to the maximum recommended dose of 1,500 mg BID *Adolescents ≥16 years*: Refer to adult dosing – IR tablets for oral suspension: *Children ≥4 years weighing 20 kg - 40 kg*: 250 mg BID; increase every 2 weeks by 250 mg/dose to the maximum recommended dose of 750 mg twice daily. *Children ≥4 years (weighing >40 kg) and adolescents*: Refer to adult dosing – ER: *Children ≥12 years and adolescents*: Refer to adult dosing – IV: *Infants 1 month to <6 months*: 7 mg/kg BID; increase every 2 weeks by 7 mg/kg/dose to a recommended dose of 21 mg/kg BID *Infants and children 6 months to <4 years*: 10 mg/kg BID; increase every 2 weeks by 10 mg/kg/dose to a recommended dose of 25 mg/kg BID *Children and adolescents 4 to <16 years*: 10 mg/kg BID; increase every 2 weeks by 10 mg/kg/dose to the recommended dose of 30 mg/kg BID *Adolescents ≥16 years*: Refer to adult dosing Generalized onset: Juvenile myoclonic epilepsy: – IR tablets/oral solution/tablets for oral suspension): *Children ≥12 years and adolescents*: Refer to adult dosing – IV: *Children ≥12 years and adolescents*: Refer to adult dosing Primary GTC seizures: – IR tablets, oral solution: *Children and adolescents 6 to <16 years*: 10 mg/kg/dose BID; increase every 2 weeks by 10 mg/kg/dose to the recommended dose of 30 mg/kg BID *Adolescents ≥16 years*: Refer to adult dosing – IR tablets for oral suspension: *Children ≥6 years and weighing 20 - 40 kg*: 250 mg BID; increase every 2 weeks by 250 mg/dose to the maximum recommended dose of 750 mg BID *Children ≥6 years (weighing >40 kg) and adolescents*: Refer to adult dosing – IV: *Children and adolescents 6 to <16 years*: 10 mg/kg BID; increase every 2 weeks by 10 mg/kg/dose to the recommended dose of 30 mg/kg BID *Adolescents ≥16 years*: Refer to adult dosing
Gabapentin (Neurontin®)	Adjunctive therapy in the treatment of focal (partial) seizures with and	Adult

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Medication	Indications	Dosing/Administration
	without secondary generalization in adults and pediatric patients 3 years of age	– 300 mg TID (some experts recommend a lower starting dose (e.g. 100 mg 3 times daily) with titration as tolerated); increase based on response and tolerability – Usual dosage: 300 to 600 mg TID (doses of 2.4 - 3.6 g/day have been tolerated in long- and short-term studies, respectively) <u>Pediatric</u> – Children 3 - 4 years: Initial: 10 to 15 mg/kg/day in 3 divided doses; titrate to effective dose over ~3 days Usual dosage: 40 mg/kg/day in 3 divided doses; dosages of up to 50 mg/kg/day have been tolerated in clinical studies – Children 5 - 11 years: Initial: 10 to 15 mg/kg/day in 3 divided doses; titrate to effective dose over ~3 days Usual dosage: 25 to 35 mg/kg/day in 3 divided doses; dosages of up to 50 mg/kg/day have been tolerated in clinical studies – Children ≥12 years and Adolescents: Refer to adult dosing.
Pregabalin (Lyrica®)	Adjunctive therapy in patients ≥1 month of age with focal onset (partial-onset) seizures	<u>Adult and Adolescents ≥17 years of age</u> – 150 mg/day in 2 or 3 divided doses (maximum: 600 mg/day) – Dosage adjustment: May increase based on response and tolerability at weekly intervals (optimal titration schedule has not been defined) <u>Pediatric</u> ≥30 kg – Initial: 2.5 mg/kg/day in 2 or 3 divided doses (maximum: 10 mg/kg/day not to exceed 600 mg/day) – Dosage adjustment: May increase weekly based on response and tolerability (optimal titration schedule has not been defined) <30 kg: – Initial dosage: 3.5 mg/kg/day in ○ 1 month to < 4 years – 3 divided doses ○ ≥ 4 years – 2 or 3 divided doses – Maximum: 14 mg/kg/day – Dosage adjustment: May increase weekly based on response and tolerability (optimal titration schedule has not been defined)
Tiagabine	Adjunctive therapy in adults and children ≥ 12 years in the treatment of partial seizures	<u>Adult</u> Patients taking enzyme-inducing AEDs – Maximum dosage: 56 mg/day – Initial dosage: 4 mg QD – Dosage titration: Increase by 4 to 8 mg at weekly intervals until response is achieved or up to 56 mg/day in 2 to 4 divided doses – Maintenance dosage: 32 to 56 mg/day in 2 to 4 divided doses (doses > 56 mg/day have not been systematically evaluated in adequate and well-controlled clinical trials. Experience is limited in patients taking total daily doses > 32 mg using BID dosing) – Dose adjustment: Should be considered whenever a change in patient's enzyme-inducing status occurs. If multiple doses are missed, evaluate if re-titration is indicated

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Medication	Indications	Dosing/Administration
		– Concomitant therapy: Modification of concomitant AEDs is not necessary unless clinically indicated Patients not taking an enzyme-inducing AED: The estimated plasma concentrations of TGB in patients not taking enzyme-inducing medications is twice that of patients receiving enzyme-inducing AEDs. Lower doses are required; slower titration may be necessary <u>Pediatric</u> Patients taking enzyme-inducing AEDs: – Maximum dosage: 32 mg/day – Initial dosage: 4 mg once daily – Dosage titration: Increase by 4 mg at the beginning of week 2. Thereafter, the total daily dose may be increased by 4 to 8 mg at weekly intervals until clinical response is achieved or up to 32 mg/day in 2 to 4 divided doses. (doses > 32 mg/day have been tolerated in a small number of adolescent patients for a relatively short duration) – Dose adjustment: Should be considered whenever a change in a patient's enzyme-inducing status occurs. If multiple doses are missed, evaluate if re-titration is clinically indicated – Concomitant therapy: Modification of concomitant AEDs is not necessary unless clinically indicated Patients not taking an enzyme-inducing AED: The estimated plasma concentrations of TGB in patients not taking enzyme-inducing medications is twice that of patients receiving enzyme-inducing AEDs. Lower doses required; slower titration may be necessary
Divalproex sodium (Depakote®) Valproic acid (Depakene®, Depacon®)	Focal (partial) onset with impairment of consciousness or awareness (complex partial) • Adjunctive • Monotherapy Generalized onset seizure and generalized onset nonmotor seizures (absence) • Adjunctive • Monotherapy Multiple seizure types • Adjunctive • May be used off-label as monotherapy for other seizure types.	<u>Adult</u> Oral: – Initial monotherapy or adjunctive therapy: 10 to 15 mg/kg/day (for complex partial seizures) or 15 mg/kg/day (for absence seizures); increase by 5 to 10 mg/kg/day at weekly intervals until optimal clinical response and/or therapeutic levels are achieved Maximum recommended dose: 60 mg/kg/day – Conversion to monotherapy: Initiate oral dosage as above; dose reduce concomitant AEDs at the same time or within 1 to 2 weeks; decrease the concomitant AED by ~25% every 2 weeks IV (for non-status epilepticus): – Total daily IV dose should be equivalent to the total daily oral dose (expressed as VPA) and divided every 6 hours; should be used only for those who temporarily cannot use oral formulations with switch to oral formulation as soon as appropriate <u>Pediatric</u> Oral*: – Aware or impaired awareness absence seizures (simple and complex absence seizures): Refer to adult dosing.^ – Focal-onset impaired awareness seizures (complex partial seizures): Children ≥10 years of age: Refer to adult dosing.^ *ER divalproex sodium is not recommended for use in children <10 years of age ^Larger maintenance doses may be required in younger children.

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Medication	Indications	Dosing/Administration
		– Conversion to monotherapy from adjunctive therapy: Refer to adult dosing. IV: – Children and adolescents: (Limited data available in some cases depending on seizure types and age) Total daily IV dose is equivalent to the total daily oral dose; however, IV dose should be divided every 6 hours; switch patients to oral product as soon as clinically possible (IV use >14 days has not been studied) Rectal (off-label route): – Dilute syrup 1:1 with water for use as a retention enema; acute and maintenance dose: 6 to 15 mg/kg/dose
Vimpat® (lacosamide)	POS in children ≥4 years and adults • Adjunctive • Monotherapy Primary GTC in children ≥4 years and adults: • Adjunctive	Adults and Adolescents ≥17 years (Oral, IV)* Initial: – *Monotherapy***: 100 mg BID; increase at weekly intervals by 50 mg BID based on response and tolerability (administer loading doses under medical supervision because of the increased incidence of CNS AEs) – *Adjunctive*: 50 mg BID – *Alternative*: 200 mg loading dose followed 12 hours later by 100 mg BID Titration: Increase by 50 mg BID every week Maintenance: *Monotherapy***: 150 to 200 mg BID *Adjunctive*: 100 to 200 mg BID Pediatric (Oral, IV)* ≥50 kg: – Initial: 50 mg BID; increase at weekly intervals of 50 mg BID based on response and tolerability – Maintenance: *Monotherapy***: 150 to 200 mg BID *Adjunctive*: 100 to 200 mg BID 30 to <50 kg, Adjunctive and monotherapy: Initial: 1 mg/kg BID; increase at weekly intervals by 1 mg/kg BID based on response and tolerability Maintenance: 2 to 4 mg/kg BID 11 to <30 kg, Adjunctive and monotherapy: Initial: 1 mg/kg; increase at weekly intervals by 1 mg/kg/dose BID based on response and tolerability Maintenance: 3 to 6 mg/kg BID **when not specified, the dosage is the same for monotherapy for POS and adjunctive therapy for POS or primary GTC seizures.* ***For POS only*
Zonisamide (Zonegran®)	Adjunct treatment of partial seizures in patients > 16 years of age with epilepsy	Adults and Pediatrics > 16 years of age Partial seizures – Initial dosage: 100 mg QD – Dosage titration: May increase to 200 mg/day after 2 weeks. Further dosage increases to 300 and 400 mg/day can then be made with a minimum of 2 weeks between adjustments. (There is

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Medication	Indications	Dosing/Administration
		some evidence of slightly greater response at doses > 100 to 200 mg/day; AEs are more frequent at doses ≥ 300 mg/day) – Maintenance dosage: Doses up to 600 mg/day have been studied; there is no evidence of increased response at > 400 mg/day
Epidiolex® (cannabidiol)	Treatment of seizures associated with LGS, Dravet syndrome or tuberous sclerosis complex in patients ≥ 1 years of age	<u>Adults and Pediatrics ≥ 1 years of age</u> LGS, Dravet syndrome – Maximum dosage: 20 mg/kg/day – Initial dosage: 2.5 mg/kg BID – Dosage titration: May increase after 1 week to a maintenance dose of 5 mg/kg BID; may increase in weekly increments of 2.5 mg/kg BID to a maximum dosage of 10 mg/kg BID. In patients needing a more rapid titration from 5 mg/kg BID to 10 mg/kg BID, may increase dose as quickly as every other day in increments of 2.5 mg/kg BID. The 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates, but with an increase in AEs. Tuberous Sclerosis Complex – Initial: 2.5 mg/kg BID – Dosage titration: Increase dose in weekly increments of 2.5 mg/kg BID to a maintenance dose of 12.5 mg/kg BID. In patients needing a more rapid titration, may increase dose as quickly as every other day in increments of 2.5 mg/kg BID.
Xcopri® (cenobamate)	Treatment of focal (partial) onset seizures in adult patients	– Weeks 1 and 2: 12.5 mg QD; increase based on response and tolerability as follows. – Weeks 3 and 4: 25 mg QD – Weeks 5 and 6: 50 mg QD – Weeks 7 and 8: 100 mg QD – Weeks 9 and 10: 150 mg QD – Week 11 and thereafter: 200 mg QD; if needed based on response and tolerability, may increase dose further in increments of 50 mg every 2 weeks to a maximum of 400 mg QD – Can be taken whole or tablets can be crushed
Felbamate (Felbatol®)	Partial seizures: Monotherapy or adjunctive therapy in the treatment of partial seizures (with and without generalization) in adults and adolescents 14 years and older LGS: Adjunctive therapy in the treatment of partial and generalized seizures associated with LGS in children	<u>Adults and Adolescents ≥ 14 years of age</u> Partial seizures, monotherapy: – Initial: 1,200 mg/day in 3 to 4 divided doses; titrate previously untreated patients under close clinical supervision, increasing the dosage in 600 mg increments every 2 weeks to 2400 mg/day based on clinical response and thereafter to 3,600 mg/day if clinically indicated – Conversion to monotherapy: Initiate at 1,200 mg/day in 3 to 4 divided doses; reduce the dosage of the concomitant anticonvulsant(s) by 33% at the initiation of felbamate therapy; at week 2, increase the felbamate dosage to 2,400 mg/day while reducing the dosage of the other anticonvulsant(s) up to an additional 33% of their original dosage; at week 3, increase the felbamate dosage up to 3,600 mg/day and continue to reduce the dosage of the other anticonvulsant(s) as clinically indicated Partial seizures, adjunctive therapy:

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr><td></td><td></td><td>– Initial: 1,200 mg/day in 3 to 4 divided doses; increase once per week by 1,200 mg/day increments up to 3,600 mg/day in 3 to 4 divided doses.
– Note: Decrease dose of concomitant CBZ (and CBZ metabolites), phenobarbital, PHT, or VPA by 20% when initiating felbamate therapy. Further dosage reductions may be necessary as dose of felbamate is increased.
Pediatrics 2 years to 14 years
– Initial: 15 mg/kg/day in 3 or 4 divided doses; increase dose by 15 mg/kg/day increments at weekly intervals (maximum: 45 mg/kg/day or 3,600 mg/day whichever is less)
– Note: At initiation of felbamate, decrease dose of concomitant CBZ, PHT, phenobarbital, or VPA by 20%. Further dosage reductions may be necessary as dose of felbamate is increased.</td></tr>
<tr><td>Fintepla® (fenfluramine)</td><td>Treatment of seizures associated with Dravet syndrome in patients ≥2 years of age</td><td>– Initial: 0.1 mg/kg BID
– Dosage titration (as needed based on response and tolerability):
○ If NOT on stiripentol, increase every 4-7 days to 0.2 mg/kg BID then to 0.35 mg/kg BID (maximum 26 mg/day)
○ If receiving concurrent stiripentol + CBZ, increase every 7 days to 0.15 mg/kg BID then to 0.2 mg/kg BID (maximum 17 mg/day)</td></tr>
<tr><td>Lamotrigine (Lamictal®)</td><td>Adjunctive therapy:
• IR: POS, generalized seizures of LGS, and primary GTC seizures in adults and children ≥ 2 years
• ER: primary GTC seizures and POS with or without secondary generalization in patients ≥ 13 years
Monotherapy:
• IR: Conversion to monotherapy in adults (≥ 16 years) with POS who are receiving treatment with CBZ, PHT, phenobarbital, primidone, or valproate as the single AED
• ER: Conversion to monotherapy in patients ≥ 13 years with POS who are receiving treatment with a single AED</td><td>Note: Whole tablets should be used for dosing, round calculated dose down to the nearest whole tablet. Alternatively, a suspension may be prepared using IR tablets.
<u>Adult</u>
Adjunctive
<table>
<tr><th></th><th></th><th colspan="3">Regimen</th></tr>
<tr><td rowspan="2">Indication</td><td></td><td>NOT containing CBZ, PHT, phenobarbital, primidone, rifampin, LPV/r, or VPA</td><td>Containing VPA</td><td>Containing CBZ, PHT, phenobarbital, primidone, rifampin, LPV/r, and withOUT VPA</td></tr>
<tr><td rowspan="5">Partial, LGS, & primary GTC seizures (IR)</td><td>Weeks 1 & 2</td><td>25 mg QD</td><td>25 mg every other day</td><td>50 mg QD</td></tr>
<tr><td>Weeks 3 & 4</td><td>50 mg QD</td><td>25 mg QD</td><td>100 mg daily in 2 divided doses</td></tr>
<tr><td>Weeks ≥ 5</td><td colspan="3">Increase every 1-2 weeks by…</td></tr>
<tr><td></td><td>50 mg daily</td><td>25-50 mg daily</td><td>100 mg daily</td></tr>
<tr><td>Usual maint-enance</td><td>225-375 mg daily in 2 divided doses</td><td>100-200 mg daily (VPA alone) or 100-400 mg daily (VPA and other drugs that induce</td><td>300-500 mg daily in 2 divided doses (doses as high as 700 mg/day have been used)</td></tr>
</table></td></tr>
</table>

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Medication	Indications	Dosing/Administration

			glucuronidation) in 1 or 2 divided doses	
Partial and primary GTC (ER)	Weeks 1 & 2	25 mg QD	25 mg every other day	50 mg QD
	Weeks 3 & 4	50 mg QD	25 mg QD	100 mg QD
	Week 5	100 mg QD	50 mg QD	200 mg QD
	Week 6	150 mg QD	100 mg QD	300 mg QD
	Week 7	200 mg QD	150 mg QD	400 mg QD
	Week ≥ 8	Dose increases should not exceed 100 mg daily at weekly intervals		
	Usual maint-enance	300-400 mg QD	200-250 mg QD	400-600 mg QD

Monotherapy
Conversion strategy from adjunctive therapy with VPA to monotherapy with LTG:

	IR	ER
Initiate and titrate as per escalation recommendations for adjunctive therapy to a LTG dose of…	200 mg daily	150 mg daily
Then taper VPA dose in decrements of not >500 mg/day/week to a VPA dose of 500 mg daily; this dosage should be maintained for 1 week. The LTG dosage should then be increased to…	300 mg daily while VPA is simultaneously decreased to 250 mg daily	200 mg daily while VPA is simultaneously decreased to 250 mg daily
	…this dosage should be maintained for 1 week	
VPA may then be discontinued, while the LTG dose is increased…	by 100 mg daily at weekly intervals to achieve a LTG maintenance dose of 500 mg daily in 2 divided doses	to achieve a maintenance dosage range of 250 to 300 mg QD

Conversion strategy from adjunctive therapy with drugs that induce LTG glucuronidation (CBZ, PHT, phenobarbital, primidone) to monotherapy with LTG:
– IR and ER:

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr><td></td><td></td><td>Initiate and titrate as per escalation recommendations for adjunctive therapy to a LTG dose of 500 mg daily
Concomitant enzyme-inducing drug should then be withdrawn by 20% decrements each week over a 4-week period
Two weeks after withdrawal of the enzyme-inducing drug, the dosage of LTG ER may be tapered in decrements of not >100 mg/day at intervals of 1 week to achieve a maintenance dosage range of 250 to 300 mg QD; no further dosage reduction is required for LTG IR
Conversion strategy from adjunctive therapy with drugs that do not inhibit or induce LTG glucuronidation to monotherapy with LTG:
– IR: No specific guidelines available
– ER: Initiate and titrate as per escalation recommendations for adjunctive therapy to a LTG dose of 250 to 300 mg daily
Concomitant drug should then be withdrawn by 20% decrements each week over a 4-week period
Conversion from IR to ER: Initial dose of the ER tablet should match the total daily dose of the IR formulation; adjust dose as needed within the recommended dosing guidelines</td></tr>
<tr><td>Lamotrigine (Lamictal®) (continued…)</td><td></td><td><u>Pediatric</u>
Adjunctive
LGS, primary GTC seizures, or partial seizures (children < 30 kg will likely require maintenance doses to be increased by as much as 50% based on clinical response regardless of regimen below)

– Children 2 to 12 years (IR):
<table>
<tr><th></th><th></th><th>Regimen</th><th></th><th></th></tr>
<tr><td>Indication</td><td></td><td>NOT containing CBZ, PHT, phenobarbital, primidone, rifampin, LPV/r, or VPA</td><td>Containing VPA</td><td>Containing CBZ, PHT, phenobarbital, primidone, rifampin, LPV/r, and withOUT VPA</td></tr>
<tr><td rowspan="4">Partial, LGS, & primary GTC seizures (IR)</td><td>Weeks 1 & 2</td><td>0.3 mg/kg/day in 1 to 2 divided doses</td><td>0.15 mg/kg/day in 1 to 2 divided doses (if dose is equal or rounds down to 1 mg/day, give 2 mg every other day instead)</td><td>0.6 mg/kg/day in 2 divided doses</td></tr>
<tr><td>Weeks 3 & 4</td><td>0.6 mg/kg/day in 2 divided doses</td><td>0.3 mg/kg/day in 1 to 2 divided doses</td><td>1.2 mg/kg/day in 2 divided doses</td></tr>
<tr><td>Weeks ≥ 5</td><td colspan="3">Increase every 1-2 weeks by…</td></tr>
<tr><td></td><td>0.6 mg/kg/day</td><td>0.3 mg/kg/day</td><td>1.2 mg/kg/day</td></tr>
</table></td></tr>
</table>

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>Usual maint-enance</td><td>4.5-7.5 mg/kg/day (maximum: 300 mg/day) in 2 divided doses</td><td>1-5 mg/kg/day (maximum: 200 mg/day) in 1-2 divided doses or 1-3 mg/kg/day with VPA alone (maximum: 200 mg/day)</td><td>5 to 15 mg/kg/day (maximum: 400 mg/day) in 2 divided doses</td></tr>
</table>
– Adolescents >12 years: Refer to adult dosing.
Conversion from adjunctive therapy with drugs that inhibit or induce LTG glucuronidation to monotherapy with LTG:
– IR: Adolescents ≥16 years: Refer to adult dosing
– ER: Adolescents ≥13 years: Refer to adult dosing</td></tr>
<tr><td>Fycompa™ (perampanel)</td><td>Treatment of POS with or without secondarily generalized seizures as adjunct or monotherapy in patients with epilepsy ≥ 4 years
Treatment of primary GTC seizures as adjunct therapy in patients with epilepsy ≥ 12 years</td><td><u>Adult</u>
POS
– Initial dose
○ Absence of enzyme-inducing AEDs: 2 mg QHS
○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): 4 mg QHS
– Dosage titration: Increase by increments of 2 mg QD no more frequently than at weekly intervals
– Maintenance dose:
○ Absence of enzyme-inducing AEDs: 8 to 12 mg QHS; some patients may respond to 4 mg QD (a dose of 12 mg QD has resulted in somewhat greater reductions in seizure rates in some patients but with substantial increase in AEs)
○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): Maintenance dose has not been established; highest dose used in clinical trials was 12 mg QD
Primary GTC seizures (adjunct)
– Maximum dosage: 12 mg QD
– Initial dosage:
○ Absence of enzyme-inducing AEDs: 2 mg QHS
○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): 4 mg QHS
– Dose titration: Increase by increments of 2 mg QD no more frequently than at weekly intervals
– Maintenance dosage:
○ Absence of enzyme-inducing AEDs: 8 mg QHS; if tolerated and further seizure control is needed, may increase up to 12 mg QD
○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): Maintenance dose has not been established; highest dose used in clinical trials was 12 mg QD
<u>Pediatric</u>
POS
– Initial dosage
○ Absence of enzyme-inducing AEDs: 2 mg QHS</td></tr>
</table>

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Medication	Indications	Dosing/Administration
		○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): 4 mg QHS – Dosage titration: Increase by increments of 2 mg QD no more frequently than at weekly intervals – Maintenance dosage ○ Absence of enzyme-inducing AEDs: 8 to 12 mg QHS; some patients may respond to 4 mg QD (a dose of 12 mg QD has resulted in somewhat greater reductions in seizure rates in some patients but with substantial increase in AEs) ○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): Maintenance dose has not been established; highest dose used in clinical trials was 12 mg QD Primary GTC seizures (adjunct) – Maximum dosage: 12 mg QD – Initial dosage: ○ Absence of enzyme-inducing AEDs: 2 mg QHS ○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): 4 mg QHS – Dosage titration: Increase by increments of 2 mg QD no more frequently than at weekly intervals – Maintenance dosage ○ Absence of enzyme-inducing AEDs: 8 mg QHS; if tolerated and further seizure control is needed, may increase up to 12 mg QD ○ Presence of enzyme-inducing AEDs (e.g. CBZ, OXC, PHT): Maintenance dose has not been established; highest dose used in clinical trials was 12 mg QD
Banzel® (rufinamide)	Adjunctive treatment of seizures associated with LGS in adults and pediatric patients ≥ 1 year	<u>Adults and Pediatrics ≥ 17 years</u> – Maximum dosage: 3,200 mg daily in 2 equally divided doses – Initial dosage: 400 to 800 mg daily in 2 equally divided doses – Dosage titration: Increase the dosage by 400 to 800 mg daily every other day until a maximum dosage of 3,200 mg daily in 2 equally divided doses is reached – Maintenance dosage: 3,200 mg daily in 2 equally divided doses <u>Pediatrics 1 to 16 years</u> – Maximum dosage: 45 mg/kg daily, not to exceed 3,200 mg daily in 2 equally divided doses – Initial dosage: Approximately 10 mg/kg daily in 2 equally divided doses – Dosage titration: Increase the dose by approximately 10 mg/kg every other day to a maximum dose of 45 mg/kg daily, not to exceed 3,200 mg daily in 2 equally divided doses – Maintenance dosage: 45 mg/kg daily or 3,200 mg daily (whichever is less) in 2 equally divided doses
Diacomit® (stiripentol)	Adjunctive treatment of refractory GTC seizures in conjunction with CBZ (and VPA, *off-label*) in patients ≥2 years of age with Dravet syndrome	<u>Adults and Pediatrics ≥ 2 years</u> 50 mg/kg/day in 2 to 3 divided doses; some experts recommend initiating with 10 to 15 mg/kg/day and increasing to a target dose of 50 mg/kg/day over 2 to 4 weeks (maximum 3 g/day)

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr>
<td>Topiramate (Topamax®, Qudexy®) Trokendi™ (topiramate)</td>
<td>Monotherapy
As initial monotherapy in patients ≥ 2 years (IR and Qudexy XR) or ≥ 6 years (Trokendi XR) with partial-onset or primary GTC seizures

Adjunctive therapy
As adjunctive therapy in patients ≥ 2 years (IR and Qudexy XR only) or ≥ 6 years (Trokendi XR only) with POS, primary GTC seizures, or seizures associated with LGS</td>
<td>Adults and Pediatrics ≥ 10 years
Monotherapy, partial-onset or primary GTC seizures
– IR, usual dosage: 400 mg/day in 2 divided doses (the mean dosage achieved in the monotherapy trial was 275 mg/day)
– ER, usual dosage: 400 mg QD
– Dosage titration
<table>
<tr><th>Week</th><th>IR Dose</th><th>ER Dose</th></tr>
<tr><td>1</td><td>25 mg BID</td><td>50 mg QD</td></tr>
<tr><td>2</td><td>50 mg BID</td><td>100 mg QD</td></tr>
<tr><td>3</td><td>75 mg BID</td><td>150 mg QD</td></tr>
<tr><td>4</td><td>100 mg BID</td><td>200 mg QD</td></tr>
<tr><td>5</td><td>150 mg BID</td><td>300 mg QD</td></tr>
<tr><td>6</td><td>200 mg BID</td><td>400 mg QD</td></tr>
</table>
Adults and Pediatrics ≥ 17 years
Adjunctive therapy, partial-onset, primary GTC seizures or LGS
IR
– Usual dosage: 100 to 200 mg BID (POS or LGS) or 200 mg BID (primary GTC seizures) (doses > 400 mg/day have not shown additional benefit for treatment of POS; doses > 1,600 mg/day have not been studied)
– Initial dosage: 25 mg QD or BID for 1 week
– Dosage titration: Increase weekly by 25 to 50 mg/day
ER
– Usual dosage: 200 to 400 mg QD (POS, LGS) or 400 mg QD (primary GTC seizures) (doses > 400 mg/day have not shown additional benefit for treatment of POS)
– Initial dosage: 25 to 50 mg QD for 1 week
– Dosage titration: Increase weekly by 25 to 50 mg QD
Pediatrics 2 years to < 10 years (IR and Qudexy XR) and 6 years to < 10 years (Trokendi XR)
Monotherapy
– Maximum dosage:
○ > 38 kg: 400 mg/day
○ 23 to 38 kg: 350 mg/day
○ 12 to 22 kg: 300 mg/day
○ ≤ 11 kg or less: 250 mg/day
– Initial dosage: 25 mg/day nightly for the first week
– Dosage titration: May increase to 25 mg BID (IR) or 50 mg QD (ER) in the second week then by 25 to 50 mg/day each subsequent week as tolerated. Titration to the minimum maintenance dose should be attempted over 5 to 7 weeks of the total titration period. Additional titration (up to the maximum maintenance dose) can be attempted at 25 to 50 mg/day weekly increments
– Maintenance dosage (administer IR in 2 divided doses, ER once daily)
<table>
<tr><th>Weight</th><th>Total daily minimum maintenance dose</th><th>Total daily maximum maintenance dose</th></tr>
</table>
</td>
</tr>
</table>

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Up to 11 kg</td><td>150 mg/day</td><td>250 mg/day</td></tr>
<tr><td>12-22 kg</td><td>200 mg/day</td><td>300 mg/day</td></tr>
<tr><td>23-31 kg</td><td>200 mg/day</td><td>350 mg/day</td></tr>
<tr><td>32-38 kg</td><td>250 mg/day</td><td>350 mg/day</td></tr>
<tr><td>> 38 kg</td><td>250 mg/day</td><td>400 mg/day</td></tr>
</table>

<u>Pediatrics 6 years to < 17 years (IR, Qudexy XR, and Trokendi XR) and 2 to 6 years (IR and Qudexy XR)</u>
Adjunctive therapy for POS, primary GTC seizures, and LGS
IR
– Usual dosage: 5 to 9 mg/kg/day in 2 divided doses
– Maximum dosage: 400 mg/day
– Initial dosage: 25 mg (1 to 3 mg/kg/day) nightly for the first week
– Dosage titration: May increase dosage at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in 2 divided doses) to achieve optimal clinical response
ER (Qudexy XR and Trokendi XR)
– Usual dosage: 5 to 9 mg/kg QD
– Maximum dosage: 400 mg/day (Trokendi XR only)
– Initial dosage: 25 mg (1 to 3 mg/kg/day) nightly for the first week
– Dosage titration: May increase dosage at 1- or 2-week intervals by increments of 1 to 3 mg/kg. If required, longer intervals between dose adjustments can be used
<u>Off-label</u>
Infantile spasms
– Therapy has been evaluated for up to 4 years. The optimal dose of has not been established
– Doses should be tapered up every 2 to 5 days until a response is reached or patients cannot tolerate the medication
– Maximum dosage: 12 to 27 mg/kg/day
– Initial dosage: 1 to 3 mg/kg/day</td></tr>
<tr><td>Vigabatrin (Sabril®)</td><td>Monotherapy for patients 1 month to 2 years with infantile spasms

Adjunctive therapy for patients ≥ 2 years with refractory complex partial seizures who have inadequately responded to several alternative treatments

Only indicated in patients for whom the potential benefits outweigh the risk of vision loss</td><td><u>Adults and Pediatrics ≥ 17 years, or ≥ 2 years weighing > 60 kg</u>
Refractory complex partial seizures
– Usual dosage: 1.5 g BID (3 g/day)
– Initial dosage: 500 mg BID
– Dosage titration: Total daily dose may be increased in 500 mg increments at weekly intervals depending on response
<u>Pediatrics</u>
Infantile spasms
Powder for suspension
– Maximum dosage: 150 mg/kg/day in 2 divided doses
– Initial dosage: 50 mg/kg/day in 2 divided doses
– Dosage titration: Titrate by 25 to 50 mg/kg/day increments every 3 days, up to a maximum of 150 mg/kg/day
– Discontinuation of therapy: Vigabatrin should be withdrawn gradually. In a study, the dose was decrease by 25 to 50 mg/kg/day increments every 3 to 4 days
Refractory complex partial seizures</td></tr>
</table>

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Medication	Indications	Dosing/Administration
		2 to 16 years of age weighing ≤ 60 kg – 10 to 15 kg: 175 mg BID initially; titrate upwards at weekly intervals based on response and tolerability; recommended maintenance dose: 525 mg twice daily (1,050 mg/day). – >15 kg to 20 kg: 225 mg BID initially; titrate upwards at weekly intervals based on response and tolerability; recommended maintenance dose: 650 mg BID (1,300 mg/day). – >20 kg to 25 kg: 250 mg BID initially; titrate upwards at weekly intervals based on response and tolerability; recommended maintenance dose: 750 mg BID (1,500 mg/day). – >25 to 60 kg: 250 mg BID initially; titrate upwards at weekly intervals based on response and tolerability; recommended maintenance dose: 1,000 mg BID (2,000 mg/day)
Hydantoins		
Phenytoin (Dilantin®, Phenytek®)	Oral: Control of GTC and complex partial (psychomotor, temporal lobe) seizures; prevention and treatment of seizures occurring during or following neurosurgery (capsule and chewable tablet only)	Adult Seizures (nonemergent) ER – Initial dosage, Treatment naïve: 100 mg TID – Loading dose: 1 g divided into 3 doses (400, 300, and 300 mg) administered at 2-hour intervals; begin maintenance dosage 24 hours after loading dose (Note: Do not use loading dose regimen in patients with a history of renal or hepatic disease. Reserve for patients who require rapid steady state serum levels, when IV administration is not desirable, and for patients in a clinic or hospital setting where phenytoin levels can be closely monitored.) – Maintenance dosage: 100 mg 3 to 4 times a day; doses of up to 200 mg TID may be necessary. May consider converting patients established on 100 mg TID to 300 mg QD – Dosage adjustment: Adjust dose at ≥ 7 to 10 day intervals IR, Tablet – Initial dosage: 100 mg TID – Maintenance dosage: 300 to 400 mg/day; an increase to 600 mg/day may be necessary – Dosage adjustment: Adjust dose at ≥ 7 to 10 day intervals IR, Suspension – Initial dosage: 125 mg TID – Dosage adjustment: Adjust dose at ≥ 7 to 10 day intervals; an increase to 625 mg/day may be necessary Pediatric Seizures (non-emergent) ER – Maximum dosage: 300 mg/day – Initial dosage: 5 mg/kg/day in 2 or 3 equally divided doses – Maintenance dosage: 4 to 8 mg/kg/day – Dosage adjustment: Adjust dose at ≥ 7 to 10 day intervals IR – Maximum dosage: 300 mg/day – Initial dosage: 5 mg/kg/day in 2 to 3 equally divided doses – Maintenance dosage: 4 to 8 mg/kg/day

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Medication	Indications	Dosing/Administration
		– Dosage adjustment: Adjust dose at ≥ 7 to 10 day intervals Seizures (*off-label*) – Initial dosage ○ 6 months to 16 years of age: 5 mg/kg/day in 2 or 3 divided doses ○ Neonates: 5 mg/kg/day in 2 divided doses – Usual dosage ○ 10 to 16 years of age: 6 to 7 mg/kg/day in 2 or 3 divided doses ○ 7 to 9 years of age: 7 to 8 mg/kg/day in 2 or 3 divided doses ○ 4 to 6 years of age: 7.5 to 9 mg/kg/day in 2 or 3 divided doses ○ 6 months to 3 years of age: 8 to 10 mg/kg/day in 2 or 3 divided doses ○ Neonates: 5 to 8 mg/kg/day in 2 or 3 divided doses
Phenytoin (Dilantin®, Phenytek®) (*continued…*)	Injection: – Control of GTC and complex partial (psychomotor, temporal lobe) seizures; prevention and treatment of seizures occurring during neurosurgery – Treatment of GTC status epilepticus	<u>Adult</u> Status epilepticus – Loading dose: 10 to 15 mg/kg slow IV at a rate ≤ 50 mg/minute – Maintenance dosage: 100 mg orally or IV every 6 to 8 hours – NCS recommendation (off-label): 20 mg/kg IV loading dose at a rate ≤ 50 mg/minute; if necessary, may give an additional dose of 5 to 10 mg/kg 10 minutes after the loading dose Off-label dosing – Rectal administration: Single dose of 7 mg/kg (parenteral solution given rectally) or 200 mg (suppositories) – Subarachnoid hemorrhage: 15 to 20 mg/kg administered as an IV loading dose, followed by a 5 mg/kg maintenance dose given daily or in divided doses. Maintenance doses are adjusted to maintain serum levels of 10 to 20 mcg/mL <u>Pediatric</u> Status epilepticus – Loading dose: 15 to 20 mg/kg slow IV at a rate ≤ 1 to 3 mg/kg/minute or 50 mg/minute (whichever is slower) – NCS recommendation (off-label): 20 mg/kg IV loading dose at a rate ≤ 1 mg/kg/minute; if necessary, may give an additional dose of 5 to 10 mg/kg 10 minutes after the loading dose <u>Adult and Pediatric</u> Seizures (nonemergent use) – Converting between IV and oral formulations: Total daily dose should be equal. Dosage adjustments and closer serum monitoring may be necessary. If using the IV route in a patient who cannot take oral formulations, convert to oral as soon as possible
Fosphenytoin (Cerebyx®)	Control of GTC status epilepticus and the prevention and treatment of seizures occurring during neurosurgery; short-term parenteral administration when oral PHT is not possible	**The dose, concentration, and infusion rates for fosphenytoin are expressed as PHT equivalents (PE); fosphenytoin should always be prescribed and dispensed in PE; fosphenytoin 1.5 mg is equivalent to PHT 1 mg and is referred to as 1 mg PE.** <u>Adult</u> Status epilepticus (IV): – AES recommendations: 20 mg PE/kg as a single dose (maximum dose: 1500 mg PE)

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Medication	Indications	Dosing/Administration
		– NCS recommendations: Loading dose: 20 mg PE/kg (maximum rate of administration: 150 mg PE/minute); if necessary, may give an additional 5 mg PE/kg 10 minutes after the loading dose – Manufacturer's labeling (may not reflect current clinical practice): Loading dose: 15 to 20 mg PE/kg administered at 100 to 150 mg PE/minute Nonemergent loading and maintenance dosing (IM, IV)*: – Loading dose: 10 to 20 mg PE/kg – Initial maintenance dose: 4 to 6 mg PE/kg/day in divided doses Substitution for oral PHT therapy (IM, IV): – May be substituted at the same total daily dose (plasma PHT concentrations may modestly increase when IM/IV fosphenytoin is substituted for oral PHT due to greater bioavailability of fosphenytoin [100%] compared to oral PHT [90%]) <u>Pediatric</u> Manufacturer's labeling notes IM administration should ordinarily not be used in pediatric patients. Status epilepticus (IV): – NCS recommendations: Loading dose: 20 mg PE/kg (maximum rate of administration: 150 mg PE/minute); if necessary, may give an additional 5 mg PE/kg 10 minutes after the loading dose – Manufacturer's labeling (may not reflect current clinical practice): Loading dose: 15 to 20 mg PE/kg administered at 2 mg PE/kg/minute or 150 mg PE/minute, whichever is slower Nonemergent loading and maintenance dosing (IV)*: – Loading dose: 10 to 15 mg PE/kg; maximum rate 2 mg PE/kg/minute or 150 mg PE/minute, whichever is slower – Initial maintenance dose: 4 to 8 mg PE/kg/day in 2 divided doses; maximum rate 1 to 2 mg PE/kg/minute or 100 mg PE/minute, whichever is slower Substitution for oral PHT therapy (IV): Refer to adult dosing *Due to risks of cardiac and local toxicity, transition to oral PHT when possible.
Peganone® (ethotoin)	Control of GTC (grand mal) and complex partial (psychomotor) seizures	<u>Adult</u> – Initial: 1 g or less daily in 4 to 6 divided doses, with subsequent gradual dosage increases over a period of several days – Maintenance: 2 to 3 g daily in 4 to 6 divided dose <u>Pediatric</u> – Initial: Do not exceed 750 mg daily in 4 to 6 divided doses. – Maintenance: 0.5 g to 1 g daily in 4 to 6 divided doses, although occasionally, 2 or (rarely) 3 g daily in 4 to 6 divided doses may be necessary
Succinimides		
Ethosuximide (Zarontin®)	Management of absence (petit mal) seizures	<u>Adult</u> – Initial: 500 mg/day (divided or, off-label, single daily); individualize dose based on patient response by increasing in small increments (e.g., ≤250 mg) (higher doses [>1,500 mg/day, in

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Medication	Indications	Dosing/Administration
		divided doses], may be necessary but should only be used under the strict supervision of a physician) Pediatric 6 years and older: – Initial: 500 mg/day; individualize based on patient response by increasing in small increments (e.g., ≤250 mg) every 4 to 7 days as needed – Maintenance: 20 mg/kg/day; dosages > 1.5 g daily, which may be necessary in some patients, should be divided and administered only under strict supervision 3 to < 6 years – Initial: 250 mg/day; individualize based on patient response by increasing in small increments (e.g., ≤250 mg) every 4 to 7 days as needed – Maintenance: 20 mg/kg/day; dosages > 1.5 g daily, which may be necessary in some patients, should be divided and administered only under strict supervision Weight-directed dosing, 2 years and older – Initial: 10 mg/kg/day; titrate to response in 5 to 10 mg/kg/day increments every 7 days as required – Usual maintenance range: 20 to 30 mg/kg/day in 2 to 3 divided doses (doses reported in literature range from 6.5 to 50 mg/kg/day); maximum 60 mg/kg/day or 2,000 mg/day, whichever is less
Celontin® (methsuximide)	Absence (petit mal) seizures that are refractory to other drugs	300 mg per day for the first week; if required, increase thereafter at weekly intervals by 300 mg/day up to a daily dosage of 1,200 mg in 2 to 4 divided doses (slower titrations may be considered to avoid toxic accumulation of active metabolite N-desmethylmethsuximide)
Barbiturates		
Phenobarbital	Oral: Treatment of generalized and partial seizures Injection: Management of GTC, status epilepticus, and partial seizures	Adult Oral – 2 mg/kg/day in divided doses. (Individualize based upon clinical response and serum concentration; 2 mg/kg/day typically produces a steady-state level of 20 mg/L) – Manufacturer's labeling (may not reflect current clinical practice): 60 to 200 mg/day or 50 to 100 mg 2 to 3 times daily Injection – Seizure, maintenance: 2 mg/kg/day IV in divided doses (off-label). (Limited data available. Individualize based upon clinical response and serum concentration; 2 mg/kg/day typically produces a steady-state level of 20 mg/L) – Status epilepticus (off-label)*: ○ AES: 15 mg/kg IV as a single dose (AES recommends phenobarbital as a second line option only if first line options [lorazepam, diazepam, or MDZ] or other second line options [e.g. fosphenytoin, VPA, LEV] are unavailable) ○ NCS: 20 mg/kg IV (infused at 50 to 100 mg/minute); may repeat once after 10 minutes with an additional 5 to 10 mg/kg

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Medication	Indications	Dosing/Administration
		Pediatric (Limited data available. Individualize based upon clinical response and serum concentration; QD doses usually administered at bedtime in children and adolescents) Seizure maintenance Oral, IV (off-label) – >12 years of age: 1 to 3 mg/kg/day in 1 to 2 divided doses – 6 to 12 years of age: ○ Usual dosage: 4 to 6 mg/kg/day in 1 to 2 divided doses ○ Initial dosage: 2 to 3 mg/kg/day in 1 to 2 divided doses – 1 to 5 years of age ○ Usual dosage: 6 to 8 mg/kg/day in 1 to 2 divided doses ○ Initial dosage: 3 to 5 mg/kg/day in 1 to 2 divided doses – Infants ○ Usual dosage: 5 to 6 mg/kg/day in 1 to 2 divided doses ○ Initial dosage: 3 to 5 mg/kg/day in 1 to 2 divided doses – *Oral only*: Manufacturer's labeling (may not reflect current clinical practice): 3 to 6 mg/kg/day Injection – *IV only*: Maintenance usually starts 12 hours after loading dose Pediatric (*Continued…*) Injection – Status epilepticus* ○ American Academy of Pediatrics: 20 mg/kg IV (maximum dose: 1,000 mg) over 10 minutes; may repeat dose after 15 minutes (maximum total dose: 40 mg/kg) ○ AES: 15 mg/kg IV as a single dose (AES recommends phenobarbital as a second line option only if first line options [lorazepam, diazepam, or MDZ] or other second line options [e.g. fosphenytoin, VPA, LEV] are unavailable) ○ NCS: 20 mg/kg IV (infused at 50 to 100 mg/minute); may repeat once after 10 minutes with an additional 5 to 10 mg/kg ○ Manufacturer's labeling (may not reflect current clinical practice): 15 to 20 mg/kg IV over 10 to 15 minutes *Respiratory support may be required particularly when maximizing loading dose or if concurrent sedative therapy. Repeating doses sooner than 10 to 15 minutes may not allow adequate time for peak CNS concentrations and lead to CNS depression
Primidone (Mysoline®)	As monotherapy or adjunct therapy for the control of GTC, psychomotor, and focal epileptic seizures; it may control GTC seizures refractory to other AEDs	Adult Seizures – Maximum dosage: 2 g/day – Initial dosage: 100 to 125 mg QHS on days 1 to 3 – Dosage titration: ○ Days 4 to 6: 100 to 125 mg BID ○ Days 7 to 9: 100 to 125 mg TID ○ Day 10 to maintenance: 250 mg TID – Maintenance dosage: 250 mg 3 to 4 times daily. If required, an increase to 1,250 to 1,500 mg daily in 3 to 4 divided doses may be made, but daily doses should not exceed 500 mg QID

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Medication	Indications	Dosing/Administration
		– Concomitant therapy with other AEDs: start at 100 to 125 mg QHS and gradually increased to maintenance level as the other AED is gradually decreased. Continue until the satisfactory dosage level is achieved for the combination, or the other AED is completely withdrawn. When primidone monotherapy is the objective, the transition should not be completed in < 2 weeks Pediatric Seizures, ≥ 8 years – Maximum dosage: 2 g/day – Initial dosage: 100 to 125 mg QHS on days 1 to 3 – Dosage titration: ○ Days 4 to 6: 100 to 125 mg BID ○ Days 7 to 9: 100 to 125 mg TID ○ Day 10 to maintenance: 250 mg TID – Maintenance dosage: 250 mg 3 or 4 times daily. If required, an increase to 1,250 to 1,500 mg daily in 3 to 4 divided doses may be made, but daily doses should not exceed 500 mg QID Seizures, < 8 years – Initial dosage: 50 mg QHS on days 1 to 3 – Dosage titration: ○ Days 4 to 6: 50 mg BID ○ Days 7 to 9: 100 mg BID ○ Day 10 to maintenance: 125 to 250 mg TID – Maintenance dosage: 125 to 250 mg TID, or 10 to 25 mg/kg/day in divided doses
Pentobarbital	Emergency control of certain convulsive episodes (e.g. status epilepticus, cholera, eclampsia, meningitis, tetanus, toxic reactions to strychnine or local anesthetics)	Adults and Pediatrics Seizures (off-label dosing) – Loading dose: 5 to 15 mg/kg administered IV at a rate of 50 mg/minute or less, may give additional 5 to 10 mg/kg; follow with a continuous infusion – Discontinuation of therapy: A period of at least 24 to 48 hours of electrographic control is recommended prior to withdrawing the continuous infusion; withdraw gradually – Continuous infusion: 0.5 to 5 mg/kg/hour IV. If the patient experiences breakthrough status epilepticus while on continuous infusion, administer an additional 5 mg/kg bolus and increase infusion rate by 0.5 to 1 mg/kg/hour every 12 hours
Carboxamides		
Carbamazepine (Carbatrol®, Tegretol®) Equetro® (carbamazepine)	Partial seizures with complex symptomatology (psychomotor, temporal lobe), GTC seizures (grand mal), or mixed seizure patterns	Adult – 400 mg/day in 2 to 4 (oral suspension only) divided doses; increase by up to 200 mg/day at weekly intervals using a BID regimen of ER capsule or tablet, or a 3 to 4 times/day regimen of other formulations Usual dose: 800 to 1,200 mg/day Maximum recommended dose: 1,600 mg/day Pediatric – Children <6 years: 0 to 20 mg/kg/day in 2 or 3 divided doses (tablet forms) or 4 divided doses (oral suspension only); increase

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Medication	Indications	Dosing/Administration
		dose every week until optimal response and therapeutic levels are achieved Maximum recommended dose: 35 mg/kg/day – Children 6 to 12 years: 200 mg/day in 2 divided doses (tablet forms) or 4 divided doses (oral suspension only); increase by up to 100 mg/day at weekly intervals using a BID regimen of ER tablets or 3 to 4 times daily regimen of other formulations until optimal response and therapeutic levels are achieved Usual maintenance dose: 400 to 800 mg/day Maximum recommended dose: 1,000 mg/day (all tablet forms and oral suspension) or 35 mg/kg/day (capsule forms) – Children >12 years: Refer to adult dosing Maximum recommended doses: ○ Children 12 - 15 years: 1,000 mg/day ○ Children >15 years: 1,200 mg/day
Aptiom® (eslicarbazine)	Monotherapy or adjunctive therapy in the treatment of POS in adults and pediatric patients ≥4 years of age	<u>Adult</u> Monotherapy: – Initial: 400 mg QD; may initiate treatment at 800 mg QD if seizure reduction outweighs risk of adverse reactions during initiation. Increase in weekly increments of 400 mg to 600 mg based on clinical response and tolerability – Maintenance: 800 mg to 1,600 mg QD. Note: Consider 800 mg QD for maintenance therapy in patients not tolerating 1,200 mg QD Adjunctive therapy: – Initial: 400 mg QD; may initiate treatment at 800 mg QD if seizure reduction outweighs risk of adverse reactions during initiation. Increase in weekly increments of 400 mg to 600 mg, based on clinical response and tolerability – Maintenance: 800 mg to 1,600 mg QD. Note: Consider 1,600 mg QD for maintenance therapy in patients not achieving response on 1,200 mg daily dosage <u>Pediatric (Monotherapy or Adjunctive)</u> Children ≥4 years and Adolescents ≤17 years: – 11 to 21 kg: Initial: 200 mg QD; may increase in weekly increments of no more than 200 mg/day, titrate based on clinical response and tolerability; maintenance dose: 400 to 600 mg QD; (maximum: 600 mg/day) – 22 to 31 kg: Initial: 300 mg QD; may increase in weekly increments of no more than 300 mg/day, titrate based on clinical response and tolerability; maintenance dose: 500 to 800 mg QD; (maximum: 800 mg/day) – 32 to 38 kg: Initial: 300 mg QD; may increase in weekly increments of no more than 300 mg/day, titrate based on clinical response and tolerability; maintenance dose: 600 to 900 mg QD; (maximum: 900 mg/day) – >38 kg: Initial: 400 mg QD; may increase in weekly increments of no more than 400 mg/day, titrate based on clinical response and tolerability; maintenance dose: 800 to 1,200 mg QD; (maximum: 1,200 mg/day)

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Medication	Indications	Dosing/Administration
		Adolescents ≥18 years: – Initial: 400 mg QD, may initiate at 800 mg QD if seizure reduction outweighs risk of adverse reactions during initiation. May increase in weekly increments of 400 to 600 mg/day, titrate dose based on clinical response and tolerability – Maintenance: 800 to 1,600 mg QD (maximum: 1,600 mg/day)
Oxcarbazepine (Trileptal®) Oxtellar™ (oxcarbazepine)	IR: • Partial seizures in adults ○ Adjunctive therapy ○ Monotherapy • Partial seizures in children ≥4 years ○ Monotherapy • Partial seizures in children ≥2 years ○ Adjunctive therapy ER: Partial seizures in adults and in children ≥6 years	<u>Adult</u> Adjunctive therapy: – IR: 300 mg BID; dose may be increased by as much as 600 mg/day increments at weekly intervals Maximum dose: 1,200 mg/day – ER: 600 mg QD; dose may be increased by 600 mg/day increments at weekly intervals. Recommended daily dose: 1,200 mg to 2,400 mg/day. (Doses >1,200 mg/day are more effective but less tolerable due to CNS effects.) Conversion to monotherapy: – IR: 300 mg BID initially, increasing in increments of 600 mg daily at weekly intervals, reaching the maximum dose (2,400 mg/day) in 2 - 4 weeks; simultaneously reduce the dose of concomitant AEDs withdrawing completely over 3 - 6 weeks Initiation of monotherapy: – IR: 300 mg BID, increase dose by 300 mg daily every third day to a dose of 1,200 mg daily; higher dosages (2,400 mg/day) have demonstrated efficacy in patients converted to monotherapy. – ER: 600 mg QD; dosage may be increased by 600 mg/day increments at weekly intervals. Recommended daily dose is 1,200 mg to 2,400 mg/day. (Doses >1,200 mg/day may be more effective but less tolerable due to increased AEs.) Dosage adjustment with concomitant strong CYP3A4 inducers or UGT inducers (e.g. CBZ, phenobarbital, PHT, rifampin): – ER: Consider initiating at 900 mg QD <u>Pediatric</u> Adjunctive treatment, partial seizures (epilepsy): – IR *Children 2 to 3 years*: ○ Initial: 8 to 10 mg/kg/day, not to exceed 600 mg/day, given in 2 divided daily doses <20 kg: Consider initiating dose at 16 to 20 mg/kg/day ○ Maintenance: Should be achieved over 2 - 4 weeks and is weight dependent (maximum 60 mg/kg/day given in 2 divided daily doses) Children 4 to 16 years: ○ Initial: 8 to 10 mg/kg/day, not to exceed 600 mg/day, given in 2 divided daily doses ○ Maintenance: 20 to 29 kg: 900 mg daily in 2 divided doses 29.1 to 39 kg: 1,200 mg daily in 2 divided doses >39 kg: 1,800 mg daily in 2 divided doses

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Medication	Indications	Dosing/Administration
		– ER Children 6 - 17 years: ○ Initial: 8 to 10 mg/kg QD (not to exceed 600 mg/day in the first week) ○ Maintenance: Should be achieved over 2 - 3 weeks with dose increases of 8 - 10 mg/kg/day increments at weekly intervals (maximum incremental dose increase: 600 mg); target dose depends on weight: 20 to 29 kg: 900 mg QD 29.1 to 39 kg: 1,200 mg QD >39 kg: 1,800 mg QD Conversion to monotherapy, partial seizures (epilepsy): – IR Children 4 to 16 years: ○ Initial: 8 to 10 mg/kg/day in BID divided doses, while simultaneously initiating the dose reduction of concomitant AEDs; the concomitant drugs should be withdrawn over 3 - 6 weeks. OXC dose may be increased by a maximum of 10 mg/kg/day at weekly intervals. See below for recommended total daily dose by weight.* Initiation of monotherapy, partial seizures (epilepsy): – IR Children 4 to 16 years: ○ Initial: 8 to 10 mg/kg/day in BID divided doses; doses may be titrated by 5 mg/kg/day every third day. ○ Maintenance: 20 kg: 600 to 900 mg daily 25 to 30 kg: 900 to 1,200 mg daily 35 to 40 kg: 900 to 1,500 mg daily 45 kg: 1,200 to 1,500 mg daily 50 to 55 kg: 1,200 to 1,800 mg daily 60 to 65 kg: 1,200 to 2,100 mg daily 70 kg: 1,500 to 2,100 mg daily Conversion from IR to ER: Children ≥6 years and adolescents: Refer to adult dosing. Dosage adjustment with concomitant AEDs: Children ≥6 years and adolescents: Refer to adult dosing
Benzodiazepines		
Clorazepate	Adjunct therapy in the management of partial seizures in patients ≥ 9 years of age	<u>Adults and Pediatrics > 12 years</u> – Initial dosage: Up to 7.5 mg TID – Dosage titration: Increase by no more than 7.5 mg at weekly intervals – Maximum 90 mg/day <u>Pediatrics 9 to 12 years of age</u> – Initial dosage: Up to 7.5 mg BID – Dosage titration: Increase by no more than 7.5 mg at weekly intervals – Maximum 60 mg/day

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Medication	Indications	Dosing/Administration
Clonazepam (Klonopin®)	Mono- or adjunctive therapy in the treatment of the LGS (petit mal variant), akinetic, and myoclonic seizures; absence seizures (petit mal) unresponsive to succinimides	Adults and Pediatrics > 10 years of age or > 30 kg – Maximum dosage: 20 mg/day – Initial dosage: Not to exceed 1.5 mg/day divided into 3 doses – Dosage titration: Increase in increments of 0.5 to 1 mg every 3 days until adequate control or AEs – Maintenance dosage: 2 to 8 mg daily in 1 to 2 divided doses Pediatrics ≤ 10 years of age or ≤ 30 kg – Initial dosage: 0.01 to 0.03 mg/kg/day given in 2 or 3 divided doses; not to exceed 0.05 mg/kg/day – Dosage titration: Increase by ≤ 0.25 to 0.5 mg every third day until adequate control or AEs – Maintenance dosage: 0.1 to 0.2 mg/kg daily divided 3 times daily Off-label Rectal administration – Single doses administered rectally were 0.05 and 0.1 mg/kg – Extemporaneous formulation (used in clinical studies): ○ IV solution administered rectally in 1 mL syringes ○ Suspension containing 1 mg/mL of clonazepam with acetic acid, ethanol, and benzyl alcohol added and diluted with 1 mL of water
Clobazam (Onfi®) Sympazan™ (clobazam)	Adjunctive treatment of seizures associated with LGS in patients ≥ 2 years	Adults and Pediatrics ≥ 2 years – Usual dosage: ○ > 30 kg: 5 mg BID for at least 1 week, then increase to 10 mg BID for at least 1 week, then increase to 20 mg BID thereafter ○ ≤ 30 kg: 5 mg QD for at least 1 week, then increase to 5 mg BID for at least 1 week, then increase to 10 mg BID thereafter – Dosage titration: According to patient tolerability and response – CYP2C19 poor metabolizers ○ > 30 kg: 5 mg QD for at least 1 week, then increase to 5 mg BID for at least 1 week, then increase to 10 mg BID; after at least 1 week may increase to 20 mg BID ○ ≤ 30 kg or less: 5 mg QD for at least 1 week, then increase to 5 mg BID; after at least 1 week may increase to 10 mg BID

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr>
<td>Diazepam
Valtoco®
(diazepam)
Libervant™
(diazepam)</td>
<td>Diazepam: Management of selected refractory patients with epilepsy who are on stable regimens of AEDs and require intermittent use of diazepam to control bouts of increased seizure activity
Off-label: status epilepticus
Valtoco: Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy
Libervant: Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 2 to 5 years of age</td>
<td>Diazepam:
Adults
Seizures (repeat in 4 to 12 hours if needed; do not use for > 5 episodes/month or > 1 episode every 5 days)
– 0.2 mg/kg rectally
Status epilepticus (*off-label*)
– The parenteral formulation may be given rectally if rectal gel is not available
– American Epilepsy Society recommendations: 0.2 to 0.5 mg/kg (maximum dose: 20 mg) rectally
– Premonitory/Out-of-hospital treatment: 10 mg once rectally; may repeat once, if necessary
Pediatrics
Seizures (repeat in 4 to 12 hours if needed; do not use for > 5 episodes/month or > 1 episode every 5 days); Status epilepticus (*off-label*)
– 2 to 5 years: 0.5 mg/kg (maximum dose: 20 mg/dose) rectally
– 6 to 11 years: 0.3 mg/kg (maximum dose: 20 mg/dose) rectally
– ≥12 years: 0.2 mg/kg (maximum dose: 20 mg/dose) rectally
Valtoco:
Adults
– Usual: 0.2 mg/kg as a single dose; may repeat once based on response and tolerability after ≥4 hours
– Maximum: 2 doses/episode; do not use for > 1 episode/5 days or > 5 episodes/month
<table>
<tr><th>Weight</th><th>Dose</th><th># NS devices</th><th># sprays</th></tr>
<tr><td>28-50 kg</td><td>10 mg</td><td>1 x 10 mg</td><td>1 spray one nostril</td></tr>
<tr><td>51-75 kg</td><td>15 mg</td><td>2 x 7.5 mg</td><td>1 spray EN</td></tr>
<tr><td>≥ 76 kg</td><td>20 mg</td><td>2 x 10 mg</td><td>1 spray EN</td></tr>
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Pediatrics
6-11 years
<table>
<tr><th>Weight</th><th>Dose</th><th># NS devices</th><th># sprays</th></tr>
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<tr><td>19 - <38 kg</td><td>10 mg</td><td>1 x 10 mg</td><td>1 spray one nostril</td></tr>
<tr><td>38 - <56 kg</td><td>15 mg</td><td>2 x 7.5 mg</td><td>1 spray EN</td></tr>
<tr><td>56-74 kg</td><td>20 mg</td><td>2 x 10 mg</td><td>1 spray EN</td></tr>
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≥ 12 years
<table>
<tr><th>Weight</th><th>Dose</th><th># NS devices</th><th># sprays</th></tr>
<tr><td>14 - <28 kg</td><td>5 mg</td><td>1 x 5 mg</td><td>1 spray one nostril</td></tr>
<tr><td>28 - <51 kg</td><td>10 mg</td><td>1 x 10 mg</td><td>1 spray one nostril</td></tr>
<tr><td>51 - <76 kg</td><td>15 mg</td><td>2 x 7.5 mg</td><td>1 spray EN</td></tr>
<tr><td>≥ 76 kg</td><td>20 mg</td><td>2 x 10 mg</td><td>1 spray EN</td></tr>
</table>
Libervant:
– Usual: Weight based as a single dose; may repeat once based on response and tolerability after ≥4 hours</td>
</tr>
</table>

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<table>
<tr><th>Medication</th><th>Indications</th><th>Dosing/Administration</th></tr>
<tr><td></td><td></td><td>– Maximum: 2 doses/episode; do not use for > 1 episode/5 days or > 5 episodes/month
<table>
<tr><th>Weight</th><th>Dose</th></tr>
<tr><td>6 – 10 kg</td><td>5 mg</td></tr>
<tr><td>11 – 15 kg</td><td>7.5 mg</td></tr>
<tr><td>16 – 20 kg</td><td>10 mg</td></tr>
<tr><td>21 – 25 kg</td><td>12.5 mg</td></tr>
<tr><td>26 – 30 kg</td><td>15 mg</td></tr>
</table></td></tr>
</table>

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Medication	Indications	Dosing/Administration
Lorazepam (Ativan®)	Treatment of status epilepticus. *Off-label*: for acute seizures that have not yet progressed to status epilepticus.	Adult – Status epilepticus: 4 mg IV given at a maximum rate of 2 mg/minute; may repeat at 3 to 5 minutes if seizures continue; a non-BZD antiseizure agent should follow to prevent seizure recurrence, even if seizures have ceased – Acute active seizures (non–status epilepticus) (*Off-label*): 4 mg IV given at a maximum rate of 2 mg/minute; may repeat at 3 to 5 minutes if seizures continue Pediatrics – Usual dosage: 0.1 mg/kg slow IV; may repeat once in 5 to 10 minutes – Maximum dosage: 4 mg/dose
Nayzilam® (midazolam)	Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥12 years of age.	Intermittent (repetitive or cluster): Can be administered by non–HCPs. In patients at increased risk of respiratory depression, the first dose should be administered under HCP supervision to assess response and tolerability. Intranasal: 5 mg (1 spray) as a single dose in 1 nostril; may repeat same dose in 10 minutes in alternate nostril based on response and tolerability (do not repeat if the patient is having trouble breathing or excessive sedation); maximum 10 mg (2 sprays) per single episode Maximum frequency: 1 episode/3 days; 5 episodes/month.

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Boxed Warnings and Contraindications

Medication	Boxed Warnings	Contraindications
Miscellaneous		
Briviact® (brivaracetam)	None	Hypersensitivity
Levetiracetam (Keppra®) Spritam® (levetiracetam)	None	Hypersensitivity to levetiracetam or any formulation component
Gabapentin (Neurontin®)	None	Hypersensitivity to gabapentin or any formulation component
Pregabalin (Lyrica®)	None	Hypersensitivity to pregabalin or any formulation component
Tiagabine	None	Hypersensitivity to TGB or any formulation component
Divalproex sodium (Depakote®) Valproic acid (Depakene®, Depacon®)	Fatal hepatic failure has occurred, usually in the initial 6 months of therapy. Children <2 years of age and patients with hereditary neurometabolic syndromes caused by DNA mutations of the mitochondrial DNA POLG gene (e.g. AHS) are at increased risk. Cases of life-threatening pancreatitis have been reported. May cause major congenital malformations such as neural tube defects (e.g. spina bifida) and decreased IQ scores following in utero exposure. Should not be administered to WOCBP unless other medications have failed to provide adequate symptom control or are otherwise unacceptable.	Hypersensitivity to VPA, divalproex, derivatives, or any formulation component; hepatic disease or significant impairment; urea cycle disorders; in patients with known mitochondrial disorders caused by POLG mutations and children <2 years suspected of having a POLG-related disorder; in pregnant women and WOCBP who are not using effective contraception for the prevention of migraine
Vimpat® (lacosamide)	None	None
Zonisamide (Zonegran®)	None	Hypersensitivity to ZNS, sulfonamides, or any formulation component (The potential for cross-reactivity between antibiotic and nonantibiotic sulfonamides is extremely low or may not occur at all; however, in cases where prior reactions were severe (SJS/TEN), some clinicians choose to avoid exposure to these classes)
Epidiolex® (cannabidiol)	None	Hypersensitivity to CBD or any formulation component
Xcopri® (cenobamate)	None	Hypersensitivity to cenobamate or any component of the formulation; familial short QT syndrome
Felbamate (Felbatol®)	Associated with a significant increased risk of aplastic anemia and has been associated with rare cases of hepatic failure (estimated > 6 cases per 75,000 patients per year)	Hypersensitivity to felbamate, carbamates, or any component of the formulation; history of any blood dyscrasia or hepatic dysfunction

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Medication	Boxed Warnings	Contraindications
Fintepla® (fenfluramine)	Valvular heart disease and PAH: There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and valvular heart disease and PAH. Echocardiogram assessments are required before, during, and after treatment with fenfluramine. The benefits vs the risks of initiating or continuing fenfluramine must be considered, based on echocardiogram findings. Because of the risks of valvular heart disease and PAH, fenfluramine is available only through a REMS program	Hypersensitivity to fenfluramine or any component of the formulation; concomitant use with or within 14 days of monoamine oxidase inhibitors
Lamotrigine (Lamictal®)	Serious skin rashes requiring hospitalization and discontinuation of treatment have been reported; incidence is higher in pediatric patients than adults; risk may be increased by coadministration with VPA, higher than recommended initial doses, exceeding recommended initial dose titration, or exceeding the recommended dose escalation	Hypersensitivity to lamotrigine or any formulation component
Fycompa™ (perampanel)	Dose-related serious or life-threatening neuropsychiatric events (including aggression, anger, homicidal ideation and threats, hostility, and irritability) have been reported most often occurring in first 6 weeks of therapy in patients with or without prior psychiatric history, aggressive behavior, or concomitant use of medications associated with hostility and aggression.	None
Banzel® (rufinamide)	None	Patients with familial short QT syndrome
Diacomit® (stiripentol)	None	None
Topiramate (Topamax®, Qudexy®) Trokendi™ (topiramate)	None	ER: Recent alcohol use (within 6 hours before and after administration) (Trokendi XR); patients with metabolic acidosis who are taking concomitant metformin (Qudexy XR) IR: None listed

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Medication	Boxed Warnings	Contraindications
Vigabatrin (Sabril®)	May cause permanent vision loss. Response to and continued need for treatment should be periodically assessed; a failure to demonstrate early, substantial clinical benefit should trigger discontinuation. The onset of vision loss is unpredictable; the risk increases with increasing dose and cumulative exposure. Vision loss can worsen despite discontinuation. Symptoms are unlikely to be recognized by the patient or caregiver before loss is severe. Vision loss of mild severity, even if unrecognized, may still adversely affect function. The possibility that vision loss may be more common, more severe or have more severe functional consequences in infants and children than in adults cannot be excluded.	None
Hydantoins		
Phenytoin (Dilantin®, Phenytek®)	The rate of IV PHT should be ≤ 50 mg/min (adults) and the slower of 1 to 3 mg/kg/min or 50 mg/min (pediatrics) due to the risk of severe HoTN and cardiac arrhythmias; these events have also been reported at or below the recommended infusion rate.	Hypersensitivity to PHT, other hydantoins, or any formulation component; concurrent use of delavirdine; history of prior acute hepatotoxicity attributable to PHT Injection: Sinus bradycardia, sinoatrial block, second- and third-degree heart block, Adams-Stokes syndrome
Fosphenytoin (Cerebyx®)	The rate of fosphenytoin IV administration should not exceed 150 mg PE/min because of the risk of CV toxicity (severe HoTN and cardiac arrhythmias). Careful cardiac monitoring is needed during and after administration. These events have also been reported at or below the recommended infusion rate.	Hypersensitivity to fosphenytoin, PHT, other hydantoins, or any formulation component; sinus bradycardia, sinoatrial block, second- and third-degree AV block, or Adams-Stokes syndrome; history of prior acute hepatotoxicity attributable to fosphenytoin or PHT; concurrent use with delavirdine
Peganone® (ethotoin)	None	Hepatic abnormalities; hematologic disorders Documentation of allergenic cross-reactivity for hydantoins is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Succinimides		
Ethosuximide (Zarontin®)	None	Hypersensitivity to ETS, succinimides, or any component of the formulation
Celontin® (methsuximide)	None	History of hypersensitivity to succinimides
Barbiturates		

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Medication	Boxed Warnings	Contraindications
Phenobarbital	None	Hypersensitivity to phenobarbital, barbiturates or any formulation component; marked hepatic impairment; dyspnea or airway obstruction; porphyria (manifest and latent); intra-arterial administration, subcutaneous administration (not recommended); use in patients with a history of sedative/hypnotic addiction; nephritic patients (large doses) Additional contraindications: IV only: Intra-arterial or subcutaneous administration; use in patients with a history of sedative/hypnotic addiction; nephritic patients (large doses)
Primidone (Mysoline®)	None	Hypersensitivity to phenobarbital; porphyria
Pentobarbital	None	Hypersensitivity to barbiturates or any formulation component; porphyria.
Carboxamides		
Carbamazepine (Carbatrol®, Tegretol®) Equetro® (carbamazepine)	Severe and sometimes fatal dermatologic reactions, including TEN and SJS, may occur. The risk is increased in patients with the variant HLA-B*1502 allele, found most often in patients of Asian ancestry. Patients with an increased likelihood of carrying this allele should be screened prior to initiating therapy. Avoid use in patients testing positive. The risk of developing anemia or agranulocytosis is increased during treatment. Complete pretreatment hematological testing should be obtained prior to use; monitor patient closely if white blood cells or platelet counts decrease during therapy; discontinue if significant bone marrow suppression occurs.	Hypersensitivity to CBZ, tricyclic antidepressants, or any formulation component; bone marrow depression; with or within 14 days of MAOI use; concomitant use of nefazodone or boceprevir; concomitant use of delavirdine or other non-nucleoside reverse transcriptase inhibitors that are substrate of CYP3A4
Aptiom® (eslicarbazine)	None	Hypersensitivity to ESL, OXC, or any component of the formulation
Oxcarbazepine (Trileptal®) Oxtellar™ (oxcarbazepine)	None	Hypersensitivity to OXC, ESL acetate, or any formulation component Documentation of allergenic cross-reactivity for CBZ and analogues is limited, but, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cannot be ruled out
Benzodiazepines		
Clorazepate Clonazepam (Klonopin®) Diazepam (Valtoco®) Libervant™ (diazepam)	Profound sedation, respiratory depression, coma, and death could occur when used concomitantly with opioids. Risk of abuse, misuse, and addiction, which can lead to overdose or death (commonly involving concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes).	Hypersensitivity to the active ingredient or any formulation component; acute narrow-angle glaucoma; the possibility of cross-sensitivity with other BZDs cannot be ruled out *Clonazepam only*: severe hepatic impairment
Clobazam (Onfi®) Sympazan™ (clobazam)		Hypersensitivity to CLB or any formulation component

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Medication	Boxed Warnings	Contraindications
Lorazepam (Ativan®)	Continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. If used more frequently than recommended, abrupt discontinuation or rapid dosage reduction may precipitate acute withdrawal reactions, which can be life-threatening.	Hypersensitivity to lorazepam, any component of the formulation (including PEG, propylene glycol, benzyl alcohol), or other BZDs; acute narrow-angle glaucoma; sleep apnea; intra-arterial injection; severe respiratory insufficiency (except during mechanical ventilation); use in premature infants
Nayzilam® (midazolam)		Hypersensitivity to the active ingredient or any component of the formulation; acute narrow-angle glaucoma

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Warnings/Precautions

	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
Concerns related to adverse effects																	
May cause CNS effects (i.e., CNS depression, dizziness and ataxia) impairing physical/mental abilities	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓	✓
Pediatric use has been associated with the occurrence of CNS AEs (e.g. emotional lability, hostility, changes in behavior and thinking, and hyperkinesia)			✓														
Moderately severe to incapacitating generalized weakness has been reported					✓												
Reversible and irreversible cerebral and cerebellar atrophy have been reported						✓											
SI: Pooled analysis of trials involving various AEDs showed an increased risk of suicidal thoughts/behavior	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Psychiatric symptoms may occur	✓	✓						✓									
Serious, sometimes fatal, hypersensitivity-type reactions have been reported (i.e., dermatologic reactions [e.g. SJS, TEN] or DRESS)		✓	✓		✓	✓	✓	✓		✓			✓	✓		✓	
Hypersensitivity reactions (i.e., anaphylaxis/ angioedema may occur and may be life-threatening			✓	✓					✓								
Various blood dyscrasias may occur	✓	✓		✓		✓							✓		✓		✓
Respiratory depression			✓	✓													
Visual disturbances have been reported				✓			✓									✓	
Possibility of long-term ophthalmologic effects					✓												
Has been associated with acute myopia and secondary angle-closure glaucoma in adults and children								✓								✓	
May cause mild pupillary dilation, which, in susceptible individuals, can lead to an episode of angle-closure glaucoma												✓					

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	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
Has been associated with increases in creatine kinase and rare cases of rhabdomyolysis				✓													
Creatinine and BUN elevations, kidney stones have been reported								✓									
Hyperammonemia with or without encephalopathy may occur and may be fatal						✓							✓			✓	
Dose-related elevations of liver transaminases (ALT and/or AST), some resulting in hospitalization, have been reported. Risk factors include high dose, concomitant hepatotoxic drugs (especially CLB and VPA), and elevated baseline transaminases									✓								
May alter cardiac conduction predisposing patients to arrhythmia				✓			✓			✓			✓				
Increased risk of developing aseptic meningitis has been reported, possibly associated with a hypersensitivity reaction (e.g. anticonvulsant hypersensitivity syndrome)													✓				
HLH, a rare, life-threatening immune system reaction, has been reported													✓				
May cause peripheral edema				✓													✓
May cause weight gain				✓													✓
May suppress appetite and cause weight loss												✓			✓		
May elevate BP and cause HTN		✓										✓					
Risk for serotonin syndrome particularly in combination with serotonergic agents or agents that impair serotonin metabolism												✓					
Use may be associated with dose-dependent metabolic acidosis; predisposing conditions/therapies include renal disease, severe respiratory disease, diarrhea, status epilepticus, ketogenic diet, and other medications								✓									
May be associated with hyperchloremic nonanion gap metabolic acidosis and increased risk kidney																✓	

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	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
stones due to inhibition of carbonic anhydrase and increased renal bicarbonate loss																	
Intramyelinic edema has been reported (rarely) in infants; peripheral neuropathy has been reported																	✓
Disease related concerns																	
Caution in hepatic impairment; dosage adjustment may be required. Depending on degree of impairment, may not be recommended for use.	✓				✓		✓	✓	✓	✓		✓	✓	✓	✓	✓	
Caution in renal impairment; dosage adjustment may be required. Depending on degree of impairment, may not be recommended for use. In the setting of hemodialysis, supplementation may be necessary.	✓	✓	✓	✓			✓	✓		✓	✓	✓	✓	✓	✓	✓	✓
Caution in patients with a history of substance abuse; potential for drug dependency exists			✓	✓													
Caution in patients with severe CV disease, including HF; may exacerbate underlying myocardial dysfunction				✓													
Not recommended for post-traumatic seizure prophylaxis in acute head trauma						✓											
Caution in depression or suicidal tendency																✓	✓
Caution in psychosis or behavioral problems																	✓
Caution in patients with eating disorders																✓	
May increase seizure frequency particularly in patients with myoclonic seizures																	✓
Concurrent drug therapy issues																	
Potentially significant drug-drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy	✓	✓	✓	✓	✓	✓	✓	✓					✓	✓		✓	✓
Dose adjustment required in the setting of renal and/or hepatic impairment and concomitant administration of strong CYP3A4 and/or CYP2C9 inhibitors							✓										

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	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
Experience in patients not receiving enzyme-inducing drugs has been limited; decreased dose and slower titration may be required when treating patients not receiving an enzyme inducer					✓												
Poor metabolizers of CYP2C19 may require dose reduction	✓																
May potentiate effects with other sedative drugs or ethanol											✓						
Special populations																	
Inadequately studied in patients >65 years of age	✓																
Caution in elderly patients who may be more sensitive to AEs and in whom drug metabolism may be impaired						✓								✓		✓	✓
Children may have increased psychiatric symptoms		✓															
Children <2 years at increased risk for fatal hepatotoxicity						✓											
Use in children ≥2 years suspected of having a POLG-related disorder only after other anticonvulsants have failed and with close monitoring						✓											
Oligohydrosis and hyperthermia requiring hospitalization have been reported in children								✓								✓	
Children may have an increased risk for and have more severe metabolic acidosis compared to adults. Untreated metabolic acidosis may increase the risk of developing nephrolithiasis and/or nephrocalcinosis, osteoporosis and/or osteomalacia (possibly resulting in rickets), and may decrease growth rates								✓									
Use is not recommended in WOCBP unless is essential to manage her condition and alternative therapies are not appropriate; effective contraception should be used						✓											

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	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
Use with extreme caution in patients at risk of falls; has been associated with falls and traumatic injury														✓			
Other																	
Tumorigenic potential per animal studies			✓	✓								✓					
New-onset seizures and status epilepticus have been reported when taken for off-label use; off-label use is not recommended					✓												
In vitro studies have suggested VPA stimulates the replication of HIV and CMV viruses						✓											
Potential for medication errors with similar-sounding medications and between different formulations													✓				
Binds to and may accumulate in melanin-rich tissues (e.g. eyes), the clinical significance of which is unknown													✓				
Safety and efficacy have not been established for use as initial monotherapy, conversion to monotherapy from AEDs other than CBZ, PHT, phenobarbital, primidone or VPA or conversion to monotherapy from ≥ 2 AEDs													✓				
Not indicated for first-line use due to substantial risk of aplastic anemia and/or liver failure											✓						
Must be used in conjunction with CBZ (labeled use) and VPA (off-label); not approved for use as monotherapy															✓		
Abnormal MRI changes, which usually resolve upon discontinuation, have been reported in some infants, but not older children and adults																	✓
Dosage form specific issues																	
Oral formulation medication residue in stool has been reported, rarely; monitor levels and clinical condition						✓											
May contain phenylalanine							✓								✓		

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	Miscellaneous																
	Briviact (brivaracetam)	Levetiracetam (Keppra) Spritam (levetiracetam)	Gabapentin (Neurontin)	Pregabalin (Lyrica)	Tiagabine	Divalproex sodium (Depakote) Valproic acid (Depakene, Depacon)	Vimpat (lacosamide)	Zonisamide (Zonegran)	Epidiolex (cannabidiol)	Xcopri (cenobamate)	Felbamate (Felbatol)	Fintepla (fenfluramine)	Lamotrigine (Lamictal)	Fycompa (perampanel)	Diacomit (stiripentol)	Topiramate (Topamax, Qudexy), Trokendi (topiramate)	Vigabatrin (Sabril)
May contain propylene glycol large amounts of which are potentially toxic							✓										
May contain polysorbate 80 (i.e. Tweens); hypersensitivity reactions (usually delayed) have been reported following exposure; thrombocytopenia, ascites, pulmonary deterioration, and renal and hepatic failure have been reported in premature neonates after receiving parenteral products containing polysorbate 80													✓				
May contain lactose														✓			
Systemic exposure is slightly higher with the powder for suspension															✓		

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	Hydantoins			Succinimides		Barbiturates			Carboxamides			
	Phenytoin (Dilantin, Phenytek)	Fosphenytoin (Cerebyx)	Peganone (ethotoin)	Zarontin (ethosuximide)	Celontin (methsuximide)	Phenobarbital	Primidone (Mysoline)	Pentobarbital	Carbamazepine (Carbatrol, Tegretol), Equetro (carbamazepine)	Aptiom (eslicarbazine)	Oxcarbazepine (Trileptal), Oxtellar (oxcarbazepine)	Banzel (rufinamide)
Concerns related to adverse effects												
May cause CNS effects (i.e., CNS depression, dizziness and ataxia) impairing physical/mental abilities				✓	✓	✓	✓	✓	✓	✓	✓	✓
Psychiatric symptoms may occur									✓			
SI: Pooled analysis of trials involving various AEDs showed an increased risk of suicidal thoughts/behavior	✓		✓	✓	✓		✓		✓	✓	✓	✓
Various blood dyscrasias have been reported and may be fatal	✓	✓	✓	✓	✓					✓	✓	✓
May decrease bone mineral density causing osteopenia, osteoporosis, and fractures	✓										✓	
Potentially serious, sometimes fatal, hypersensitivity-type reactions have been reported (i.e., SCARs [e.g. AGEP, SJS, TEN] or DRESS)	✓	✓		✓		✓			✓	✓	✓	✓
Hypersensitivity, including angioedema, has been reported. Consider alternative therapy in patients who have experienced hypersensitivity to structurally similar drugs such as carboxamides (e.g., CBZ), barbiturates, succinimides, and oxazolidinediones.	✓	✓										
Increased risk of hypersensitivity with HLA-A*3101 allele									✓			
Increased risk of hypersensitivity with HLA-B*1502 allele	✓	✓									✓	
Avoid extravasation which may cause soft tissue irritation, inflammation, and skin necrosis at IV site; avoid IV administration in small veins. “Purple glove syndrome" (i.e. discoloration with edema and pain of distal limb) may occur following peripheral IV administration and may or may not be associated with drug extravasation. Skin necrosis and limb ischemia may occur; interventions such as	✓	✓										

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	Hydantoins			Succinimides		Barbiturates			Carboxamides			
	Phenytoin (Dilantin, Phenytek)	Fosphenytoin (Cerebyx)	Peganone (ethotoin)	Zarontin (ethosuximide)	Celontin (methsuximide)	Phenobarbital	Primidone (Mysoline)	Pentobarbital	Carbamazepine (Carbatrol, Tegretol), Equetro (carbamazepine)	Aptiom (eslicarbazine)	Oxcarbazepine (Trileptal), Oxtellar (oxcarbazepine)	Banzel (rufinamide)
fasciotomies, skin grafts, and amputation (rare) may be required.												
Hepatic effects ranging from mild to moderate elevations in transaminases (>3x ULN) to rare cases of concomitant elevations of total bilirubin (>2x ULN) have been reported.										✓		
Hepatitis has been reported rarely											✓	
Cases of acute, sometimes fatal, hepatotoxicity (including acute hepatic failure) have been reported	✓	✓							✓			
Changes in renal function have been reported				✓								
Renal toxicity has been reported									✓			
Hyponatremia and SIADH may occur; elderly, patients taking diuretics are at increased risk									✓	✓	✓	
Thyroid function abnormalities (decreased T3/T4) and the potential for hypothyroidism										✓	✓	
May alter cardiac conduction predisposing patients to arrhythmia												✓
Local or generalized lymphadenopathy may occur including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin disease	✓	✓										
Sensory disturbances (e.g. severe burning or itching, and/or paresthesias, mostly perineal)		✓										
Cases of SLE have been reported				✓	✓							
May cause paradoxical responses (e.g. agitation and hyperactivity, particularly in patients with pain and pediatric patients)						✓	✓	✓				
Respiratory depression						✓	✓	✓				
Disease related concerns												
Caution in patients with underlying CV disease	✓	✓				✓			✓		✓	
Caution in patients with hemodynamic instability (i.e., HoTN, shock)		✓				✓						
Caution in patients with DM	✓	✓				✓						

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	Hydantoins			Succinimides		Barbiturates			Carboxamides			
	Phenytoin (Dilantin, Phenytek)	Fosphenytoin (Cerebyx)	Peganone (ethotoin)	Zarontin (ethosuximide)	Celontin (methsuximide)	Phenobarbital	Primidone (Mysoline)	Pentobarbital	Carbamazepine (Carbatrol, Tegretol), Equetro (carbamazepine)	Aptiom (eslicarbazine)	Oxcarbazepine (Trileptal), Oxtellar (oxcarbazepine)	Banzel (rufinamide)
Caution in patients with hypothyroidism	✓	✓										
Caution in patients with hyperthyroidism						✓						
Caution in patients with hypoadrenalism						✓	✓					
Caution in patients with hepatic impairment	✓	✓		✓	✓	✓	✓	✓	✓			✓
Avoid use in patients with hepatic porphyria									✓			
Caution in patients with renal impairment	✓	✓		✓	✓	✓	✓	✓	✓		✓	
Caution in patients with any condition associated with low serum albumin levels	✓	✓										
Caution in patients with porphyria	✓	✓										
Caution in patients with severe anemia						✓						
Caution in patients with depression or suicidal tendencies						✓	✓	✓				
Caution in patients with a history of drug abuse; tolerance, psychological, and physical dependence may occur						✓	✓	✓				
Caution in patients with anticholinergic sensitivity									✓			
Exacerbation of or new onset primary generalized seizures has been reported, particularly in children											✓	
Concurrent drug therapy issues												
Potentially significant drug-drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy	✓	✓				✓	✓	✓	✓		✓	✓
May potentiate effects with other sedative drugs or ethanol					✓							
Special populations												
Caution in critically ill, debilitated, and elderly patients	✓	✓				✓	✓	✓				
May activate latent psychosis, confusion, or agitation in elderly									✓			
Use with caution in patients with a fever; has been associated with cognitive deficits in children receiving therapy for complicated febrile seizures						✓	✓					

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	Hydantoins			Succinimides		Barbiturates			Carboxamides			
	Phenytoin (Dilantin, Phenytek)	Fosphenytoin (Cerebyx)	Peganone (ethotoin)	Zarontin (ethosuximide)	Celontin (methsuximide)	Phenobarbital	Primidone (Mysoline)	Pentobarbital	Carbamazepine (Carbatrol, Tegretol), Equetro (carbamazepine)	Aptiom (eslicarbazine)	Oxcarbazepine (Trileptal), Oxtellar (oxcarbazepine)	Banzel (rufinamide)
In pediatric and neonatal patients <3 years of age and patients in 3rd trimester of pregnancy, the repeated or lengthy exposure to sedatives or anesthetics may have detrimental effects on brain development contributing to various cognitive and behavioral problems								✓				
Exacerbation of certain seizure types has occurred in children with mixed seizure disorders									✓			
Other												
Not indicated for the treatment of absence seizures or seizures due to hypoglycemia or other metabolic causes	✓											
Supratherapeutic plasma concentrations may produce confusional states and, rarely, irreversible cerebellar dysfunction and/or cerebellar atrophy	✓	✓										
Use only when oral administration is not possible; preferred for rapid loading		✓										
May increase tonic-clonic seizures when used alone in patients with mixed seizure disorders				✓	✓							
Not effective in absence, myoclonic, or akinetic seizures; may increase the frequency of seizures in patients with these types of seizures									✓			
Dosage form specific issues												
May contain sodium benzoate/benzoic acid (a metabolite of benzyl alcohol) large amounts of which have been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates	✓			✓		✓	✓					
May contain propylene glycol large amounts of which are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures and respiratory depression	✓					✓		✓				✓
PHT sodium equivalent: Do not change recommended doses when interchanging		✓										

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	Hydantoins			Succinimides		Barbiturates			Carboxamides			
	Phenytoin (Dilantin, Phenytek)	Fosphenytoin (Cerebyx)	Peganone (ethotoin)	Zarontin (ethosuximide)	Celontin (methsuximide)	Phenobarbital	Primidone (Mysoline)	Pentobarbital	Carbamazepine (Carbatrol, Tegretol), Equetro (carbamazepine)	Aptiom (eslicarbazine)	Oxcarbazepine (Trileptal), Oxtellar (oxcarbazepine)	Banzel (rufinamide)
fosphenytoin and PHT, they are not equivalent on a mg basis												
Injection: Vials contain the excipient cyclodextrin (sulfobutylether beta-cyclodextrin), which may accumulate in renal insufficiency (clinical significance is unknown)									✓			
Suspension: May contain sorbitol (avoid in patents with hereditary fructose intolerance); yields higher peak and lower trough serum levels than an equal dose of the tablet form, consider a lower starting dose given more frequently (same total daily dose)									✓			

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	Benzodiazepines					
	Clorazepate	Clonazepam (Klonopin)	Diazepam (Valtoco), Libervant (diazepam)	Clobazam (Onfi), Sympazan (clobazam)	Lorazepam (Ativan)	Nayzilam (midazolam)
Concerns related to adverse effects						
Anterograde amnesia and paradoxical reactions (e.g. hyperactive or aggressive behavior)	✓	✓	✓	✓	✓	✓
May cause CNS depression, which may impair physical or mental abilities	✓	✓	✓	✓	✓	✓
May cause HoTN, particularly in pediatric patients, patients with hemodynamic instability, and patients receiving opioid analgesics.						✓
SI: Pooled analysis of trials involving various AEDs showed an increased risk of suicidal thoughts/behavior	✓	✓	✓	✓		✓
An increased risk for hazardous sleep-related activities such as sleep-driving, cooking and eating food, and making phone calls while asleep have been noted with BZDs	✓	✓	✓	✓	✓	
Serious reactions, including SJS and TEN, have been reported				✓		
Disease related concerns						
Caution in patients with depression, particularly if suicidal risk may be present; not recommended for use in depressive neuroses	✓	✓	✓	✓	✓	
Caution in patients with a history of drug abuse or alcoholism and those with significant personality disorders; tolerance, psychological, and physical dependence may occur	✓	✓	✓	✓	✓	
Caution in patients with hepatic and/or renal impairment	✓	✓	✓		✓	
Caution in patients with renal impairment; half-life of MDZ and metabolites may be prolonged						✓
Caution in patients with respiratory disease	✓	✓	✓	✓	✓	✓
Use with caution in patients with HF; adverse hemodynamic events have been reported in pediatric patients with CV instability						✓
Caution in patients with impaired gag reflex	✓	✓	✓	✓		
Caution in patients who have difficulty handling secretions; may increase salivation		✓				
Caution in patients with porphyria		✓				
May be used in patients with appropriately-treated open-angle glaucoma		✓	✓			✓
When used adjunctively to treat convulsive disorders, an increased frequency/severity of tonic-clonic seizures requiring dose adjustment may occur			✓			
Concurrent drug therapy issues						
Potentially significant drug-drug interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy	✓	✓	✓	✓		
Special populations						

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	Benzodiazepines					
	Clorazepate	Clonazepam (Klonopin)	Diazepam (Valtoco), Libervant (diazepam)	Clobazam (Onfi), Sympazan (clobazam)	Lorazepam (Ativan)	Nayzilam (midazolam)
Caution in elderly patients; may increase risk of death	✓	✓	✓	✓	✓	✓
Caution in debilitated patients and patients at risk of falls	✓	✓	✓		✓	✓
Caution in obese patients due to risk for prolonged action post-discontinuation	✓	✓	✓			✓
Concentrations of the active metabolite are 3 to 5 times higher in CYP2C19 poor metabolizers compared to extensive metabolizers; dose adjustment is needed in poor CYP2C19 metabolizers				✓		
Pediatric patients with cardiac or respiratory compromise may be sensitive to the respiratory depressant effects. Pediatric patients undergoing procedures involving the upper airway are vulnerable to episodes of desaturation and hypoventilation.						✓
In pediatric and neonatal patients <3 years of age and patients in 3rd trimester of pregnancy, the repeated or lengthy exposure to sedatives or anesthetics during surgery/procedures may have detrimental effects on the child's brain development and contribute to various cognitive and behavioral problems.					✓	✓
Other						
Does not have analgesic, antidepressant, or antipsychotic properties	✓	✓	✓	✓	✓	✓
Tolerance develops to the anticonvulsant effects	✓	✓	✓	✓	✓	✓
Worsening of seizures may occur in the setting of multiple seizure types		✓				
Status epilepticus should not be treated with injectable BZDs alone; requires close observation and management and possibly ventilatory support					✓	
Withdrawal: A longer sleep-onset latency and increased awakenings during sleep may occur for 1 to 2 days following discontinuation. A more severe withdrawal syndrome may rarely occur following abrupt discontinuation or large decreases in dose after sustained use.					✓	
Dosage form specific issues						
May contain sodium benzoyl alcohol/benzoate/benzoic acid (a metabolite of benzyl alcohol) large amounts of which have been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates			✓		✓	✓
Parenteral formulation may contain PEG and associated with toxicity in high-dose and/or longer-term therapy					✓	
May contain propylene glycol large amounts of which are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures and respiratory depression			✓		✓	
Administration of rectal gel should only be performed by individuals trained to recognize characteristic seizure activity for which the product is indicated, and capable of monitoring response to determine need for additional medical intervention. Not recommended for chronic, daily use. Caution in patients with neurologic damage.			✓			

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Practice Guidelines

Pack AM, Oskoui M, Williams Roberson S, Donley DK, French J, Gerard EE, Gloss D, Miller WR, Munger Clary HM, Osmundson SS, McFadden B, Parratt K, Pennell PB, Saade G, Smith DB, Sullivan K, Thomas SV, Tomson T, Dolan O'Brien M, Botchway-Doe K, Silsbee HM, Keezer MR. Teratogenesis, Perinatal, and Neurodevelopmental Outcomes After In Utero Exposure to Antiseizure Medication: Practice Guideline From the AAN, AES, and SMFM. Neurology. 2024 Jun;102(11):e209279.

- Clinicians should engage in joint decision-making with people with epilepsy of childbearing potential (PWECP), taking individual preferences into account when selecting anti-seizure medications (ASMs) and monitoring their dosing (Level B).
- When treating PWECP, clinicians should recommend ASMs and doses that optimize both seizure control and fetal outcomes should pregnancy occur, at the earliest possible opportunity preconceptionally (e.g., at the time of starting an ASM in a person post-menarche) (Level B).
- Clinicians must minimize the occurrence of convulsive seizures (generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures) in PWECP during pregnancy to minimize potential risks to the birth parent (e.g., seizure-related mortality) and to the fetus (Level A).
- Once a PWECP is already pregnant, clinicians should exercise caution in attempting to remove or replace an ASM that is effective in controlling generalized tonic-clonic or focal-to-bilateral tonic-clonic seizures, even if it is not an optimal choice with regards to the risk to the fetus (e.g., valproic acid) (Level B).
- Clinicians should monitor ASM levels in PWECP throughout pregnancy as guided by individual ASM pharmacokinetics and patient clinical presentation (Level B).
- Clinicians should adjust the dose of ASMs at their clinical discretion during the pregnancy in response to (1) decreasing serum ASM levels or (2) worsening seizure control (observed or anticipated based on the clinician's judgment and known pharmacokinetics of ASMs in the pregnant state) (Level B).
- Clinicians treating PWECP using acetazolamide, eslicarbazepine, ethosuximide, lacosamide, nitrazepam, perampanel, piracetam, pregabalin, rufinamide, stiripentol, tiagabine, or vigabatrin should counsel their patients that there are limited data on pregnancy-related outcomes for these drugs (Level B).
- Clinicians must counsel their patients with epilepsy that the birth prevalence of any major congenital malformation (MCM) in the general population is approximately 2.4%–2.9%, providing a comparison framework for their individual risk (Level A).
- Clinicians must consider using lamotrigine, levetiracetam, or oxcarbazepine in PWECP when appropriate based on the patient's epilepsy syndrome, likelihood of achieving seizure control, and comorbidities, to minimize the risk of MCMs (Level A).
- Clinicians must avoid the use of valproic acid in PWECP to minimize the risk of MCMs (composite outcome) or neural tube defects (NTDs), if clinically feasible (Level A).
- Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that the risk of any MCM is the highest with valproic acid as compared with other studied ASMs (Level A).
- To reduce the risk of cardiac malformations, clinicians must avoid the use of phenobarbital in PWECP, if clinically feasible (Level A).
- To reduce the risk of oral clefts, clinicians should avoid the use of phenobarbital and topiramate in PWECP, if clinically feasible (Level B).

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- To reduce the risk of urogenital and renal malformations, clinicians should avoid the use of valproic acid in PWECP, if clinically feasible (Level B).
- To enable early detection and timely intervention of MCMs, obstetricians should recommend fetal screening for MCMs (e.g., a detailed anatomical ultrasound, where available) for PWECP who are treated with any ASM during pregnancy (Level B).
- To enable early detection and timely intervention of congenital heart defects, obstetricians should recommend screening cardiac investigations of the fetus among PWECP who are treated with phenobarbital during pregnancy (Level B).
- Clinicians should counsel PWECP that the prevalence of intrauterine death does not differ among different ASM exposures in monotherapy (Level B).
- Clinicians should avoid the use of valproic acid or topiramate in PWECP to minimize the risk of offspring being born small for gestational age, if clinically feasible (Level B).
- To enable early identification of fetal growth restriction, obstetricians should recommend screening of fetal growth throughout pregnancy among PWECP who are treated with valproic acid or topiramate (Level B).
- To reduce the risk of poor neurodevelopmental outcomes, including ASD and lower IQ, in children born to PWECP, clinicians must avoid the use of valproic acid in PWECP, if clinically feasible (Level A).
- Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is likely or possibly associated with a decrease in full scale, verbal, and non-verbal IQ, as compared with other studied ASMs (i.e., carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, and topiramate) (Level A).
- Clinicians must counsel PWECP who are treated with, or are considering starting, valproic acid that in utero exposure to valproic acid is possibly associated with an increased risk of ASD as compared with other studied ASMs (i.e., carbamazepine, clonazepam, levetiracetam, and lamotrigine) (Level A).
- Clinicians should implement age-appropriate developmental screening in children exposed to any ASM in utero born to PWECP (Level B).
- Clinicians should prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to decrease the risk of NTDs in the offspring (Level B).
- Clinicians must prescribe at least 0.4 mg of folic acid supplementation daily preconceptionally and during pregnancy to any PWECP treated with an ASM to possibly improve neurodevelopmental outcomes such as ASD and global IQ in the offspring (Level A).
- Clinicians should counsel PWECP treated with an ASM that adherence to recommended folic acid supplementation preconceptionally and during pregnancy is important to minimize the risk of MCMs and poor neurodevelopmental outcomes (Level B).

Recommendation Definitions

Class/Level	Definition
A	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
B	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the CI is > 2).

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Class/Level	Definition
Class I	Randomized controlled clinical trial (RCT) in a representative population. Masked or objective outcome assessment. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences. Also required: Concealed allocation. Primary outcomes clearly defined. Exclusion/inclusion criteria clearly defined. Adequate accounting for dropouts.
Class II	Cohort study meeting criteria for Class I or a RCT that lacks one or two of those other criteria. All relevant baseline characteristics are present and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. Masked or objective outcome assessment.
Class III	Controlled studies (including well-defined natural history controls or patients serving as their own controls). A description of major confounding differences between treatment groups that could affect outcome. Outcome assessment masked, objective or performed by someone who is not a member of the treatment team.
Class IV	Did not include patients with the disease. Did not include patients receiving different interventions. Undefined or unaccepted interventions or outcome measures. No measures of effectiveness or statistical precision present or calculable.

Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2015; 84:1705. (Reaffirmed January 2018)

- Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21%–45%) (Level A).
- Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma (Level A), an EEG with epileptiform abnormalities (Level A), a significant brain-imaging abnormality (Level B), or a nocturnal seizure (Level B).
- Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure (Level B), it may not improve QOL (Level C).
- Clinicians should advise patients that over the longer term (>3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission (Level B).
- Patients should be advised that their risk for AED AEs ranges from 7% to 31% (Level B) and that these AEs are predominantly mild and reversible.

Recommendation Definitions

Class/Level	Definition
A	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
B	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the CI is > 2).

Class/Level	Definition
Class I	Randomized controlled clinical trial (RCT) in a representative population. Masked or objective outcome assessment. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is

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Class/Level	Definition
	appropriate statistical adjustment for differences. Also required: Concealed allocation. Primary outcomes clearly defined. Exclusion/inclusion criteria clearly defined. Adequate accounting for dropouts.
Class II	Cohort study meeting criteria for Class I or a RCT that lacks one or two of those other criteria. All relevant baseline characteristics are present and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. Masked or objective outcome assessment.
Class III	Controlled studies (including well-defined natural history controls or patients serving as their own controls). A description of major confounding differences between treatment groups that could affect outcome. Outcome assessment masked, objective or performed by someone who is not a member of the treatment team.
Class IV	Did not include patients with the disease. Did not include patients receiving different interventions. Undefined or unaccepted interventions or outcome measures. No measures of effectiveness or statistical precision present or calculable.

Hirtz D, Berg A, Bettis D, et al. Practice parameter: Treatment of the child with a first unprovoked seizure. Neurology Jan 2003, 60 (2) 166-175. (Reaffirmed October 20, 2018)

- Treatment with AED is not indicated for the prevention of the development of epilepsy (Level B).
- Treatment with AED may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects (Level B).

Recommendation Definitions

Class/Level	Definition
A	Requires at least one convincing Class I study or at least two consistent, convincing Class II studies. Rating of recommendation: established as effective, ineffective, or harmful for the given condition in the specified population.
B	Requires at least one convincing Class II study or overwhelming Class III evidence. Rating of recommendation: probably effective, ineffective, or harmful for the given condition in the specified population.
C	Requires at least two convincing Class III studies. Rating of recommendation: possibly effective, ineffective, or harmful for the given condition in the specified population.
U	Data inadequate or conflicting. Given current knowledge, treatment is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the CI is > 2).

Class/Level	Definition
Class I	Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: a. Primary outcome(s) is/are clearly defined. b. Exclusion/inclusion criteria are clearly defined. c. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias. d. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class II	Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a randomized, controlled trial in a representative population that lacks one criteria a–d.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion.

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Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology Jul 2018, 91 (2) 74-81.

Monotherapy in adults with new-onset epilepsy with focal epilepsy or unclassified tonic-clonic seizures

- LTG use should be considered to decrease seizure frequency (Level B)
- LTG use should be considered (Level B) and GBP use may be considered (Level C) to decrease seizure frequency in patients aged ≥60 years
- LEV use may be considered to decrease seizure frequency (Level C)
- ZNS use may be considered to decrease seizure frequency (Level C)
- VGB use appears to be less efficacious than CBZ-IR use and may not be offered (Level C); furthermore, toxicity profile precludes VGB use as first-line therapy
- PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d (Level C)
- Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ (Level U)
- Evidence is insufficient to consider TPM instead of PHT in urgent treatment of new-onset or recurrent focal epilepsy, unclassified GTC seizures, or GE presenting with GTC seizures (Level U)
- Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy (Level U)
- Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures (Level U)

Monotherapy in children with new-onset epilepsy with either focal epilepsy or unclassified GTC seizures

- Although the data from this study would suggest that TPM monotherapy is possibly more efficacious at 400 mg/d than at 50 mg/d for treating children and adolescents with new-onset focal epilepsy or generalized-onset GTC seizures (1 Class II study), no recommendations can be made regarding TPM use at the studied doses, particularly in new-onset epilepsy and pediatric patients.

Monotherapy in adults and children with new-onset GE or unclassified GTC seizures

- Evidence is insufficient to compare efficacy of LTG and TPM with that of VPA in children and adults with new-onset or relapsing GE (1 Class III study).

Monotherapy in adults and adolescents with new-onset focal, GE, or unclassified GTC seizures

- Evidence is insufficient to compare efficacy of CBZ-CR, LEV, and VPA-ER in adolescents and adults with new-onset GE and focal epilepsy (1 Class III study).

Childhood absence epilepsy

- Unless there are compelling reasons based on AE profile, ETS or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy (level B).
- No high-quality studies suggest CLB, ESL, EZG, FBM, GBP, LCM, LEV, LTG, OXC, PER, PGB, RFN, TGB, TPM, VGB, or ZNS is effective in treating new-onset epilepsy.

Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs II: Treatment-resistant epilepsy: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American

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Academy of Neurology and the American Epilepsy Society. Neurology. 2018 Jul 10;91(2):82-90.

For adult patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency?

- For TRAFE, IR PGB and PER are established as effective to reduce seizure frequency (Level A). LCM, ESL, and TPM-XR use should also be considered to decrease seizure frequency in this population (Level B). VGB and RFN should be considered established as effective for decreasing seizure frequency in TRAFE (Level A) but are not first-line agents (retinopathy risk with VGB and modest benefit with RFN). EZG use should be considered to decrease seizure frequency in this population (Level B) but carries a serious risk of skin and retinal discoloration. CLB and OXC-XR use may be considered to decrease seizure frequency in TRAFE (Level C).

For adult patients with TR focal epilepsy, are these AEDs effective in reducing seizure frequency when used as monotherapy?

- ESL use may be considered to decrease seizure frequency as monotherapy for TRAFE (Level C).
- Data are insufficient to recommend the use of second- and the other third-generation AEDs as monotherapy in TRAFE (Level U).

For adult and pediatric patients with TR GE, are these AEDs effective in reducing seizure frequency when used as adjunctive therapy (compared with no adjunctive therapy)?

- For add-on therapy for GE, IR and XR LTG use should be considered as add-on therapy to decrease seizure frequency in treating adults with TR GTC seizures secondary to GE (Level B). LEV use should be considered to decrease seizure frequency as add-on therapy for TR GTC seizures and for TR JME (Level B).

For adult and pediatric patients with LGS, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

- For LGS, RFN use should be considered established as effective to decrease seizure frequency as add-on therapy (Level A), and CLB use should be considered (Level B).

For pediatric patients with TR focal epilepsy, are these AEDs effective as adjunctive therapy in reducing seizure frequency (compared with no adjunctive therapy)?

- For add-on therapy for TR focal epilepsy, LEV use should be considered to decrease seizure frequency (Level B for ages 1 month to 16 years), ZNS use should be considered to decrease seizure frequency (Level B for ages 6–17 years), and OXC use should be considered to decrease seizure frequency (Level B for ages 1 month to 4 years).
- Data are unavailable on the efficacy of CLB, ESL, LCM, PER, PGB, RFN, TGB, or VGB as add-on therapy for the treatment of these children or adolescents (Level U).

For pediatric patients with TR focal epilepsy, are these AEDs effective as monotherapy in reducing seizure frequency?

- No data are available to answer this question. Thus, no recommendation is made.

Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 2015 Aug;56(8):1185-1197.

Summary of published studies addressing AED treatment for infants with seizures

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Epilepsy Type	AED Therapy	Recommendation Seizures[b]	Strength Efficacy[c]	AAN Recommendations
Focal	Levetiracetam	**Effective**	**Strong**	**A**
	Topiramate	**Ineffective**	**Strong**	**A**
	Lamotrigine	**Ineffective**	**Strong**	**A**
	Gabapentin	**Ineffective**	**Strong**	**A**
	Oxcarbazepine	**Ineffective**	**Strong**	**A**
	Felbamate	No data		U
	Tiagabine	No data		U
	Zonisamide	No data		U
Generalized seizures	Levetiracetam	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
	Lamotrigine	Possibly effective	Weak	C
	Topiramate	Possibly effective	Weak	C
	Clobazam	Possibly effective	Weak	C
Epileptic spasms	Low dose ACTH	Probably effective	**Strong**	**B**
	High dose ACTH	Probably effective	**Strong**	**B**
	Prednisone	Possibly effective	Weak	C
	Vigabatrin	Possibly effective	Weak except tuberous sclerosis complex	C
	Carbamazepine	Possibly effective	Weak	C
	Phenobarbital	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
Dravet syndrome	**Stiripentol[a]**	**Effective**	**Strong**	**A**
	Topiramate	Possibly effective	Weak	C
	Zonisamide	Possibly effective	Weak	C
	Valproate	Possibly effective	Weak	C
	Bromide	Possibly effective	Weak	C
	Ketogenic diet	Possibly effective	Weak	C
	Lamotrigine	**Exacerbate**	**Strong**	**A**
	Carbamazepine	**Exacerbate**	**Strong**	**A**
	Phenytoin	**Exacerbate**	**Strong**	**A**
Benign myoclonic epilepsy of infancy	Valproate	Possibly effective	Weak	C
	Topiramate	Possibly effective	Weak	C
	Lamotrigine	Possibly effective	Weak	C
	Clonazepam	Possibly effective	Weak	C
Ohtahara syndrome	Topiramate	Poorly effective	Weak	C
	Conventional AEDs	Poorly effective	Weak	C
	ACTH, prednisone	Poorly effective	Weak	C
	Pyridoxine	Poorly effective	Weak	C
Provoked or situational seizures	Carbamazepine	Possibly effective	Weak	C
	Phenobarbital	Ineffective	Weak	B

Columns marked in bold correlate where recommendations are supported by strong level of evidence.

[a] In combination with valproate and clobazam.

[b] The author of this class review is of the opinion that there was an error in the publication of the table. Column three should probably read "Seizure Efficacy." The table was reproduced as published.

[c] The author of this class review is of the opinion that there was an error in the publication of the table. Column four should probably read "Recommendation Strength." The table was reproduced as published.

Recommendation Definitions

Class/Level	Definition
Strong recommendation	Most people should receive the intervention

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Class/Level	Definition
Weak recommendation	Examine the evidence or a summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences
No recommendation	The advantages and disadvantages are equivalent. The target population has not been identified. Insufficient evidence on which to formulate a recommendation.

Class/Level	Definition
A	Established as effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
B	Probably effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
C	Possibly effective, ineffective, or harmful, or as useful/predictive or not useful/predictive
U	Data are inadequate or conflicting; treatment, test or predictor unproven

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Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: Medical treatment of infantile spasms Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology Jun 2012, 78 (24) 1974-1980.

- Short-term outcomes.
  - Other forms of corticosteroids. > Are other forms of corticosteroids as effective as ACTH for treatment of infantile spasms?
    - The evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as ACTH for short-term treatment of infantile spasms (Level U).
  - Low-dose ACTH. > Are low-dose ACTH regimens effective for short-term treatment of infantile spasms?
    - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms (Level B).
  - ACTH vs vigabatrin. > Is ACTH more effective than vigabatrin for short-term treatment of infantile spasms?
    - ACTH (Level B) or VGB (Level C) may be offered for short-term treatment of infantile spasms. Evidence suggests that ACTH may be offered over VGB (Level C).
  - Other agents. > What other agents are as effective as ACTH for treatment of infantile spasms?
    - The evidence is insufficient to recommend other therapies (VPA, vitamin B6, NZP, LEV, ZNS, TPM, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms (Level U).
  - Intermediate to long-term outcomes. > Does successful early treatment of infantile spasms lead to long-term improvement of neurodevelopmental outcomes or decreased incidence of epilepsy?
    - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to VGB in infants with cryptogenic infantile spasms, to possibly improve developmental outcome (Level C).
    - A shorter lag time to treatment of infantile spasms with either hormonal therapy or VGB may be considered to improve long-term cognitive outcomes (Level C).

Recommendation Definitions

Class/Level	Definition
A	Established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population. (Level A rating requires at least two consistent Class I studies.)*
B	Probably effective, ineffective or harmful (or probably useful/predictive or not useful/predictive) for the given condition in the specified population. (Level B rating requires at least one Class I study or two consistent Class II studies.)
C	Possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population. (Level C rating requires at least one Class II study or two consistent Class III studies.)
U	Data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.

*In exceptional cases, one convincing Class I study may suffice for an "A" recommendation if 1) all criteria are met, 2) the magnitude of effect is large (relative rate improved outcome > 5 and the lower limit of the CI is > 2).

Class/Level	Definition
Class I	An RCT trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required:

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Class/Level	Definition
	a. concealed allocation b. primary outcome(s) clearly defined c. exclusion/inclusion criteria clearly defined d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias. e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*: i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority. ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective). iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. iv. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets be above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**
Class IV	Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Glauser T, Shinnar S, Gloss D, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016 Jan-Feb;16(1):48-61.

Proposed Treatment Algorithm for Status Epilepticus

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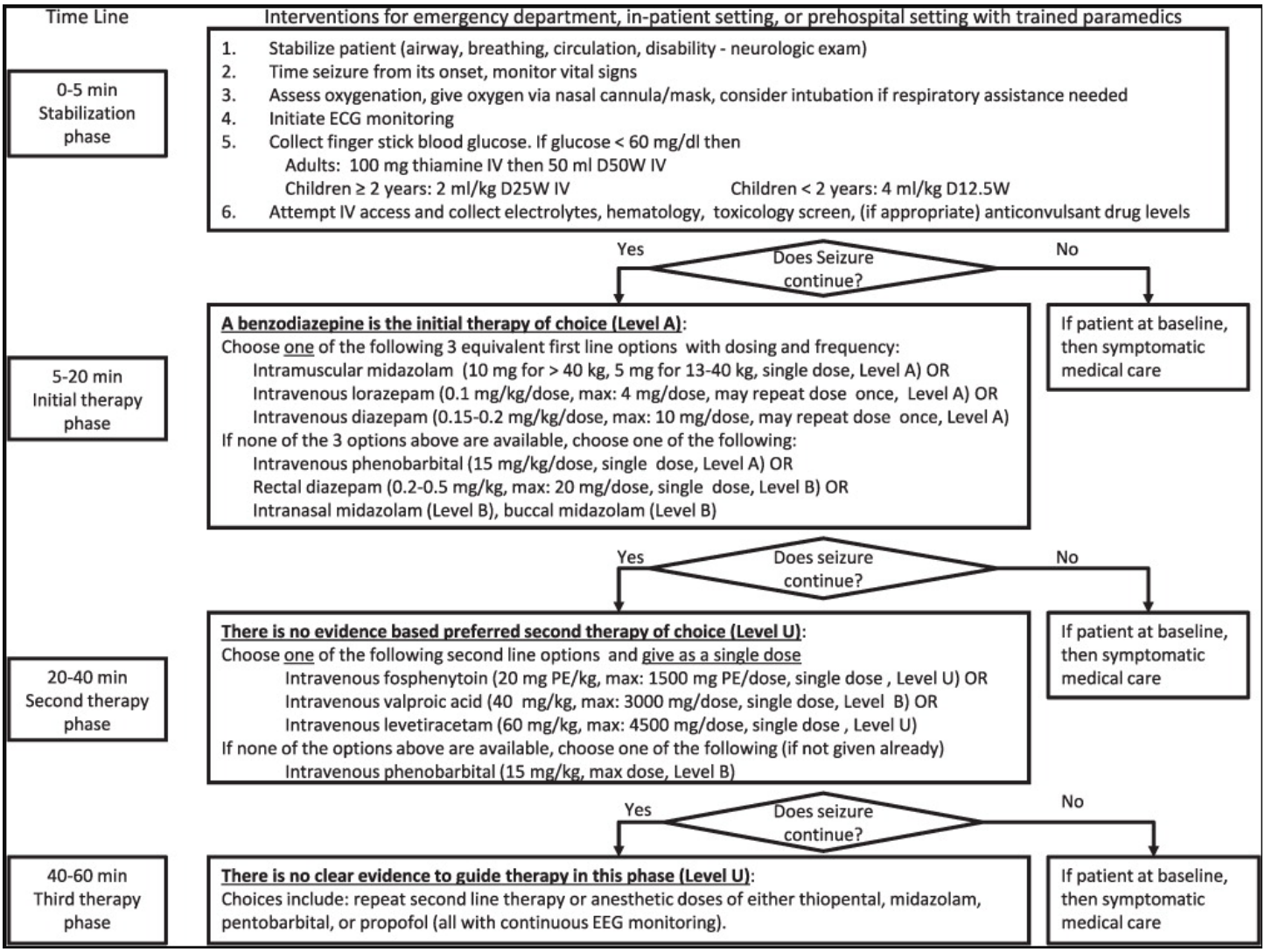

Recommendation Definitions

Class/Level	Definition
A	One or more class I studies or two or more consistent class II studies. Conclusion, level A: Established as effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be done or should not be done
B	One or more class II studies or three or more consistent class III studies. Conclusion, level B: Probably effective, ineffective, or harmful for the given condition in the specified population Recommendation: Should be considered or should not be considered
C	Two or more consistent class III studies Conclusion, level C: Possibly effective, ineffective, or harmful for the given condition in the specified population Recommendation: May be considered or may not be considered
U	Lack of studies meeting level A, B, or C designation Conclusion, level U: Data inadequate or insufficient. Given current knowledge, treatment is unproven. Recommendation: None

Class/Level	Definition
Class I	Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The

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Class/Level	Definition
	following are also required: a. No more than two primary outcomes specified b. Concealed allocation c. Exclusion/inclusion criteria clearly defined d. Relevant baseline characteristics presented and substantially equivalent between treatment groups, or appropriate statistical adjustment for differences e. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) with numbers sufficiently low to have minimal potential for bias f. Demonstration of superiority in a superiority study design or demonstration of noninferiority using a 10% margin in a noninferiority design
Class II	A prospective, randomized, controlled clinical trial with masked outcome assessment that lacks one or two criteria a–e (see class I) or a prospective matched group cohort study in a representative population with masked outcome assessment that meets criteria a–e
Class III	All other controlled trials in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion

Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012 Aug;17(1):3-23.

- The treatment of convulsive SE should occur rapidly and continue sequentially until clinical seizures are halted (strong recommendation, high quality).
- The treatment of SE should occur rapidly and continue sequentially until electrographic seizures are halted (strong recommendation, moderate quality).
- Critical care treatment and monitoring should be started simultaneously with emergent initial therapy and continued until further therapy is consider successful or futile (strong recommendation, moderate quality).
- Treatment options
    - Benzodiazepines should be given as emergent initial therapy (strong recommendation, high quality).
        - Lorazepam is the drug of choice for IV administration (strong recommendation, moderate quality).
        - MDZ is the drug of choice for IM administration (strong recommendation, moderate quality).
        - Rectal diazepam can be given when there is no IV access and IM administration of MDZ is contraindicated (strong recommendation, moderate quality).
    - Urgent control AED therapy recommendations include use of IV fosphenytoin/PHT, VPA, or LEV (strong recommendation, moderate quality).
    - Refractory SE therapy recommendations should consist of continuous infusion AEDs, but vary by the patient's underlying condition (strong recommendation, low quality).
    - Dosing of continuous infusion AEDs for RSE should be titrated to cessation of electrographic seizures or burst suppression (strong recommendation, very low quality).
    - A period of 24–48 h of electrographic control is recommended prior to slow withdrawal of continuous infusion AEDs for RSE (weak recommendation, very low quality).
    - During the transition from continuous infusion AEDs in RSE, it is suggested to use maintenance AEDs and monitor for recurrent seizures by cEEG (continuous electroencephalogram) during the titration period. If the patient is being treated for RSE at a facility without cEEG capabilities, consider transfer to a facility that can offer cEEG monitoring (strong recommendation, very low quality).

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- Alternative therapies can be considered if cessation of seizures cannot be achieved; however, it is recommended to reserve these therapies for patients who do not respond to RSE AED treatment and consider transfer of the patient if they are not being managed by an ICU team that specialize in the treatment of SE and/or cannot provide cEEG monitoring (weak recommendation, very low quality)

Recommendation Definitions

Class/Level	Definition
Strong recommendation	Most people should receive the intervention
Weak recommendation	Examine the evidence or a summary of the evidence yourself and be prepared to discuss that evidence with patients, as well as their values and preferences
No recommendation	The advantages and disadvantages are equivalent. The target population has not been identified. Insufficient evidence on which to formulate a recommendation.

Class/Level	Definition
High quality	Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality	Any estimate of effect is very uncertain

Wirrell EC, Laux L, Donner E, et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel. Pediatr Neurol. 2017 Mar;68:18-34.e3.

Treatment of Seizures

	AAN Class of Evidence	Finding	Strength of Agreement
Prophylactic AEDs	-	-	-
First-line agents	III	CLB and VPA are the optimal first-line medications in Dravet syndrome. Treatment should be initiated with one of these agents and the other added if control remains suboptimal	Strong
Second-line agents	I, stiripentol III, topiramate	Stiripentol and TPM are the optimal second-line medications. One of these should be used if seizure control remains poor after use of both first-line therapies Stiripentol should be used in combination with VPA and CLB, and there is no evidence to support its use as monotherapy.	Strong Strong
Later therapeutic options	III, levetiracetam IV, bromides, rufinamide NA, others	In patients with suboptimal response to first- and second-line therapies: Clonazepam, LEV, and ZNS are moderately effective ETS (for atypical absences) and phenobarbital may be effective No consensus regarding efficacy of RFN, acetazolamide, or bromides	 Strong Moderate No consensus

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Exacerbating therapies	II	CBZ, OXC, LTG, PHT, and VGB often exacerbate seizures and should be avoided	Strong
Rescue medication for home use	-	-	-
Need for home rescue medication	II	All patients need both a home rescue medication and seizure protocol, which can be carried out at their local hospital	Strong
Optimal rescue therapies for age	NA	For children 6 years*: Rectal diazepam Buccal/nasal MDZ For children aged 7-12 years and teens/adults*: Buccal/nasal MDZ	 Strong Strong Strong
Management of SE	-	-	-
Recommended first-line agents	III	IV benzodiazepines should be the first medication administered if a patient presents to hospital with an ongoing seizure, and a second dose of benzodiazepine should be given if the seizure persists, particularly if the patient did not receive a home dose of rescue medication*	Strong
Recommended therapies if convulsive seizure persists after IV benzodiazepine	III	If the patient continues to convulse despite IV benzodiazepine, a VPA load is an appropriate next option There was no consensus regarding other abortive therapies in the management of convulsive status epilepticus	Strong No consensus

NA – Not available
*Standard of care for all persons with epilepsy, not unique to Dravet syndrome.

Recommendation Definitions

Class/Level	Definition
Strong	More than 75% of respondents strongly agreed or agreed
Moderate	More than 75% of respondents strongly agreed, agreed, or somewhat agreed
Modest	Less than 75% of respondents strongly agreed, agreed, or somewhat agreed and none disagreed
No consensus	Less than 75% of respondents strongly agreed, agreed, or somewhat agreed and some disagreed at any level

Class/Level	Definition
Class I	An RCT trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. The following are also required: a. concealed allocation b. primary outcome(s) clearly defined c. exclusion/inclusion criteria clearly defined d. adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias. e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required*: i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.

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Class/Level	Definition
	ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective). iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment. iv. The interpretation of the results of the study is based upon a per-protocol analysis that takes into account dropouts or crossovers.
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e above (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets be above (see Class I). Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurement.**
Class IV	Studies not meeting Class I, II, or III criteria, including consensus or expert opinion.

* Note that numbers 1–3 in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Duffner PK, Baumann RJ, Berman P, et al. Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics. 2008 Jun;121(6):1281-6.

- On the basis of the risks and benefits of the effective therapies, neither continuous nor intermittent anticonvulsant therapy is recommended for children with 1 or more simple febrile seizures.
    - Aggregate evidence quality: B (randomized, controlled trials and diagnostic studies with minor limitations).
    - Benefit: prevention of recurrent febrile seizures, which are not harmful and do not significantly increase the risk for development of future epilepsy.
    - Harm: adverse effects including rare fatal hepatotoxicity (especially in children younger than 2 years who are also at greatest risk of febrile seizures), thrombocytopenia, weight loss and gain, gastrointestinal disturbances, and pancreatitis with VPA and hyperactivity, irritability, lethargy, sleep disturbances, and hypersensitivity reactions with phenobarbital; lethargy, drowsiness, and ataxia for intermittent diazepam as well as the risk of masking an evolving central nervous system infection.
    - Benefits/harms assessment: preponderance of harm over benefit.
    - Policy level: recommendation.

Recommendation Definitions

Class/Level	Definition
Strong Recommendation	A strong recommendation in favor of a particular action is made when the anticipated benefits of the recommended intervention clearly exceed the harms (as a strong recommendation against an action is made when the anticipated harms clearly exceed the benefits) and the quality of the supporting evidence is excellent. In some clearly identified circumstances, strong recommendations may be made when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.
Recommendation	A recommendation in favor of a particular action is made when the anticipated benefits exceed the harms but the quality of evidence is not as strong. Again, in some clearly identified circumstances, recommendations may be made when high-quality evidence is impossible to obtain but the anticipated benefits outweigh the harms.

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Class/Level	Definition
Option	Options define courses that may be taken when either the quality of evidence is suspect or carefully performed studies have shown little clear advantage to 1 approach over another.
No Recommendation	No recommendation indicates that there is a lack of pertinent published evidence and that the anticipated balance of benefits and harms is presently unclear.

Class/Level	Definition
A	Well-designed RCTs or diagnostic studies on relevant populations
B	RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies
C	Observational studies (case-control and cohort design)
D	Expert opinion, case reports, reasoning from first principles
X	Exceptional situation which validating studies cannot be performed and there is a clear preponderance of benefit or harm

French J, Smith M, Faught E, Brown L. Practice advisory: The use of felbamate in the treatment of patients with intractable epilepsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 1999 May 12;52(8):1540-5. (Reaffirmed 2019)

A. Patients for whom risk/benefit ratio supports use because there is Class I evidence for benefit.
   1. Lennox–Gastaut patients over age 4 unresponsive to primary AEDs
   2. Intractable partial seizures in patients over 18 years of age who have failed standard AEDs at therapeutic levels (monotherapy: data indicate a better risk/benefit ratio for felbamate used as monotherapy)
   3. Patients on felbamate more than 18 months

B. Patients for whom the current risk/benefit assessment does not support the use of felbamate:
   1. New onset epilepsy in adults or children
   2. Patients who have experienced significant prior hematologic adverse events
   3. Patients in whom follow-up and compliance will not allow careful monitoring
   4. Patients unable to discuss risks/benefits (i.e., with mental retardation, developmental disability) and for whom no parent or legal guardian is available to provide consent

C. Patients in whom risk/benefit ratio is unclear and based on case reports and expert opinion (Class III) only, but under certain circumstances depending on the nature and severity of the patient's seizure disorder, felbamate use may be appropriate:
   1. Children with intractable partial epilepsy
   2. Other generalized epilepsies unresponsive to primary agents
   3. Patients who experience unacceptable sedative or cognitive side effects with traditional AEDs
   4. Lennox–Gastaut syndrome under age 4 unresponsive to other AED

Recommendation Definitions

Class/Level	Definition
Standard	A principle for patient management that reflects a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).
Guideline	A recommendation for patient management that reflects moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).
Practice opinion	A strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

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Class/Level	Definition
Practice advisory	A practice recommendation for emerging and/or newly approved therapies or technologies based on evidence from at least one Class I study. The evidence may demonstrate only a modest statistical effect or limited (partial) clinical response, or significant cost-benefit questions may exist. Substantial (or potential) disagreement among practitioners or between payers and practitioners may exist.

Class/Level	Definition
Class I	Well-designed, prospective, blinded, controlled studies.
Class II	Well-designed clinical studies, such as case control, cohort studies, etc.
Class III	Evidence provided by expert opinion, nonrandomized historic controls, or case reports of one or more.

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Clinical Trials/Systematic Reviews/Meta-Analyses

Citation	Design	Endpoints
Hemery C, Ryvlin P, Rheims S. Prevention of generalized tonic-clonic seizures in refractory focal epilepsy: a meta-analysis. Epilepsia. 2014 Nov;55(11):1789-99. doi: 10.1111/epi.12765.	Meta-analysis of RCTs of adjunctive AED where information on efficacy outcomes (i.e. responder rate and/or frequency per 28 days relative to baseline) were available both for all seizure types and for SGTCS	• Primary: the efficacy, as measured by relative risk, of AEDs on all types of seizure and on SGTCS by comparing the responder rates for AED and for PBO
Results: Three AEDs—LCM, PER and TPM—showed greater efficacy in treating SGCTS than PBO; although, CIs of relative risks overlapped for all AEDs excepting pregabalin, which demonstrated significantly lower efficacy. There was a nonsignificant trend toward a lower relative risk of responder rate for SGTCS than for all seizure types, seemingly related to a greater PBO response. **Conclusion**: This indirect comparison did not demonstrate robust differences between AEDs to prevent SGTCS. More research is needed to determine if there is a difference in this setting.		

Citation	Design	Endpoints
Hu Q, Zhang F, Teng W, et al. Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis. J Neurol. 2018 Jan;265(1):1-11. doi: 10.1007/s00415-017-8621-x. Epub 2017 Sep 22.	Network meta-analysis performed with a Bayesian random-effects model N=76 RCTs, 17 AEDs, 20,711 patients Inclusion criteria: randomized, double-blind, PBO-controlled or active-controlled add-on trials; sample size > 10 patients per group and patients older than 2 years of age with a clinical diagnosis of drug-resistant partial epilepsy (simple, complex, or secondarily tonic–clonic seizures) as defined by the International Classification of Seizures (Commission on Classification and Terminology of the ILAE, 1981); a prospective baseline period of 4 weeks and minimum follow-up of 8 weeks for the treatment period (excluding titration), as this is considered to represent the minimum period over which changes in seizure frequency can be determined; the following outcomes were reported: seizure freedom and withdrawal rate due to treatment-emergent adverse effects (TEAE) Exclusion criteria: Studies comparing a drug in different pharmaceutical formulations or doses; trials that incorporated a surgical intervention, use of other therapies that may affect seizure frequency, trials of open-label design, observational studies, conference proceedings, and publications available only in abstract form.	• Primary efficacy: seizure freedom, defined as the number of patients who experienced 100% seizure reduction in the maintenance or double-blind (titration plus maintenance) treatment period of RCTs • Primary safety: withdrawal rate due to TEAE
Results:		

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Primary efficacy: Compared to other AEDs, TGB had the greatest likelihood of allowing patients to attain seizure freedom, and this result is consistent with the ranking probability for the surface under the cumulative ranking curve (SUCRA). BRV, TPM, LEV, OXC, VPA, and VGB which had a lower likelihood of efficacy for seizure freedom when compared to RFN. [BRV: OR = 12.64, 95% CI (1.57–129.61); TPM: OR = 9.93, 95% CI (5.54–79); LEV: OR = 11.44, 95% CI (2.20–73.46); OXC: OR = 14.27, 95% CI (2.01–121.09); VGB: OR = 8.76, 95% CI (1.24, 80.42); VPA: OR = 12.77, 95% CI (1.35, 163.66)]. Rank probability analysis showed that TGB had the highest probability of improving seizure freedom (SUCRA = 98.5%), followed by BRV (SUCRA = 73.8%) and VPA (SUCRA = 71.5%).

Primary safety: LEV was associated with a lower withdrawal rate due to adverse effects than LCM [OR = 2.72, 95% CI (1.05–7.48)], ESL [OR = 2.31, 95% CI (1.02–5.48)], OXC [OR = 3.48, 95% CI (1.43–8.43)], PGB [OR = 2.16, 95% CI (1.13–4.34)], and RTG [OR = 3.27, 95% CI (1.38–7.52)] (Table 2). Rank probability analysis showed that PBO was best tolerated AED in terms of safety outcomes (SUCRA = 94.6%), followed by LEV (SUCRA = 84.8%), BRV (SUCRA = 70.6%), and PER (SUCRA = 58%).

Conclusion: The most relevant findings are as follows: (1) BRV, TPM, LEV, OXC, VPA, and likely VGB are more efficacious for controlling seizure frequency (as measured by analysis of the seizure freedom), whereas RUF is less efficacious than all other AEDs; (2) safety (as measured by analysis of the withdrawal rate due to adverse effects) was poorer with OXC, RTG, and RUF, whereas LEV was better tolerated; and (3) LEV, VGB, VPA, and BRV emerged as the agents with the best combination of properties when considering the efficacy and safety outcomes based on the full double-blind treatment period. Although TGB has a high probability (determined by the SUCRA) to be the best choice when analyzing the seizure freedom outcome, it was not included among the optimal AEDs due to its adverse events.

Citation	Design	Endpoints
Devinsky O, Cross JH, Laux L, et. al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med. 2017;376(21):2011-2010. doi. 10.1056/NEJMoa1611618.	Phase III, multinational, randomized (1:1), double-blind, PBO-controlled trial N=120 Baseline characteristics: – Mean age of the patients was 9.8 years and 52% were male – Baseline convulsive-seizure frequency was a median of 13.0 seizures per month – Previously tried a median of 4 AEDs and were taking a median of 3 AEDs Patients were randomly assigned to receive 100 mg/mL CBD oral solution escalated up to 20 mg/kg/day in 2 divided doses or matching PBO in addition to their stable AED regimen. A total of 108 patients (90%) completed the treatment period (85% in the CBD group and 95% in the PBO group). The trial comprised a 4-week baseline period, a 14-week treatment period (2 weeks of dose escalation and 12 weeks of dose maintenance), a 10-day taper period, and a 4-week safety follow-up period.	• Primary: percent change per 28 days from the 4-week baseline period in convulsive seizure frequency during the 14-week treatment period among patients who received treatment compared to PBO as reported by patients or their caregiver.

Results: The adjusted median difference in convulsive seizures between the CBD group and the PBO group was −22.8 percentage points (95% CI, −41.1 to −5.4; P=0.01). CBD displayed a median percent change of -38.9% per 28 days from 4-week baseline period in convulsion seizure frequency during the 14-week treatment period among patients who received CBD as compared to -14.9% in PBO.

Conclusion: CBD reduced the frequency of convulsive seizures among children and young adults with the Dravet syndrome but was associated with adverse events including somnolence and vomiting.

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Citation	Design	Endpoints
Thiele EA, Marsh ED, French JA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018 Mar 17;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3.	Phase III, randomized (1:1), double-blind, 14-week comparison of CBD vs PBO N=171 Baseline characteristics: – Patients on average had not responded to an average of six AEDs – Patients on average were concomitantly taking three AEDs – Patients on average had an average of 73.8 drop seizures per 28 days – At least 90% of patients were Caucasian Patients received 100 mg/mL CBD oral solution 20 mg/kg/day or PBO for 14 weeks	• Primary: percentage change from baseline in monthly frequency of drop seizures during the treatment period, analyzed in all patients who received at least one dose of study drug and had post-baseline efficacy data
Results: Patients taking CBD had a significantly greater median reduction in drop seizures compared to PBO (44 percent vs. 22 percent; p=0.0135). Sensitivity analyses confirmed that the treatment effect of CBD was established during the first month of treatment and was sustained over the entire treatment period. **Conclusion**: Adjunctive CBD is efficacious for the treatment of patients with drop seizures associated with LGS and is generally well tolerated.		

Citation	Design	Endpoints
Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox-Gastaut Syndrome. N Engl J Med. 2018 May 17;378(20):1888-1897. doi: 10.1056/NEJMoa1714631.	Phase III, randomized (1:1:1), double-blind, PBO-controlled trial with a 14-week comparison of two dose levels of GWP42003-P versus PBO N = 225 Baseline characteristics: – Patients in each arm had a mean age range of 14.73 to 16.54 years old and were mostly males – Patients in each arm had a median range of 6.79-7.18 previous AEDs tried – Patients in each arm had a median range of 2.84-2.94 current AEDs being used Patients were randomly assigned to receive 100 mg/mL CBD oral solution high dose (20 mg/kg/day), low dose (10 mg/kg/day) or PBO. The following doses will be given with the treatment period consisting of a two-week titration period followed by a 12-week maintenance period.	• Primary: The percent change from baseline in number of drop seizures (average per 28 days) during the treatment period (time frame of 0-14 weeks) via non-parametric analyses.
Results: There was a significant reduction in drop seizures from baseline in the high dose group (N = 42 [55%], p<0.005) and the low dose group (N=37 [51%], p<0.005) during the treatment period of 0 to 14 weeks. **Conclusion**: CBD as an adjunct to standard of care dosed at 10 and 20 mg/kg/day produced significantly greater reductions in drop seizures compared to PBO patients with LGS, greater reported improvement in overall condition on the Subject/Caregiver Global Impression of Change scale, and was generally well-tolerated.		

Citation	Design	Endpoints

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Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-response trial. Lancet Neurol. 2020;19(1):38-48.	Phase 2, multicenter, randomized, double-blind, PBO controlled, dose-response trial of cenobamate as adjunctive therapy in subjects with partial onset seizures, with optional open-label extension N=434 Arms: cenobamate 200 mg/day vs PBO Inclusion criteria: Weight at least 40 kg; diagnosis of partial epilepsy established by clinical history and an electroencephalogram (EEG) that is consistent with localization related epilepsy; uncontrolled partial seizures despite having been treated with at least 1 AED within the past 2 years; during the 8-week baseline period, patients must have at least 8 partial seizures including only simple partial seizures with motor component, complex partial seizures, or secondarily generalized seizures without a seizure-free interval of > 25 days any time during the baseline period; patients must have at least 3 of these partial seizures during each of the two consecutive 4-week segments of the baseline period; on a stable antiepileptic treatment regimen Exclusion criteria: History of non-epileptic or psychogenic seizures; presence of only non-motor simple partial seizures or primary generalized epilepsies; presence or previous history of LGS; active CNS infection, demyelinating disease, degenerative neurologic disease, or any CNS disease; any clinically significant psychiatric illness, psychological, or behavioral problems; history of alcoholism, drug abuse, or drug addiction within the past 2 years; history of status epilepticus within past 3 months; history of suicide attempt	• Primary end point: Percent change from baseline in seizure frequency per 28 days • Secondary end points: Response rate, defined as ≥50% reduction in seizure frequency; safety

Results:

- Primary: Median percentage changes in seizure frequency were −24.3% for the PBO group, compared with −36.3% (P=0.006) for the 100 mg group, −55.2% (P<0.001) for the 200 mg group, and −55.3% (P<0.001) for the 400 mg group
- Secondary: Responder rates were 25% for the PBO group, compared with 40% (P=0.037) for the 100 mg group, 56% (P<0.001) for the 200 mg group, and 64% (P<0.001) for the 400 mg group
- Safety: TEAEs occurred in 70% in the PBO group, 65% in the 100 mg group, 76% in the 200 mg group, and 90% in the 400 mg group. TEAEs led to discontinuation in 5% of patients in the PBO group, 10% in the 100 mg group, 14% in the 200 mg group, and 20% in the 400 mg group

Conclusion: Adjunctive cenobamate reduced focal (partial)-onset seizure frequency, in a dose-related fashion. Treatment-emergent adverse events were most frequent in the highest dose group. Cenobamate appears to be an effective treatment option in patients with uncontrolled focal seizures.

Citation	Design	Endpoints

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Chung SS, French JA, Kowalski J, et al. Randomized phase 2 study of adjunctive cenobamate in patients with uncontrolled focal seizures. Neurology. 2020 Jun 2;94(22):e2311-e2322. doi: 10.1212/WNL.0000000000009530. Epub 2020 May 14.	Phase 2, multicenter, randomized, double-blind, PBO controlled, dose-response trial of YKP3089 (cenobamate) as adjunctive therapy in subjects with partial onset seizures, with optional open-label extension N=221 Arms: Cenobamate 100 mg, 200 mg or 400 mg/day vs PBO Inclusion criteria: Diagnosis of treatment resistant partial epilepsy; history of epilepsy for at least 2 years; have at least 3 simple partial with motor component, complex partial or secondarily generalized seizures per month with no consecutive 21 day seizure free period; currently treated on a stable dose of 1 to 3 AED's for at least 12 weeks prior to randomization Exclusion criteria: History of alcoholism, drug abuse, or drug addiction within the past 2 years; status epilepticus within past 1 year; > 2 allergic reactions to an AED or one serious hypersensitivity reaction to an AED; patients taking FBM with < 18 months continuous exposure; patients receiving PHT, phenobarbitone or metabolites of these drugs; history of suicide attempt in the past 2 years; current major depressive episode (within 6 months); use of intermittent rescue BZDs > once per month (1-2 doses in a 24-hour period is considered one rescue) in the past month	• Primary end point: Percent change from baseline in seizure frequency per 28 days • Secondary end points: Response rate, defined as ≥50% reduction in seizure frequency; safety

Results:

Efficacy: The median percent reduction in seizure frequency per 28 days (primary outcome) was 55.6% and 21.5% for cenobamate- and PBO-treated patients, respectively ($p < 0.0001$). The ≥50% responder rate was also significantly greater for patients treated with cenobamate (50.4%) vs PBO (22.2%) (odds ratio 3.94, 95% CI 2.14–7.24; $p < 0.0001$).

Safety: During the 12-week treatment period, TEAEs were reported in 86 of 113 cenobamate-treated patients (76.1%) and 69 of 109 PBO-treated patients (63.3%). The most frequently (>10%) reported TEAEs for cenobamate were somnolence (22.1%), dizziness (22.1%), headache (12.4%), nausea (11.5%), and fatigue (10.6%). For PBO, they were dizziness (16.5%), headache (12.8%), and somnolence (11.9%). Most TEAEs were mild or moderate in severity (cenobamate: mild or moderate 74.3%, severe 1.8%; PBO: mild or moderate 56.9%, severe 6.4%). One TEAE of suicidal ideation was reported in each treatment group. Columbia Suicide Severity Rating Scale responses did not reveal any increases in suicidal ideation, intensity, or behavior from baseline with cenobamate. Among infectious TEAEs, only urinary tract infections (8.0% cenobamate vs 1.8% PBO) and nasopharyngitis (6.2% cenobamate vs 0.9% PBO) occurred with at least a 5–percentage point difference between groups. Treatment-related TEAEs occurring in >5% of cenobamate-treated patients with a ≥5% difference over the PBO group included somnolence (22.1% vs 10.1%), dizziness (20.4% vs 13.8%), balance disorder (7.1% vs 0.9%), and nystagmus (9.7% vs 0%).

Conclusion: Adjunctive treatment with cenobamate 200 mg/d significantly improved seizure control in adults with uncontrolled focal seizures and was well tolerated.

Citation	Design	Endpoints
Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomized	Randomized, double-blind, PBO-controlled N=41	• Primary endpoint: Percentage of responders on stiripentol and on PBO, defined as having experienced at least a

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placebo-controlled syndrome-dedicated trial. Lancet. 2000 Nov 11;356(9242):1638-42. doi: 10.1016/s0140-6736(00)03157-3.	Arms: Stiripentol capsules at the dose of 50 mg/kg a day, twice or three times daily vs. PBO capsules given two or three times daily (maximum dose of co-medication was limited to 30 mg/kg a day for VPA and 0.5 mg/kg a day for CLB) Inclusion criteria: 3 years and older; severe myoclonic epilepsy in infants (SMEI), defined as onset of the epilepsy in the first year of life with clonic (or tonic-clonic) generalized seizures but normal psychomotor development and normal EEG; appearance of myoclonia after 1 year of age; atypical absences; generalized spikes and waves on EEG; mental delay; at least four clonic (or tonic-clonic) generalized seizures a month; VPA and CLB as ongoing antiepileptic drugs Exclusion criteria: Patients receiving other drugs (except progabide) and those whose parents were unable to comply regularly with drug delivery and daily seizure diary were not included.	50% reduction of clonic (or tonic-clonic) seizure frequency during the second month of the double-blind period compared with baseline • Secondary: Safety
Results: The frequency of responders was greater on stiripentol at 71% (95% CI 52.1–90.7) than on PBO at 5% (0–14.6) with a high significance (p<0.0001). During the double-blind period, nine (43%) patients on stiripentol but none on PBO became free of clonic (or tonic-clonic) seizures. Drug-related adverse events were noticed in the 21 (100%) patients on stiripentol versus five (25%) on PBO (p=0.0009). The adverse events most frequently observed on stiripentol were drowsiness and loss of appetite, which could result in loss of weight, whereas weight gain was equally reported for stiripentol and PBO. Adverse events were regarded as severe in five patients on stiripentol (drowsiness in three, loss of weight in two) and in one on PBO (drowsiness). Only one patient was withdrawn from the study because of an adverse event; he was on PBO. **Conclusion:** This controlled trial shows the antiepileptic efficacy, of add-on stiripentol in children with SMEI. The results also provide good reason to focus studies on a specific epilepsy syndrome—a small sample of patients is sufficient to show the efficacy that might have been missed in a heterogeneous population.		

Citation	Design	Endpoints
Brigo F, Storti M. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. Cochrane Database Syst Rev. 2013 Nov 19;(11):CD010483. doi: 10.1002/14651858.CD010483.pub2.	Meta-analysis using the MantelHaenszel method for analyzing dichotomous data N=2 studies, 64 participants Inclusion criteria: • Types of studies: RCTs or quasi-RCTs (e.g. sequence generated by date of birth or by clinical record number); double-blinded, single-blinded or unblinded trials; parallel-group studies • Types of participants: People with a defined diagnosis of SMEI/Dravet syndrome made according to ILAE criteria, regardless of age, sex, ethnicity and prior therapy, including children with disabilities • Types of interventions: any trial that compares at least one AED against PBO/no therapy/another therapy/a different dose of the same therapy; trials evaluating ketogenic diet; he therapies may be given singly (monotherapy) or in combination (add-on therapy) • Types of outcome measures:	Primary: • Proportion of participants with 50% or greater reduction in seizure frequency at the end of the study compared with the pre-randomization baseline period. • Proportion of participants achieving total cessation of seizures at the end of the trial (using the most current ILAE proposed definition of seizure freedom: no seizures of any type for either 12 months or 3 times the longest (pre-intervention) seizure-free interval, whichever is longest) Secondary:

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	○ Primary: 50% or greater reduction in seizure frequency; seizure freedom ○ Secondary: Adverse effects; proportion of dropouts/withdrawals due to side effects, lack of efficacy or other reasons Exclusion criteria: all other study designs, including cohort studies, case-control studies, outcomes research, case studies, case series and expert opinion	• Adverse effects; proportion of dropouts/withdrawals due to side effects, lack of efficacy or other reasons; improvement in quality of life (QoL)

Results:

Primary:

- 50% or greater reduction in seizure frequency: A statistically significant higher proportion of participants had 50% or greater reduction in seizure frequency from the pre-randomization baseline period in the STP group compared with the PBO group (22/33 vs 2/31 participants; RR 10.40, 95% CI 2.64 to 40.87).
- Seizure freedom: A statistically significant higher proportion of participants with seizure freedom was reported in the STP group compared with the PBO group (12/33 vs 1/31 participants; RR 7.93, 95% CI 1.52 to 41.21).

Secondary:

- Adverse events: Only one study explicitly reported adverse events preventing meta-analysis pooling. For adverse events reported by the other study, see Chiron 2000.
- Proportion of dropouts: No statistically significant difference in proportion of dropouts was reported in the STP group compared with the PBO group (2/33 vs 8/31 participants; RR 0.24, 95% CI 0.06 to 1.03).

Conclusion: Data derived from two small RCTs indicate that STP is significantly better than PBO with regards to 50% or greater reduction in seizure frequency and seizure freedom. Adverse effects occurred more frequently with STP. Further adequately powered studies with long-term follow-up should be conducted to unequivocally establish the long-term efficacy and tolerability of STP in the treatment of SMEI.

Citation	Design	Endpoints
Lagae L, Sullivan J, Knupp K, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019 Dec 21;394(10216):2243-2254. doi: 10.1016/S0140-6736(19)32500-0. Epub 2019 Dec 17.	Phase 3, multicenter, double-blind, PBO-controlled, parallel-group randomized clinical trial N=87 Arms: Fenfluramine 0.4 mg/kg/day (maximum 17 mg/day) or PBO Inclusion criteria: Male or non-pregnant, non-lactating female, age 2 to 18 years with uncontrolled Dravet syndrome; receiving a stable, stiripentol-inclusive AED regimen; free of CV disease Exclusion criteria: PAH; current or past history of CV or cerebrovascular disease, such as cardiac valvulopathy, MI or stroke; current or recent history of anorexia nervosa, bulimia, or depression; current or past history of glaucoma; receiving concomitant therapy with: centrally-acting anorectic agents, MAOIs, modulators of serotonergic activity, triptans, atomoxetine, cyproheptadine, and/or CYP 2D6/3A4/2B6 inhibitors/substrates; receiving concomitant or recent therapy with CBZ, OXC, ESL,	Primary: • Change in mean monthly convulsive seizure frequency between fenfluramine and PBO relative to baseline Secondary: • Proportion of patients achieving ≥ 50% reduction from baseline levels in mean monthly convulsive seizure frequency • Duration of the longest seizure-free interval • Safety

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	phenobarbital, PHT; positive urine test for THC or a positive whole blood test for cannabidiol at screening	

Results:

Primary:

- Change in mean monthly convulsive seizure frequency: Fenfluramine achieved 54.0% (95% CI, 35.6% to 67.2%; P<0.001) greater reduction in mean monthly convulsive seizure frequency compared to those receiving PBO.

Secondary:

- Proportion of patients achieving ≥ 50% reduction from baseline levels in mean monthly convulsive seizure frequency: With fenfluramine, 54% of patients demonstrated a clinically meaningful (≥50%) reduction in monthly convulsive seizure frequency vs. 5% with PBO (P<0.001).
- Duration of the longest seizure-free interval: Median longest seizure-free interval was 22 days with fenfluramine and 13 days with PBO (P=0.004)
- Safety: Most common adverse events were decreased appetite (44% for fenfluramine vs. 11% for PBO), fatigue (26% vs. 5%), diarrhea (23% vs. 7%), and pyrexia (26% vs. 9%). Cardiac monitoring demonstrated no clinical or echocardiographic evidence of valvular heart disease or PAH.

Conclusion: Fenfluramine demonstrated significant improvements in monthly convulsive seizure frequency in patients with Dravet syndrome whose conditions were insufficiently controlled with stiripentol-inclusive AED regimens. Fenfluramine was generally well tolerated.

Citation	Design	Endpoints
Nabbout R, Mistry A, Zuberi S, et al. Fenfluramine for Treatment-Resistant Seizures in Patients With Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2019; 77(3):300-308.	Phase 3, randomized, double-blind, PBO-controlled clinical trial N=119 Arms: Fenfluramine 0.2 mg/kg/day, 0.7 mg/kg/day, or PBO Inclusion criteria: Male or non-pregnant, non-lactating female, age 2 to 18 years with uncontrolled Dravet syndrome; at least 4 convulsive seizures in a 4-week period during the 12 weeks prior to the screening period; all medications or interventions for epilepsy (including KD and VNS) must be stable for at least 4 weeks prior to screening and are expected to remain stable throughout the study Exclusion criteria: PAH; current or past history of CV or cerebrovascular disease, such as cardiac valvulopathy, MI or stroke; current or past history of glaucoma; moderate or severe hepatic impairment; receiving concomitant therapy with: centrally-acting anorectic agents, MAOIs; any centrally acting agent with serotonin agonist or antagonist properties, atomoxetine, cyproheptadine, and/or CYP 2D6/3A4/2B6 inhibitors/substrates; receiving concomitant or recent therapy with CBZ, OXC, ESL, phenobarbital, or PHT; positive urine test for THC or a positive whole blood test for cannabidiol at screening	Primary: • Change in mean monthly convulsive seizure frequency between fenfluramine 0.7 mg/kg/day and PBO relative to baseline Secondary: • Change in mean monthly convulsive seizure frequency between fenfluramine 0.2 mg/kg/day and PBO relative to baseline • Proportion of patients achieving 50% or greater reduction from baseline levels in mean monthly convulsive seizure frequency • Duration of the longest seizure-free interval • Safety

Results:

Primary:

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- Change in mean monthly convulsive seizure frequency between fenfluramine 0.7 mg/kg/day and PBO relative to baseline: Fenfluramine 0.7 mg/kg/day demonstrated a 62.3% greater reduction in mean monthly convulsive seizure frequency compared with PBO (95% CI, 47.7% to 72.8%; P<0.0001).

Secondary:

- Change in mean monthly convulsive seizure frequency between fenfluramine 0.2 mg/kg/day and PBO relative to baseline: Fenfluramine 0.2 mg/kg/day showing a 32.4% reduction in mean monthly convulsive seizure frequency compared with PBO (95% CI, 6.2% to 52.3%; P=0.0209).
- Proportion of patients achieving 50% or greater reduction from baseline levels in mean monthly convulsive seizure frequency: 68% of patients in the fenfluramine 0.7 mg/kg/day group (P<0.0001) and 38% of patients in the fenfluramine 0.2 mg/kg/day group (P=0.0091) had a reduction in convulsive seizure frequency of at least 50%, compared to 12% of patients in the PBO group.
- Duration of the longest seizure-free interval: Median longest seizure-free intervals were 25 days in the fenfluramine 0.7 mg/kg/day group (P<0.0001), 15 days in the fenfluramine 0.2 mg/kg/day group (P=0.0352), and 9.5 days in the PBO group.
- Safety: Most common adverse events (≥10% of patients and more frequently in the fenfluramine groups) were decreased appetite, diarrhea, fatigue, lethargy, somnolence, and decreased weight. Echocardiographic examinations revealed valve function within the normal physiological range in all patients during the trial and no signs of PAH.

Conclusion: In Dravet syndrome, fenfluramine provided significantly greater reduction in convulsive seizure frequency compared with PBO and was generally well tolerated, with no observed valvular heart disease or PAH.

Citation	Design	Endpoints
Detyniecki K, Van Ess PJ, Sequeira DJ, Wheless JW, Meng TC, Pullman W. Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters-a randomized, double-blind, placebo-controlled trial. Epilepsia. 2019 Sep;60(9):1797-1808. doi: 10.1111/epi.15159. Epub 2019 May 29.	Phase 3, randomized (2:1), double-blind, PBO-controlled trial N=292 Arms: Following an in-clinic test dose phase (TDP), patients entered an outpatient comparative phase (CP) and received double-blind MDZ–NS 5 mg or PBO nasal spray, administered by caregivers when they experienced an SC. The double-blind dose could be followed by an optional, open-label 5-mg MDZ–NS dose if the cluster did not terminate within 10 minutes, or another seizure occurred up to 6 hours after initial drug administration and the patient did not have <8 breaths/minute, did not require emergency rescue treatment and assisted breathing or intubation, and did not have excessive sedation. Inclusion criteria: Patients had to be on a stable regimen of AEDs; use of BZDs was allowed as rescue therapy, or for nonepilepsy indications, if used ≤3 days in a 7-day period, but not for maintenance therapy as an AED. Exclusion criteria: status epilepticus due to cluster progression within the prior 2 years; psychogenic nonepileptic seizure(s) within the prior 5 years; major depressive episode within the prior 6 months; suicidal ideation/attempts, nonpostictal psychosis, or drug or alcohol abuse 1 year before screening; acute narrow-angle glaucoma, or progressive neurologic or severe cardiorespiratory disease. Restrictions on concomitant	Primary: • Treatment success (seizure termination within 10 minutes and no recurrence 10 minutes to 6 hours after trial drug administration) Secondary: • Proportion of patients with seizure recurrence 10 minutes to 4 hours • Time-to-next seizure >10 minutes • Safety

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	medications included those with potential relevant pharmacokinetic (e.g., significant cytochrome P450 (CYP)3A4 inhibitors or inducers) or pharmacodynamic (e.g., opioids) interactions with MDZ.	

Results:

Primary:

- Treatment success: Among patients who received MDZ–NS, 53.7% (95% CI 45.3-62.2) experienced treatment success compared with 34.3% (23.0-45.7) who received PBO. The difference was statistically significant (P = 0.0069, one-sided Fisher's exact test; P = 0.0109, two-sided). Results of the sensitivity analysis based on PPP data were consistent with those of the mITT analysis, with a significantly greater proportion of MDZ–NS-treated patients achieving treatment success than PBO-treated patients (54.4% [45.7, 63.1] vs 32.8% [21.3, 44.3]; P = 0.0056, Fisher's exact test; P = 0.0049, chi-square test).

Secondary:

- Proportion of patients with seizure recurrence 10 minutes to 4 hours: A significantly smaller proportion of patients in the MDZ–NS group experienced seizure recurrence 10 minutes to 4 hours after drug administration than those in the PBO group (38.1% vs 59.7%; P = 0.0043, Fisher's exact test).
- Time-to-next seizure >10 minutes: Time-to-next seizure after double-blind drug administration was longer (P = 0.0124) in the MDZ–NS group than in the PBO group (25th percentile, 2.6 vs 0.9 hours); median time-to-next seizure could not be estimated since <50% of cluster episodes for which patients received a first MDZ–NS dose were followed by another seizure within 24 hours.
- Safety: Sixteen patients (5.5%) discontinued because of a TEAE during the TDP and none during the CP. During the CP, 27.6% and 22.4% of patients in the MDZ–NS and PBO groups, respectively, experienced ≥1 TEAE.

Conclusion: MDZ–NS was superior to PBO in providing rapid, sustained seizure control when administered to patients experiencing an SC in the outpatient setting and was associated with a favorable safety profile.

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Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Barbiturates								
pentobarbital sodium 50 mg/mL injection solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
phenobarbital 15 mg, 30 mg, 60 mg, 100 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
phenobarbital 16.2 mg, 32.4 mg, 64.8 mg, 97.2 mg tablet	2	1	$18.32	$9.16	0	0 (0%)	F	No change
phenobarbital 20 mg/5 mL (4 mg/mL) oral elixir	0	0	$0.00	$0.00	0	0 (0%)	F	No change
phenobarbital sodium 65 mg/mL, 130 mg/mL injection solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Sezaby® (phenobarbital sodium) 100 mg vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Benzodiazepines								
clobazam (Onfi®) 10 mg, 20 mg tablet	1	1	$35.77	$35.77	1	1 (100%)	NF	No change
clobazam (Onfi®) 2.5 mg/mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Sympazan™ (clobazam) 5 mg, 10 mg, 20 mg oral film	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
clonazepam (Klonopin®) 0.5 mg, 1 mg, 2 mg tablet	22	15	$30.05	$1.37	0	0 (0%)	F-QL (90/30)	No change
clonazepam 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg disintegrating tablet	0	0	$0.00	$0.00	0	0 (0%)	F-QL 90/30)	No change
clorazepate dipotassium 3.75 mg, 7.5 mg, 15 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
diazepam 2.5 mg, 10 mg, 20 mg rectal gel (2 pk)	0	0	$0.00	$0.00	0	0 (0%)	F-QL (2/365days)	No change
Libervant™ (diazepam) 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg buccal film	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Valtoco® (diazepam) 5 mg/spray (0.1 mL), 10 mg/spray (0.1 mL), 15 mg/2 spray(7.5mg/0.1mL x2), 20 mg/2 spray (10mg/0.1mL x2) nasal spray	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
lorazepam (Ativan®) 2 mg/mL, 4 mg/mL injection solution	0	0	$0.00	$0.00	0	0 (0%)	F-2mg/ml NF-4mg/ml	No change
Nayzilam® (midazolam) 5 mg/spray (0.1 mL) nasal spray	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydantoins								
Dilantin® (phenytoin) 30 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
phenytoin (Dilantin® Infatabs®) 50 mg chewable tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change

phenytoin sodium (Dilantin® Extended) extended 100 mg capsule	4	2	$129.50	$32.38	0	0 (0%)	F	No change
phenytoin (Dilantin-125®) 125 mg/5 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	F	No change
phenytoin sodium (Phenytek®) 200 mg, 300 mg capsule, extended release	0	0	$0.00	$0.00	0	0 (0%)	F	No change
phenytoin sodium 50 mg/mL intravenous solution, vial	0	0	$0.00	$0.00	0	0 (0%)	F	No change
fosphenytoin (Cerebyx®) 100 mg PE/2 mL, 500 mg PE/10 mL injection solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Succinimides								
methsuximide (Celontin®) 300 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
ethosuximide (Zarontin®) 250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
ethosuximide (Zarontin®) 250 mg/5 mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Miscellaneous								
gabapentin (Neurontin®) 100 mg, 300 mg, 400 mg capsule	164	128	$2,272.58	$13.86	0	0 (0%)	F	No change
gabapentin (Neurontin®) 600 mg, 800 mg tablet	47	29	$1,340.77	$28.53	0	0 (0%)	F	No change
gabapentin (Neurontin®) 250 mg/5 mL, 300 mg/6 mL oral solution	1	1	$283.15	$283.15	0	0 (0%)	F	No change
pregabalin (Lyrica®) 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg capsule	21	14	$370.96	$17.66	0	0 (0%)	F-QL (90/30)	No change
pregabalin (Lyrica®) 20 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
levetiracetam (Keppra®) 250 mg, 500 mg, 750 mg, 1000 mg tablet	16	11	$718.07	$44.88	0	0 (0%)	F	No change
levetiracetam (Keppra XR™) 500 mg, 750 mg tablet extended release 24 hr	1	1	$117.38	$117.38	0	0 (0%)	F-QL (120/30)	No change
Elepsia™ XR (levetiracetam) 1,000 mg, 1,500 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
levetiracetam (Keppra®) 100 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
levetiracetam 500 mg/5 mL (5 mL) oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-QL (900/30)	No change
levetiracetam (Keppra®) 500 mg/5 mL intravenous solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
levetiracetam 500 mg/100 mL, 1000 mg/100 mL, 1500 mg/100 mL in sodium chloride (iso-osm) IV piggyback	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Spritam® (levetiracetam) 250 mg, 500 mg, 750 mg, 1000 mg tablet for oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
lacosamide (Vimpat®) 50 mg, 100 mg, 150 mg, 200 mg tablet	5	4	$302.71	$60.54	2	1 (50%)	F-QL (60/30)	No change

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Vimpat® (lacosamide) 10 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
lacosamide (Vimpat®) 200 mg/20 mL intravenous solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
lacosamide 50 mg/5 mL cup	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Motpoly XR™ (lacosamide) 100 mg, 150 mg, 200 mg extended release capsules	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
divalproex (Depakote®) 125 mg, 250 mg, 500 mg tablet, delayed release	0	0	$0.00	$0.00	0	0 (0%)	F	No change
divalproex ER (Depakote® ER) 250 mg, 500 mg tablet,extended release 24 hr	4	3	$240.88	$60.22	0	0 (0%)	F	No change
divalproex (Depakote® Sprinkles) 125 mg capsule, delayed release sprinkle	0	0	$0.00	$0.00	0	0 (0%)	F	No change
valproic acid 250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
valproic acid (as sodium salt) 250 mg/5 mL (5 mL), 500 mg/10 mL (10 mL) oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-250mg/5ml NF- 500mg/10ml	No change
valproate sodium 500 mg/5 mL (100 mg/mL) intravenous solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
primidone (Mysoline®) 50 mg, 125 mg, 250 mg tablet	3	1	$62.37	$20.79	0	0 (0%)	F-50mg & 250mg NF- 125mg	No change
carbamazepine 100 mg, 200 mg chewable tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
carbamazepine (Tegretol®) 200 mg tablet	5	5	$833.99	$166.80	0	0 (0%)	F	No change
carbamazepine ER (Carbatrol®) 100 mg, 200 mg, 300 mg capsule, extended release mphase 12 hr	2	2	$866.20	$433.10	0	0 (0%)	F	No change
carbamazepine ER (Tegretol® XR) 100 mg, 200 mg, 400 mg tablet, extended release 12 hr	1	1	$15.52	$15.52	0	0 (0%)	F	No change
Equetro® (carbamazepine) 100 mg, 200 mg, 300 mg capsule, extended release	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
carbamazepine (Tegretol®) 100 mg/5 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	F	No change
oxcarbazepine (Trileptal®) 150 mg, 300 mg, 600 mg tablet	4	2	$127.14	$31.79	0	0 (0%)	F	No change
oxcarbazepine (Trileptal®) 300 mg/5 mL (60 mg/mL) oral suspension	0	0	$0.00	$0.00	0	0 (0%)	F	No change
oxcarbazepine (Oxtellar XR™) 150 mg, 300 mg, 600 mg tablet, extended release	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Aptiom® (eslicarbazepine acetate) 200 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
zonisamide (Zonegran®) 25 mg, 50 mg, 100 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F QL (180/30)	No change

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zonisamide (Zonegran®) 100 mg/5 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
lamotrigine (Lamictal®) 5 mg, 25 mg chewable dispersible tablet	0	0	$0.00	$0.00	0	0 (0%)	F-QL 5mg (150/30)	No change
lamotrigine (Lamictal®) 25 mg, 100 mg, 150 mg, 200 mg tablet	12	8	$83.31	$6.94	0	0 (0%)	F	No change
lamotrigine (Lamictal®) Starter (Blue) Kit 25 mg (35); (Green) Kit 25 mg (84)-100 mg (14); (Orange) Kit 25 mg (42)-100 mg (7) tablets in a dose pack	0	0	$0.00	$0.00	0	0 (0%)	F NF- 25 mg (84)-100 mg (14)	No change
lamotrigine (Lamictal® ODT) 25 mg, 50 mg, 100 mg, 200 mg disintegrating tablet	0	0	$0.00	$0.00	0	0 (0%)	F NF-200mg	No change
lamotrigine (Lamictal® ODT) Starter (Blue) 25 mg (21)-50 mg (7); (Green) 50 mg (42)-100 mg (14); (Orange) 25 mg(14)-50 mg(14)-100 mg(7) tablets, orally disintegrating	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
lamotrigine ER (Lamictal® XR) 25 mg, 50 mg, 100 mg, 200 mg, 250 mg, 300 mg tablet, extended release 24 hr	3	2	$448.60	$149.53	0	0 (0%)	F-PA	No change
Lamictal® XR (lamotrigine ER) Starter (Blue) 25 mg (21)-50 mg (7); (Green) 50 mg(14)-100 mg(14)-200 mg(7); (Orange) 25 mg(14)-50 mg(14)-100 mg(7) tablets, extend release	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
rufinamide (Banzel®) 200 mg, 400 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
rufinamide (Banzel®) 40 mg/mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Fycompa® (perampanel) 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Fycompa® (perampanel) 0.5 mg/mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
topiramate (Topamax®) 15 mg sprinkle capsule	0	0	$0.00	$0.00	1	0 (0%)	F-PA	No change
topiramate (Topamax®) 25 mg, 50 mg, 100 mg, 200 mg tablet	27	19	$247.07	$9.15	0	0 (0%)	F	No change
topiramate XR (Qudexy® XR) 25 mg, 50 mg, 100 mg, 150 mg, 200 mg capsule sprinkle, extended release 24 hr†	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
topiramate (Trokendi XR®) 25 mg, 50 mg, 100 mg, 200 mg capsule, extended release	4	1	$2,127.25	$531.81	1	1 (100%)	NF	No change
Eprontia® (topiramate) 25 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
tiagabine 2 mg, 4 mg, 12 mg, 16 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
felbamate (Felbatol®) 400 mg, 600 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
felbamate (Felbatol®) 600 mg/5 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Briviact® (brivaracetam) 10 mg, 25 mg, 50 mg, 75 mg, 100 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Briviact® (brivaracetam) 10 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change

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Briviact® (brivaracetam) 50 mg/5 mL intravenous solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Xcopri® (cenobamate) 25 mg, 50 mg, 100 mg, 150 mg, 200 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Xcopri® Titration Pack (cenobamate) 12.5 mg (14)-25 mg (14); 50 mg (14)-100 mg (14); 150 mg (14)-200 mg (14) tablets in a dose pack	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Xcopri® Maintenance Pack (cenobamate) 250 mg/day (200 mg x 1 and 50 mg x 1); 350 mg/day (200 mg x 1 and 150 mg x 1) tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
vigabatrin (Sabril®) 500 mg oral powder packet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
vigabatrin (Sabril®) 500 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
vigabatrin (Vigafyde®) 100 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Diacomit® (stiripentol) 250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diacomit® (stiripentol) 250 mg, 500 mg oral powder packet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Epidiolex® (cannabidiol) 100 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Fintepla® (fenfluarmine) 2.2 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Total	**349**	**251**	**$10,671.59**	**$30.58**	**5**	**3 (60%)**		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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Prior Authorization Criteria

Recommendation: No changes

Aptiom (eslicarbazepine)	
Therapeutic Classes (AHFS)	Anticonvulsants, miscellaneous
Medications	Formulary, PA required Aptiom (eslicarbazepine) tablet
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Member must be 4 years of age or older Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist or specialist in treatment of seizure disorders.
Coverage Duration	**Initial Approval** If the criteria are met, the initial request may be approved for up to a 6-month duration. **Reauthorization** Reauthorization requests may be approved for 12 months. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	Initial criteria for authorization: • Dose is within FDA approved limits • Diagnosis of partial onset seizures for monotherapy or adjunctive therapy • Documented trial and failure or intolerance to at least two formulary medications that are used to treat partial onset seizures as monotherapy or adjunctive therapy (e.g., carbamazepine, levetiracetam, phenytoin) Reauthorization criteria • Dose is within FDA approved limits • Documentation has been provided that demonstrates reduction or stabilization of seizure frequency
	Aptiom is reserved for members with partial onset seizures as monotherapy or adjunctive therapy who have used (or cannot/should not use) two other formulary

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	medications (e.g., carbamazepine, levetiracetam, phenytoin) used to treat this diagnosis.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: No changes

Lamotrigine ER	
Therapeutic Classes (AHFS)	Anticonvulsants, miscellaneous
Medications	Formulary, PA required Lamotrigine ER (Lamictal XR) tablets
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Lamotrigine ER is approved when the following criteria are met: • Documentation the patient having compliance issues using immediate release lamotrigine or is already stable on lamotrigine ER
Criteria Statement	Lamotrigine ER is reserved for members who are having compliance issues using immediate release lamotrigine or are already stable on lamotrigine ER.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: No changes

Rufinamide (Banzel)	
Therapeutic Classes (AHFS)	Anticonvulsants, Miscellaneous
Medications	Formulary, PA required • Rufinamide (Banzel) tablet • Rufinamide (Banzel) 40mg/ml suspension
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	None
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	Member must be ≥ 1 year old. Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	None.
Coverage Duration	**Initial/ Later Approval**: If all criteria are met, approve for up to a 12 month duration for up to 16 tablets/day of 200 mg and 8 tablets/day for 400 mg or the liquid equivalent. If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	CRITERIA FOR AUTHORIZATION • Diagnosis of Lennox-Gastaut syndrome AND • Member ≥ 1 years old AND • Patient is currently receiving another anticonvulsant medication at a therapeutic dosage and seizures are not controlled
Criteria Statement	Rufinamide (Banzel) tablets or liquid are reserved for patients at least 1 year of age, with a diagnosis of Lennox-Gastaut syndrome, and are already taking another anti-seizure medication at a therapeutic dose.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: No changes

Topiramate (Topamax) sprinkles	
Therapeutic Classes (AHFS)	ANTICONVULSANTS, MISCELLANEOUS
Medications	Formulary, Prior Authorization Required Topiramate (Topamax) sprinkles Non-Formulary Topiramate (Qudexy) XR sprinkle capsule
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	CRITERIA FOR AUTHORIZATION • Diagnosis of epilepsy or migraine prophylaxis AND • Documentation of inability to swallow generic topiramate tablets AND • For topiramate (Qudexy) XR sprinkle capsule, trial and failure or contraindication to use both topiramate tablets AND topiramate (Topamax) sprinkles
Criteria Statement	Topiramate (Topamax) sprinkles are reserved for members who have epilepsy or require migraine prophylaxis and cannot swallow topiramate tablets. Qudexy (topiramate) XR sprinkle capsules are reserved for members who have epilepsy or require migraine prophylaxis and cannot swallow topiramate tablets and who have used (or cannot/should use) topiramate (Topamax) sprinkles.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: No changes

Tiagabine (Gabitril)	
Therapeutic Classes (AHFS)	Anticonvulsants, Miscellaneous
Medications	Formulary, PA required • Tiagabine (Gabitril)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	None
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist or specialist in treatment of seizure disorders.
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	CRITERIA FOR AUTHORIZATION • Diagnosis of partial seizures AND • Seizures remain uncontrolled with adequate trial of one formulary oral antiepileptic medication AND • Documentation tiagabine will be used in combination with other anticonvulsants
Criteria Statement	Tiagabine (Gabitril) tablet is reserved for members who have a diagnosis of partial seizures and are still having seizures, despite taking another anti-seizure medication, and will take tiagabine (Gabitril) in combination with the other anti-seizure medication.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: No changes

vigabatrin (Sabril)	
Therapeutic Classes (AHFS)	Anticonvulsants, Miscellaneous
Medications	Formulary, PA required • Vigabatrin (Sabril) powder packet and vigabatrin (Sabril) tablet • Vigafyde (vigabatrin) oral solution
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	None
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist or specialist in treatment of seizure disorders.
Coverage Duration	**Initial Approval** 3 months **Later Approval** 12 months If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.

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PA Review Criteria	**Initial criteria:** Diagnosis of refractory complex partial seizures • Member is ≥ 2 years of age • Seizures remain uncontrolled with adequate trial of formulary oral antiepileptic medication • Documentation vigabatrin (Sabril) will be used in combination with other anticonvulsants Diagnosis of infantile spasms (powder for oral suspension or oral solution) • Member is age 1 month to 2 years • Vigabatrin (Sabril or Vigafyde) is being used as monotherapy **Reauthorization criteria:** • Documentation has been provided that demonstrates reduction or stabilization of seizure frequency • Dose and age are within FDA approved limits, per diagnosis
Criteria Statement	**Vigabatrin powder for oral suspension and Vigabatrin oral solution:** Vigabatrin (Sabril) powder for oral suspension and vigabatrin (Vigafyde) oral solution are reserved for members who are aged 1 month to 2 years who have a diagnosis of infantile spasms and are not on any other anti-seizure medications at the same time. **Vigabatrin (Sabril) tablet:** Vigabatrin (Sabril) tablet and vigabatrin (Sabril) powder for oral suspension are reserved for members who have a diagnosis of refractory complex partial seizures, who are at least 2 years of age, and are still having seizures, despite taking another anti-seizure medication, and will take vigabatrin (Sabril) in combination with the other anti-seizure medication.
Last P&T Review Date	~~12/2024~~6/2025

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Recommendation: No changes

Epidiolex (cannabidiol)	
Therapeutic Classes (AHFS)	Anticonvulsant – Cannabinoid type
Medications	Formulary, PA required Epidiolex (cannabidiol)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist or specialist in treatment of seizure disorders.
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Initial: • Clinical diagnosis of Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis complex • Documented trial and failure or intolerance to at least two antiepileptic drugs within the member's lifetime • Patient is currently taking a stable dose of at least one other antiepileptic medication • Member's weight • Dose is within FDA approved limits Reauthorization: • Documentation has been provided that demonstrates reduction or stabilization of seizure frequency • Member's weight • Dose is within FDA approved limits
Criteria Statement	Epidiolex is reserved for members who have Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis complex who have used (or cannot/should not use)

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Epidiolex (cannabidiol)	
	at least two antiepileptic drugs within the member's lifetime and are taking a stable dose of at least one other antiepileptic medication.
Last P&T Review Date	~~6/2024~~6/2025

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Glossary of Abbreviations

AAN=American Academy of Neurology
AED= antiepileptic drug
AES= American Epilepsy Society
AGEP=acute generalized exanthematous pustulosis
AHS=Alpers-Huttenlocher syndrome
BID=twice daily
BP=blood pressure
BRV=brivaracetam
BZD=benzodiazepine
CBD=cannabidiol
CBZ=carbamazepine
CI=confidence interval
CLB=clobazam
COPD=chronic obstructive pulmonary disease
CR=controlled-release
CV=cardiovascular
DF=dosage form
DM=diabetes mellitus
DRESS= drug reaction with eosinophilia and systemic symptoms (e.g. multiorgan hypersensitivity)
EN=each nostril
ER=extended-release
ESL=eslicarbazepine
ESRD=end stage renal disease
ETS=ethosuximide
FBM=felbamate
GBP=gabapentin
GE=generalized epilepsy
GTC=generalized tonic-clonic
HCP=healthcare professional
HF=heart failure
HLH=Hemophagocytic lymphohistiocytosis
HoTN=hypotension
HTN=hypertension
IOP=intraocular pressure
ILAE= International League Against Epilepsy
IM=intramuscular
IR=immediate-release
IV=intravenous
JME=juvenile myoclonic epilepsy
KD=ketogenic diet
LCM=lacosamide
LEV=levetiracetam
LGS=Lennox-Gastaut Syndrome
LPV/r=lopinavir/ritonavir
LTG=lamotrigine
MDZ=midazolam
MI=myocardial infarction
MAOI=monoamine-oxidase inhibitor
NCS=Neurocritical Care Society
NS=nasal spray
OXC=oxcarbazepine
PAH=pulmonary arterial hypertension
PBO=placebo
PEG=polyethylene glycol
PER=perampanel
PGB=pregabalin
PHT=phenytoin
POLG=polymerase gamma
POS=partial onset seizures
QD=once daily
QID=four times daily
QHS=at bedtime
REMS=Risk Evaluation and Mitigation Strategy
RFN=rufinamide
RSE=refractory status epilepticus
RTG=retigabine
SC=seizure cluster
SCARS=severe cutaneous adverse reactions
SQ=subcutaneously
SE=status epilepticus
SGTCS=secondarily generalized tonic-clonic seizures
SI=suicidal ideation
SIADH= syndrome of inappropriate antidiuretic hormone secretion
SJS=Stevens-Johnson syndrome
SLE=systemic lupus erythematous
TBI=traumatic brain injury
TEN= toxic epidermal necrolysis
TGB=tiagabine
THC=tetrahydrocannabinol
TID=three times daily
TPM=topiramate
TR=treatment resistant
TRAFE=treatment-resistant adult focal epilepsy
ULN=upper limit of normal
VGB=vigabatrin

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VNS=vagus nerve stimulation
VPA=valproic acid, valproate
WBC=white blood cell
WHO=World Health Organization
WOCBP=women of child-bearing potential
ZNS=zonisamide

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Contraceptives – Foams and Devices (abbreviated)

Executive Summary

Class Overview

This review covers contraceptive foams, films, gels, jellies, sponges and other devices including condoms and diaphragms. Phexxi™ (lactic acid, citric acid monohydrate, and potassium bitartrate) and all diaphragms are prescription-only products. The remaining products are available over-the-counter. All products reviewed herein are used to prevent pregnancy. Some (e.g. latex condoms) are also indicated to prevent the transmission of sexually transmitted infections.

Utilization Findings

There were no claims and no prior authorization requests.

Recommendations

- No changes

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Practice Guidelines

Centers for Disease Control and Prevention. (2016). US Medical Eligibility Criteria for Contraceptive Use, 2024. https://www.cdc.gov/contraception/hcp/usmec/index.html. Accessed on January 27, 2025.

The Centers for Disease Control and Prevention (CDC) published contraceptive guidance for healthcare providers in 2024. This guidance is referred to as the "US Medical Eligibility Criteria for Contraceptive Use (US MEC)" and comprises recommendations for the use of specific contraceptive methods by women and men who have certain characteristics or medical conditions. The choice of contraceptive agent (both hormonal and non-hormonal) should be made on a patient-specific basis. Please refer to CDC guidelines for more information.

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PERFORMRX℠

Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Diaphragms/Cervical Caps (Prescription-only)								
Caya® Contoured Diaphragm 60 mm - 85 mm vaginal insert	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Femcap™ Cervical Cap 22, 26, 30 mm vaginal insert	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Wide-Seal Diaphragm 60, 65, 70, 75, 80, 85, 90, 95 mm vaginal insert	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Omniflex Diaphragm 65 mm vaginal insert	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Condoms (Over-the-counter)								
Condoms, latex, non-lubricated (Trustex®, Kimono®)	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Condoms, latex, lubricated (Trustex®, Kimono®, Aimsco®, Durex®, Trojan®, Fantasy®)	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Condoms, non-latex, lubricated (Durex® Avanti)	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Condoms, female (FC2® Female Condom)	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Spermicides, Intravaginal (Over-the-counter)								
Encare (nonoxynol-9) 100 mg suppository	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Gynol II (nonoxynol-9) 3% gel	0	0	$0.00	$0.00	0	0 (0%)	F	No change
VCF® (nonoxynol-9) 28% vaginal film	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Nonoxynol-9 (VCF®) 4% Gel/PF Applicator	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Today Contraceptive Sponge® (nonoxynol-9) 1000 mg	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Other Contraceptives, Intravaginal (Prescription-only)								
Phexxi™ (lactic acid, citric acid monohydrate, and potassium bitartrate) 1.8 %-1 %-0.4 % vaginal gel	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Total	**0**	**0**	**$0.00**	**$0.00**	0	0 (0%)		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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1. Centers for Disease Control and Prevention. (2024). US Medical Eligibility Criteria for Contraceptive Use, 2024. https://www.cdc.gov/contraception/hcp/usmec/index.html. Accessed on January 27, 2025.

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Parkinson's Disease

Executive Summary

Class Overview

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by four cardinal features: tremors, bradykinesia, rigidity, and postural instability. PD is pathologically defined as a degeneration of dopaminergic neurons predominately concentrated in the substantia nigra. Dopamine is a critical neurotransmitter that aids in the regulation of smooth, coordinated body movement. As PD progresses and dopamine-producing neurons die, the dopamine concentration in the brain decreases resulting in a decline in motor and cognitive function as well as increased mortality. Accurate clinical diagnosis is difficult, especially in the early stages, as these motor symptoms are seen in other neurologic conditions (e.g. essential tremor, drug-induced Parkinsonism). PD is diagnosed more frequently in males, and it affects 1% of the population above 60 years. The progression of PD is variable and the future course for any given individual cannot be accurately predicted.

The American Academy of Neurology (AAN), International Parkinson and Movement Disorder Society (MDS), European Federation of Neurological Societies (EFNS), and National Institute for Health and Care Excellence (NICE) provide recommendations for the current treatment of early (uncomplicated) PD and late (complicated) PD. Levodopa is the most effective agent for motor symptoms, but as PD progresses, patients do not respond well resulting in the reappearance of Parkinsonism and other motor complications (i.e., dyskinesias, wearing-off). Carbidopa is used in combination to prevent breakdown of levodopa. Dopamine agonists (non-ergot preferred) can be used as first-line agents in early PD and late PD. Monoamine oxidase B (MAO-B) inhibitors are also considered first-choice option in early PD and an adjunct treatment option in late PD. Catechol-O-Methyltransferase (COMT) inhibitors should be used adjunctively in late PD to help treat motor fluctuations in patients taking levodopa. Anticholinergics can be used in both early and late PD but are restricted to younger patients with severe tremors since they are known to cause cognitive dysfunction in the elderly. Amantadine can be used in early and late PD for symptomatic treatment but is not a drug of choice due to lack of evidence.

Over the past few years, several newer options for managing motor fluctuations and dyskinesia in PD have hit the market. Inbrija® (levodopa oral inhalation) is indicated for the intermittent treatment of "off" episodes in patients with PD in addition to levodopa/carbidopa. It is the first inhaled therapy for patients experiencing "off" episodes for more than two hours per day. Nourianz® (istradefylline) is as adjunctive treatment to levodopa/carbidopa in adult patients with PD experiencing "off" episodes. This is the first adenosine A_{2A} receptor antagonist approved in the United States and is a novel non-dopaminergic pharmacologic approach to treating the "off" episodes associated with PD. Finally, in 2024, a new extended-release (ER) formulation of carbidopa/levodopa called Crexont® became available, as did the first subcutaneous continuous infusion of levodopa-based therapy, called Vyalev™ (foscarbidopa/foslevodopa).

Utilization Findings

There were 12 claims for 9 members, for a total cost of $630.67 and an average cost per claim of $52.56. The most highly utilized medication was carbidopa/levodopa tablets, with 4 claims, followed by ropinirole tablets with 2 claims. There were no prior authorization requests.

Recommendations

- No changes

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Clinical Summary

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by four cardinal features: tremors, bradykinesia, rigidity, and postural instability. PD is pathologically defined as a degeneration of dopaminergic neurons predominately concentrated in the substantia nigra. Dopamine is a critical neurotransmitter that aids in the regulation of smooth, coordinated body movement. As PD progresses and dopamine-producing neurons die, the dopamine concentration in the brain decreases resulting in a decline in motor and cognitive function as well as increased mortality. Accurate clinical diagnosis is difficult, especially in the early stages, as these motor symptoms are seen in other neurologic conditions (e.g. essential tremor, drug-induced Parkinsonism). In addition to the typical motor symptoms, patients can also experience nonmotor complications in the form of neuropsychiatric manifestations (e.g. cognitive dysfunction, depression, sleep disorders). Currently, no diagnostic tests have been developed to distinguish PD from other conditions and remains a clinical diagnosis based on the ability to recognize the key signs/symptoms. At a minimum, bradykinesia with either tremor or rigidity must be present. PD is diagnosed more frequently in males, and it affects 1% of the population above 60 years. The progression of PD is variable and the future course for any given individual cannot be accurately predicted. Many studies have suggested that the risk of mortality is slightly increased for patients with PD.

The American Academy of Neurology (AAN), International Parkinson and Movement Disorder Society (MDS), European Federation of Neurological Societies (EFNS), and National Institute for Health and Care Excellence (NICE) provide recommendations for the current treatment of early (uncomplicated) PD and late (complicated) PD. Patients with early PD typically have the disease for less than 5 years or they have not developed motor complications from levodopa. Late-stage PD includes patients already receiving carbidopa/levodopa who have motor complications. Multiple guidelines have a general agreement on overall treatment of PD, but they all emphasize that it is not possible to identify a single, universal first-choice drug therapy for patients with early PD or a first-choice adjuvant therapy for people with later PD. The choice of therapy must be individualized for each patient. Clinicians must consider patient symptoms, age, needs, expectations, comorbidities, and past medication experience. The main goals for symptomatic treatment are to provide symptom control while minimizing adverse effects.

Levodopa is the most effective agent for motor symptoms, but as PD progresses, patients do not respond well resulting in the reappearance of Parkinsonism and other motor complications (i.e., dyskinesias, wearing-off). Carbidopa is used in combination to prevent breakdown of levodopa. Dopamine agonists (non-ergot preferred) can be used as first-line agents in early PD and late PD. MAO-B inhibitors are also considered a first-choice option in early PD and an adjunct treatment option in late PD. COMT inhibitors should be used adjunctively in late PD to help treat motor fluctuations in patients taking levodopa. Anticholinergics can be used in both early and late PD but are restricted to younger patients with severe tremors since they are known to cause cognitive dysfunction in the elderly. Amantadine can be used in early and late PD for symptomatic treatment but is not a drug of choice due to lack of evidence.

Over the past few years, several newer options for managing motor fluctuations and dyskinesia in PD have hit the market. Inbrija® (levodopa oral inhalation) is indicated for the intermittent treatment of "off" episodes in patients with PD in addition to levodopa/carbidopa. It is the first inhaled therapy for patients experiencing "off" episodes for more than two hours per day. Oral levodopa is combined with a peripheral decarboxylase inhibitor to block its conversion to dopamine before crossing the blood-brain barrier. Inhaled levodopa mitigates the necessity of this drug combination as it will readily cross the blood-brain barrier. Currently, apomorphine (Apokyn®) and Duopa® (carbidopa/levodopa

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continuous gel infusion via J-peg tube) are also available for this indication but do not have the ease of use that comes with using an inhaler. Along with reported efficacy, studies showed good safety as inhaled levodopa has no observable impact on lung function compared to placebo.

Nourianz® (istradefylline) is as adjunctive treatment to levodopa/carbidopa in adult patients with PD experiencing “off” episodes. It is the first adenosine A2A receptor antagonist approved in the US and is a novel non-dopaminergic pharmacologic approach to treating the “off” episodes associated with PD. The existing oral therapies used for the same indication include COMT inhibitors, MAO-B inhibitors, and dopamine agonists. A new COMT inhibitor, Ongentys® (opicapone), was approved in 2020 as an adjunct to levodopa/carbidopa in patients with PD experiencing “off” episodes. When compared with entacapone, another COMT inhibitor, Ongentys® was found to be non-inferior at reducing mean daily “off” time. While entacapone may remain as the preferred COMT inhibitor, due it being available generically and as a combination preparation with carbidopa/levodopa; Ongentys® has the advantage of less frequent dosing, as it is only dosed once daily, whereas entacapone has to be taken as many as 8 times a day.

Finally, in 2024, two new treatments for PD became available. Crexont® (carbidopa/levodopa) is a new ER formulation of carbidopa/levodopa that was found to have a statistically significant improvement in “good on” time compared to immediate-release (IR) carbidopa/levodopa, while being dosed less frequently. Vyalev™ (foscarbidopa/foslevodopa) is the first subcutaneous continuous infusion of levodopa-based therapy. It is a soluble formulation of foscarbidopa and foslevodopa, which are prodrug versions of levodopa and carbidopa. Vyalev™ is only indicated to be used in the advanced PD setting, which is estimated to be around 1-3% of the PD population. Vyalev™ allows for personalized dosing based on individual needs throughout the day, and given its route of administration, it may serve as a bridge for patients with advanced PD who are no longer adequately controlled with oral medications but whose PD is not advanced enough to warrant deep brain stimulation.

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Indications, Dosing and Administration

Medication	Indications	Dosing/Administration
Decarboxylase Inhibitors		
Carbidopa (Lodosyn®)	For use with carbidopa-levodopa or with levodopa in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism, which may follow injury to the nervous system by carbon monoxide intoxication and/or manganese intoxication	Whether given with carbidopa-levodopa or with levodopa, the optimal daily dose of carbidopa must be determined by careful titration. Most patients respond to a 1:10 proportion of carbidopa and levodopa, provided the daily dosage of carbidopa is 70 mg or more a day. The maximum daily dosage of carbidopa should not exceed 200 mg.
Dopamine Replacement		
Carbidopa/Levodopa (Sinemet®, Dhivy®)	Treatment of Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	The optimum daily dosage must be determined by careful titration in each patient. The tablets are available in a 1:4 ratio of carbidopa to levodopa as well as 1:10 ratio Tablets of the two ratios may be given separately or combined as needed to provide the optimum dosage. Initial: 12.5 mg/50 mg or 25 mg/100 mg orally 2 to 3 times daily; may increase daily dose by 1 tablet of 25 mg/100 mg every 1 to 2 days For patients who require higher doses of levodopa for symptom control, titrating with a tablet that has a carbidopa: levodopa ratio of 1:10 may allow for better symptom control without exceeding the usual maximum dosage of carbidopa. Usual max daily dose: carbidopa 200 mg/day and levodopa 2 g/day; dosing frequency ≥4 times daily may be required
Carbidopa/Levodopa ER		50 mg/200 mg orally twice daily, at intervals not <6 hours; may adjust dose no faster than every 3 days to a maximum dose of levodopa 2.4 g/day
Rytary® (carbidopa/levodopa ER)		23.75 mg/95 mg orally 3 times daily for 3 days; on day 4, may increase to 36.25 mg/145 mg 3 times daily. May increase dose further based on response and tolerability in levodopa 50 mg increments at intervals ≥1 week up to 97.5 mg/390 mg 3 times daily. Frequency of dosing may be increased to a maximum of 5 times daily if needed and tolerated (maximum:612.5 mg/2.45 g per day).

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Medication	Indications	Dosing/Administration
Crexont® (carbidopa/levodopa ER)	Treatment of motor fluctuations in patients with advanced Parkinson's disease	35 mg/140 mg twice daily for 3 days; may increase dose gradually up to a maximum of 525 mg/2.1 g per day, in up to 4 divided doses
Duopa™ (carbidopa/levodopa)		Prior to initiation, convert patients from all forms of levodopa to oral IR carbidopa/levodopa tablets (1:4 ratio). Titrate total daily dose based on clinical response for the patient. Administer into the jejunum through a percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Maximum daily dose is levodopa 2 g administered over 16 hours.
Vyalev™ (foscarbidopa/foslevodopa)		Administered as a subcutaneous infusion based on total levodopa dosage (TLD). The hourly base continuous infusion rate (mL/hr) = [(TLD x 1.3)/240] / [number of hours the patient is typically awake (e.g., 16 hours). Adjust the hourly infusion rate based on response and tolerability in increments of 0.01 mL/hour (foslevodopa 2.4 mg/hour, equivalent to levodopa ~1.7 mg/hour). Max dose is 14.69 mL/day (foslevodopa 3.525 g/day, equivalent to levodopa ~2.5 g/day).
Inbrija® (levodopa)	Intermittent treatment of "off" episodes in patients with Parkinson's disease treated with carbidopa/levodopa	84 mg inhaled up to 5 times daily as needed when symptoms of an "off" period return; maximum: 84 mg/dose and 420 mg/day
Dopamine Agonists		
Ropinirole	Treatment of Parkinson's disease Treatment of moderate-to-severe primary restless legs syndrome (*IR tablets only*)	Initial: 0.25 mg orally 3 times daily; may increase daily dose based on response and tolerability: • For doses up to 3 mg/day, may increase daily dose by 0.75 mg every 7 days • For doses from 3 to 9 mg/day, may increase daily dose by 1.5 mg every 7 days • For doses >9 mg/day, may increase daily dose by 3 mg every 7 days Max dose: 24 mg/day in 3 divided doses
Ropinirole ER		Initial: 2 mg orally once daily for 1 to 2 weeks, may increase daily dose by 2 mg at weekly or longer intervals based on response and tolerability. Max dose: 24 mg/day

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Medication	Indications	Dosing/Administration
Bromocriptine (Parlodel®)	Treatment of the signs and symptoms of idiopathic or post-encephalitic Parkinson disease; as adjunctive treatment to levodopa (alone or with a peripheral decarboxylase inhibitor) Treatment of prolactin-secreting pituitary adenoma or disorders associated with hyperprolactinemia including amenorrhea with or without galactorrhea, hypogonadism, or infertility Neuroleptic malignant syndrome (*off-label*)	1.25 mg orally twice daily, increased by 2.5 mg daily in 2- to 4-week intervals as needed (max: 100 mg/day)
Pramipexole	Treatment of Parkinson's disease Treatment of moderate-to-severe primary restless legs syndrome (*IR tablets only*)	0.125 mg orally 3 times daily, increase gradually every 5 to 7 days based on response and tolerability up to 4.5 mg/day
Pramipexole ER		0.375 mg orally once daily, increase by 0.375 mg every 5 to 7 days based on response and tolerability; max: 4.5 mg/day
Apomorphine (Apokyn®)	Treatment of hypomobility, "off" episodes in patients with Parkinson disease	Starting dose is 0.1 ml (1 mg) to 0.2 mL (2 mg). Give the first dose under medical supervision. Titrate the dose to effect and tolerance; the maximum recommended dose is 0.6 mL (6 mg). Treatment with a concomitant antiemetic, is recommended, beginning 3 days prior to the initial dose.
Neupro® (rotigotine)	Treatment of Parkinson's disease Treatment of moderate-to-severe primary restless legs syndrome	Early-stage: 2 mg/24 hours patch applied topically once daily, may increase by 2 mg/24 hours weekly based on clinical response and tolerability. Max: 6 mg/24 hours according to the prescribing information; higher doses (8 mg/24 hours) have been studied in clinical trials. Advanced-stage: 4 mg/24 hours patch applied topically once daily, may increase by 2 mg/24 hours weekly based on clinical response and tolerability. Max: 8 mg/24 hours; in clinical trials maximum doses up to 16 mg/24 hours were used.
MAO-B Inhibitors		
Selegiline	Adjunct in the management of patients with Parkinson's disease being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy	5 mg orally twice daily with breakfast and lunch with concomitant carbidopa/levodopa therapy; max: 10 mg/day
Zelapar® ODT (selegiline)		1.25 mg orally once daily with concomitant carbidopa/levodopa therapy for at least 6

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Medication	Indications	Dosing/Administration
		weeks; may increase to 2.5 mg once daily based on clinical response and tolerability; max: 2.5 mg/day
Rasagiline (Azilect®)	Treatment of Parkinson's disease	Monotherapy or adjunctive (not including levodopa): 1 mg orally once daily (max: 1mg/day) Adjunctive with levodopa: 0.5 mg orally once daily; may increase to 1 mg once daily based on response and tolerability (max: 1 mg/day)
Xadago® (safinamide)	Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes	50 mg orally once daily; after 2 weeks may increase to 100 mg once daily based on response and tolerability
COMT Inhibitors		
Entacapone	Adjunct to levodopa/carbidopa therapy in patients with idiopathic Parkinson's Disease who experience the signs and symptoms of end-of-dose "wearing-off"	200 mg orally with each dose of levodopa/carbidopa, up to a maximum of 8 times daily (max daily dose: 1600 mg)
Tolcapone (Tasmar®)	Adjunct to levodopa and carbidopa for the treatment of signs and symptoms of idiopathic Parkinson disease in patients with motor fluctuations not responsive to other therapies	100 mg orally 3 times daily as an adjunct to levodopa/carbidopa; may increase as tolerated to 200 mg 3 times daily only if clinical benefit is justified (dosage associated with an increased incidence of alanine aminotransferase [ALT] elevations)
Ongentys® (opicapone)	Adjunct levodopa/carbidopa in patients with Parkinson disease experiencing "off" episodes	50 mg orally once daily at bedtime
Dopamine Replacement/COMT Inhibitor Combination		
Carbidopa/Levodopa/Entacapone	Treatment of Parkinson disease	Dose should be individualized based on therapeutic response; doses may be adjusted by changing strength or adjusting interval. Fractionated doses are not recommended and only 1 tablet should be given at each dosing interval. Max daily dose: 8 tablets of 50 mg, 75 mg, 100 mg, 125 mg, or 150 mg levodopa, or 6 tablets of 200 mg levodopa.
Anticholinergic		
Benztropine	Adjunctive therapy of all forms of parkinsonism Acute treatment drug-induced extrapyramidal symptoms (excluding tardive dyskinesia)	Initial: 1 mg/day in 2 to 4 divided doses; may titrate in increments of 0.5 mg/day at intervals of ≥5 days based on response and tolerability to 4 mg/day; max: 6 mg/day

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Medication	Indications	Dosing/Administration
Trihexyphenidyl	Adjunct in the treatment of all forms of parkinsonism (post-encephalitic, arteriosclerotic, and idiopathic For the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes, and butyrophenones.	Initial: 1 mg/day orally; increase by 2 mg increments at intervals of 3 to 5 days Usual maintenance dose: 6 to 10 mg/day in 3 to 4 divided doses; doses of 12 to 15 mg/day may be required. Consider dosage reduction when used concomitantly with levodopa (usual range: 3 to 6 mg/day in divided doses).
Other		
Amantadine	Treatment of idiopathic Parkinson disease (paralysis agitans), postencephalitic parkinsonism, parkinsonism in association with cerebral arteriosclerosis, and symptomatic parkinsonism, which may follow injury to the nervous system by carbon monoxide intoxication Treatment of drug-induced parkinsonism Multiple sclerosis–related fatigue (*off-label*)	100 mg orally twice daily; after 1 week may increase based on response and tolerability to usual maximum dose of 300 mg/day in divided doses; some patients with dyskinesias may require up to 400 mg/day in 2 to 4 divided doses
Gocovri® (Amantadine)	Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications Treatment of "off" episodes in patients with Parkinson disease receiving levodopa/carbidopa	137 mg orally once daily; after 1 week, increase to usual dose of 274 mg once daily
Nourianz® (Istradefylline)	Adjunctive treatment to levodopa/carbidopa in adult patients with Parkinson's disease experiencing "off" episodes	20 mg orally once daily; may further increase dose based on response and tolerability to a maximum dose of 40 mg once daily

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Boxed Warnings and Contraindications

Medication	Boxed Warnings	Contraindications
Decarboxylase Inhibitors		
Carbidopa (Lodosyn®)	None	Use of nonselective MAO inhibitor therapy with or within prior 14 days (however, may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B); narrow-angle glaucoma
Dopamine Replacement		
Carbidopa/Levodopa (Sinemet®, Dhivy®) Carbidopa/Levodopa ER Rytary® (Carbidopa/Levodopa ER) Crexont® (carbidopa/levodopa) Duopa™ (carbidopa/levodopa)	None	Concurrent use or within 14 days of nonselective MAO inhibitor use; narrow angle glaucoma (*tablets only*)
Vyalev™ (foscarbidopa/foslevodopa)		Concurrent use or within 14 days of nonselective MAO inhibitor use
Inbrija® (levodopa)		
Dopamine Agonists		
Ropinirole	None	None
Bromocriptine (Parlodel®)		Hypersensitivity to ergot alkaloids; uncontrolled hypertension; pregnancy; postpartum women with a history of coronary artery disease or other severe cardiovascular conditions (unless withdrawal of medication is medically contraindicated)
Pramipexole		None
Apomorphine (Apokyn®)		Hypersensitivity to a sulfite; concomitant use with 5-HT3 antagonists
Neupro® (rotigotine)		None
MAO-B Inhibitors		
Selegiline Zelapar® ODT (selegiline)	None	Concomitant use of meperidine Additional contraindications (*Zelapar® ODT only*): Concomitant use of methadone, other MAO inhibitors (selective or non-selective), propoxyphene, or tramadol within 14 days of selegiline; concomitant use with cyclobenzaprine, dextromethorphan, or St John's wort
Rasagiline (Azilect®)		Concomitant use of an MAO inhibitor (including selective MAO-B inhibitors), meperidine, methadone, propoxyphene, or

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Medication	Boxed Warnings	Contraindications
		tramadol within 14 days of rasagiline; concomitant use with cyclobenzaprine, dextromethorphan, or St John's wort
Xadago® (safinamide)		Severe hepatic impairment (Child-Pugh class C); concomitant use of methylphenidate, amphetamine, and their derivatives, or dextromethorphan; concomitant use with or within 2 weeks of other monoamine oxidase inhibitors or other drugs that are potent inhibitors of monoamine oxidase (including linezolid), opioids (e.g., meperidine, methadone, propoxyphene, tramadol), serotonin-norepinephrine reuptake inhibitors, tricyclic, tetracyclic, or triazolopyridine antidepressants, cyclobenzaprine, St John's wort
COMT Inhibitors		
Entacapone	None	None
Tolcapone (Tasmar®)	Hepatotoxicity	Patients with liver disease or a history of tolcapone-induced hepatocellular injury; history of non-traumatic rhabdomyolysis or hyperpyrexia and confusion potentially related to medication
Ongentys® (opicapone)	None	Concomitant use of nonselective MAO inhibitors; pheochromocytoma, paraganglioma, or other catecholamine secreting neoplasms
Dopamine Replacement/COMT Inhibitor Combination		
Carbidopa/Levodopa/Entacapone	None	Use of nonselective MAO inhibitor therapy with or within 14 prior days; narrow-angle glaucoma
Anticholinergics		
Benztropine	None	Children <3 years of age (due to atropine-like adverse effects including severe anhidrosis and fatal hyperthermia) and should be used cautiously in older children
Trihexyphenidyl		Narrow angle glaucoma
Other		
Amantadine Gocovri® (Amantadine)	None	End-stage renal disease (CrCl <15 mL/minute/1.73 m^2) (*Gocovri® only*)
Nourianz® (Istradefylline)		None

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Warnings/Precautions

Medication	Warnings/Precautions
Decarboxylase Inhibitors	
Carbidopa (Lodosyn®)	**Concerns related to adverse effects:** Depression, dyskinesia, impulse control disorders (ICDs), psychotic effects, somnolence **Disease-related concerns:** Psychotic disorders
Dopamine Replacement	
Carbidopa/Levodopa (Sinemet®, Dhivy®) Carbidopa/Levodopa ER Rytary® (Carbidopa/Levodopa ER) Crexont® (carbidopa/levodopa) Duopa™ (carbidopa/levodopa)	**Concerns related to adverse effects:** Somnolence **Disease-related concerns:** Cardiovascular disease, endocrine disease, glaucoma, hepatic impairment, peptic ulcer disease, renal impairment, respiratory disease **Special populations**: Elderly **Dosage forms specific issues:** Gastrointestinal complications (Duopa® only) **Other warnings/precautions:** Body fluid discoloration, dietary protein
Vyalev™ (foscarbidopa/foslevodopa)	**Concerns related to adverse effects:** Dyskinesias, hallucinations, ICDs, infusion-site reactions, melanoma, polyneuropathy, somnolence, neuroleptic malignant syndrome **Disease-related concerns:** Cardiovascular disease, glaucoma, psychiatric disorders **Other warnings/precautions:** Discontinuation of therapy
Inbrija® (levodopa)	**Concerns related to adverse effects:** Abnormal thinking/behavior changes, central nervous system (CNS) depression, dyskinesia, hallucinations, ICDs, neuroleptic malignant syndrome **Disease-related concerns:** Glaucoma, psychotic disorders, respiratory disease **Other warnings/precautions:** Body fluid discoloration, discontinuation of therapy
Dopamine Agonists	
Ropinirole	**Concerns related to adverse effects:** Dyskinesias, pleural/retroperitoneal fibrosis, retinal changes **Disease-related concerns:** Cardiovascular disease, hepatic impairment, psychotic disorder renal impairment **Dosage forms specific issues:** Extended-release ropinirole is designed to release medication over a 24-hour period. If rapid gastrointestinal transit occurs, there may be risk of incomplete release of medication and medication residue being passed in the stool.
Bromocriptine (Parlodel®)	**Concerns related to adverse effects:** Cardiac valvular fibrosis, cardiovascular effects, CNS depression, hallucinations, ICDs, pleural/retroperitoneal fibrosis **Disease-related concerns:** Cardiovascular disease, dementia, galactose intolerance/malabsorption, macroadenomas, hepatic impairment, peptic ulcer disease, prolactin-secreting adenomas, psychosis **Other warnings/precautions:** Discontinuation of therapy, visual monitoring
Pramipexole	**Concerns related to adverse effects:** Dyskinesia, postural deformity, **Disease-related concerns:** Psychotic disorder, renal impairment **Dosage forms specific issues**: Tablet residue resembling a swollen whole or partial tablet may be visible in the stool after taking the extended-release formulation. Some patients reported a worsening of their Parkinson disease symptoms when tablet residue was observed.
Apomorphine (Apokyn®)	**Concerns related to adverse effects:** Gastrointestinal effects, hallucinations/psychosis, hemolytic anemia, hypersensitivity, ICDs, orthostatic hypotension/syncope, pleural retroperitoneal fibrosis, priapism, somnolence **Disease-related concerns:** Cardiovascular disease, cerebrovascular disease, dyskinesia, hepatic impairment, renal impairment

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Medication	Warnings/Precautions
	Special populations: Elderly, patients at risk of torsades de pointes **Dosage forms specific issues:** May contain benzyl alcohol which has been associated with "gasping syndrome" in neonates; contains metabisulfite **Other warnings/precautions:** Abuse (rare), appropriate administration, discontinuation of therapy, falls risk
Neupro® (rotigotine)	**Concerns related to adverse effects:** Application site reactions, fibrosis, fluid retention, hallucinations/psychosis, ICDs, orthostatic hypotension, somnolence **Disease-related concerns:** Cardiovascular disease, dyskinesia **Special populations:** Restless leg syndrome **Dosage forms specific issues:** Aluminum, heat application, sulfites **Other warnings/precautions:** Discontinuation of therapy
MAO-B Inhibitors	
Selegiline Zelapar® ODT (selegiline)	**Concerns related to adverse effects:** Blood pressure effects, CNS depression, dyskinesia, ICDs, psychosis, serotonin syndrome **Disease-related concerns**: Hepatic impairment, mania/hypomania, renal impairment **Special populations:** Surgical patients **Concurrent drug therapy concerns:** Drug-drug interactions **Dosage forms specific issues:** Zelapar® ODT may cause irritation of buccal mucosa including swelling pain, mouth pain, discrete areas of focal reddening, multiple foci of reddening, edema, and/or ulceration); Zelapar® ODT may contain phenylalanine, use caution in patients with phenylketonuria **Other warnings/precautions:** Antiparkinsonism discontinuation syndrome, tyramine containing products
Rasagiline (Azilect®)	**Concerns related to adverse effects:** CNS effects, dyskinesia, ICDs, hypertension, melanoma, orthostatic hypotension, serotonin syndrome, somnolence **Disease-related concerns:** Hepatic impairment, psychotic disorders **Special populations:** Surgical patients **Other warnings/precautions:** Antiparkinsonism discontinuation syndrome, tyramine containing products
Xadago® (safinamide)	**Concerns related to adverse effects:** CNS depression, dyskinesia, hypertension, ICDs, serotonin syndrome **Disease-related concerns:** Hepatic impairment, psychotic disorder, ophthalmic disorder **Other warnings/precautions:** Parkinsonism-hyperpyrexia syndrome, tyramine containing products
COMT Inhibitors	
Entacapone	**Concerns related to adverse effects**: Abnormal thinking/behavioral changes, diarrhea, dyskinesia, hallucinations, ICDs, melanoma, neuroleptic malignant syndrome, orthostatic hypotension, pleural/retroperitoneal fibrosis, rhabdomyolysis, somnolence **Disease-related concerns:** Cardiovascular disease, hepatic impairment, psychotic disorders **Concurrent drug therapy concerns:** Sedatives **Other warnings/precautions:** Discontinuation of therapy, urine discoloration
Tolcapone (Tasmar®)	**Concerns related to adverse effects:** CNS depression, diarrhea, hepatotoxicity (boxed warning), ICDs, orthostatic hypotension, pleural/retroperitoneal fibrosis, psychiatric effects **Disease-related concerns:** Dyskinesia/dystonia, psychotic disorders, renal impairment **Other warnings/precautions:** Discontinuation of therapy
Ongentys® (opicapone)	**Disease-related concerns:** Hepatic impairment, renal impairment

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Medication	Warnings/Precautions
	Other warnings/precautions: Discontinuation of therapy
Dopamine Replacement/COMT Inhibitor Combination	
Carbidopa/Levodopa/Entacapone	**Concerns related to adverse effects:** Diarrhea, dyskinesia, hallucinations, ICDs, melanoma, neuroleptic malignant syndrome, orthostatic hypotension, pleural/retroperitoneal fibrosis, rhabdomyolysis, somnolence **Disease-related concerns:** Endocrine disease, glaucoma, hepatic impairment, peptic ulcer disease, psychotic disorders, renal impairment **Special populations:** Elderly **Dosage forms specific issues:** Sucrose **Other warnings/precautions:** Discontinuation of therapy, body fluid discoloration
Anticholinergics	
Benztropine	**Concerns related to adverse effects:** Muscle weakness **Disease-related concerns:** Cardiovascular disease, gastrointestinal obstruction, glaucoma, prostatic hyperplasia/urinary stricture **Special populations:** Pediatric **Other warnings/precautions:** Tardive dyskinesia
Trihexyphenidyl	**Concerns related to adverse effects:** Anhidrosis/hyperthermia, anticholinergic effects, CNS depression, ocular effects **Disease-related concerns:** Cardiovascular disease, gastrointestinal obstruction, glaucoma, hepatic impairment, prostatic hyperplasia/urinary stricture, psychiatric effects, renal impairment, tardive dyskinesia **Other warnings/precautions:** Discontinuation of therapy
Other	
Amantadine Gocovri® (amantadine)	**Concerns related to adverse effects:** CNS depression, melanoma, suicidal ideation/depression **Disease-related concerns:** Cardiovascular disease, eczema, glaucoma, hepatic impairment, psychotic disorder, renal impairment, seizure disorder **Special populations:** Elderly **Dosage form specific issues:** Propylene glycol **Other warnings/precautions:** Tolerance
Nourianz® (Istradefylline)	**Concerns related to adverse effects:** Dyskinesias, ICDs, psychotic effects **Disease-related concerns:** Hepatic impairment **Special populations:** Tobacco smoker

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Practice Guidelines

Pringsheim T, Day GS, Smith DB, et al. Dopaminergic therapy for motor symptoms in early parkinson disease practice guideline summary: a report of the American Academy of Neurology (AAN) guideline subcommittee. Neurology. 2021;97(20):942-957.

- Levodopa vs. Dopamine Agonists vs. MAO-B Inhibitors
    - Clinicians should counsel patients with early PD on the benefits and risks of initial therapy with levodopa, dopamine agonists, and MAO-B inhibitors based on the individual patient's disease characteristics to inform treatment decisions. (Level B)
    - In patients with early PD who seek treatment for motor symptoms, clinicians should recommend levodopa as the initial preferential dopaminergic therapy. (Level B)
    - Clinicians may prescribe dopamine agonists as the initial dopaminergic therapy to improve motor symptoms in select early PD patients <60 years who are at higher risk for the development of dyskinesia. (Level C)
    - Clinicians should not prescribe dopamine agonists to patients with early-stage PD at higher risk of medication-related adverse effects, including individuals >70 years, patients with a history of ICDs, and patients with preexisting cognitive impairment, excessive daytime sleepiness (EDS), or hallucinations. (Level B)
- Prescribing Levodopa
    - Clinicians should initially prescribe IR levodopa rather than controlled release (CR) levodopa or levodopa/carbidopa/entacapone in patients with early PD. (Level B)
    - In patients with early PD, clinicians should prescribe the lowest effective dose of levodopa (i.e., the lowest dose that provides adequate symptomatic benefit) to minimize the risk of dyskinesia and other adverse effects. (Level B)
    - Clinicians should routinely monitor patients taking levodopa for their motor response to treatment and for the presence of dyskinesia, motor fluctuations, ICDs, EDS, postural hypotension, nausea, and hallucinations, to guide dosage titration over time. (Level B)
    - Clinicians should counsel patients taking levodopa that higher dosages are more likely to cause dyskinesia. (Level B)
    - Clinicians should counsel patients that in later disease stages, taking levodopa with meals may affect levodopa absorption and efficacy, but this is usually not problematic at the time of levodopa initiation in early PD. (Level B)
- Prescribing Dopamine Agonists
    - Clinicians should integrate patient preferences concerning formulation, mode of administration, and cost when prescribing a dopamine agonist. (Level B)
    - Clinicians should prescribe the lowest dose of dopamine agonist required to provide therapeutic benefit. (Level B)
- Tapering and Discontinuing Dopamine Agonists)
    - Clinicians should recommend tapering or discontinuation of dopamine agonists if patients experience disabling medication-related adverse effects, including ICDs, EDS, sudden-onset sleep, cognitive impairment, or hallucinations. (Level B)

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- When dopamine agonists must be discontinued due to adverse effects, clinicians should monitor patients for symptoms of dopamine agonist withdrawal syndrome and, when possible, gradually decrease the dosage to minimize symptoms. (Level B)

- Prescribing MAO-B Inhibitors
  - Clinicians should counsel patients with early PD on the greater motor benefits of initial therapy with levodopa compared with MAO-B inhibitors to inform treatment decisions. (Level B)
  - Clinicians may prescribe MAO-B inhibitors as the initial dopaminergic therapy for mild motor symptoms in patients with early PD. (Level C)

Recommendation Definitions

Level of Recommendation	Phrasing	Definition
Level A	"Must"	Strongest recommendation level; these recommendations are rare, as they are based on high confidence in the evidence and require both a high magnitude of benefit and low risk.
Level B	"Should"	More common recommendations, as the requirements are less stringent but still based on the evidence and benefit–risk profile.
Level C	"May"	Represents the lowest allowable recommendation level the AAN considers useful within the scope of clinical practice and can accommodate the highest degree of practice variation.

Seppi K, Ray Chaudhuri K, Coelho M, et al. Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. Mov Disord. 2019 Feb;34(2):180-198.

- Interventions to treat depression, including depressive symptoms in PD
  - Dopamine agonists
    - Pramipexole: efficacious, acceptable risk without specialized monitoring, clinically useful
    - Rotigotine: unlikely efficacious, acceptable risk without specialized monitoring, investigational
  - MAO-B Inhibitors
    - Rasagiline and selegiline: insufficient evidence, acceptable risk without specialized monitoring, investigational
- Interventions to treat apathy in PD
  - Rotigotine: unlikely efficacious, acceptable risk without specialized monitoring, investigational
- Interventions to treat impulse control and related disorders in PD
  - Amantadine: insufficient evidence, acceptable risk without specialized monitoring, investigational
- Interventions to treat dementia and non-dementia cognitive impairment in PS
  - Rasagiline: insufficient evidence, acceptable risk without specialized monitoring, investigational
- Interventions to treat insomnia for those with PD
  - Levodopa (CR formulation of levodopa/carbidopa): insufficient evidence, acceptable risk without specialized monitoring, investigational
- Interventions to treat fatigue in PD
  - Rasagiline: efficacious, acceptable risk without specialized monitoring, possibly useful
- Interventions to treat pain in PD

  Rotigotine: insufficient evidence, acceptable risk without specialized monitoring, investigational

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Grimes D, Fitzpatrick M, Gordon J, et al. Canadian guideline for Parkinson's disease. CMAJ. 2019;191:E989-1004.

- Pharmacologic therapy in early PD
  - Levodopa may be used as a symptomatic treatment for people with early PD. (Grade A)
  - The dose of levodopa should be kept as low as possible to maintain good function in order to reduce the development of motor complications. (Grade A)
  - Controlled-release formulations of levodopa or adding entacapone are not effective for delaying motor complications. (Grade A)
  - Dopamine agonists may be used as a symptomatic treatment for people with early PD. (Grade A)
  - A dopamine agonist should be titrated to a clinically efficacious dose. If adverse effects prevent this, another agonist or a drug from another class should be used in its place. (Grade D, GPP)
  - Ergot-derived dopamine agonists should not be used as first-line treatment for PD. (Grade B)
  - MAO-B inhibitors may be used as a symptomatic treatment for people with early PD. (Grade A)
  - There is insufficient evidence to support the use of amantadine in the treatment of patients with early PD. (Grade A)
  - Anticholinergic drugs should not be used as first-line treatment in patients with PD. (Grade B)
- Pharmacologic therapy for motor symptoms in later PD
  - COMT inhibitors (entacapone) and MOA-B inhibitors (rasagiline) may be considered for the reduction in off-time in patients with advanced PD who have motor fluctuations. (Grade A)
  - Dopamine agonists (oral [pramipexole, ropinirole] or transdermal [rotigotine]) may be considered for the management of motor complications in patients with advanced PD. (Grade A)
  - Levodopa controlled release may improve wearing-off (grade: C) and nighttime akinesia (grade: GPP)
  - Subcutaneous apomorphine infusions or injections may be considered for the management of severe motor complications, but should be provided only in units that have sufficient experience and resources. (Grade C)
  - Intrajejunal levodopa-carbidopa enteric gel administered through percutaneous gastrostomy may be considered for the reduction of off-time or to reduce dyskinesia. (Grade C)
  - Amantadine is recommended for the treatment of dyskinesia in PD (200–400 mg/d). (Grade A)

Recommendation Definitions

Grade of Recommendation	Definition
Grade A	At least 1 meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
Grade B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+.
Grade C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++.
Grade D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+.
Grade GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.
Level of Evidence	**Definition**
1++	High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias

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Grade of Recommendation	Definition
1+	Well-conducted meta-analyses, systematic reviews or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews or RCTs with a high risk of bias. High-quality systematic reviews of case–control or cohort studies
2++	High-quality case–control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding or bias and a substantial risk that the relationship is not causal
3	Nonanalytic studies (e.g., case reports, case series)
4	Expert opinion

Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease. Movement Disorders 2018; 00:1-16.

- For monotherapy of early PD, nonergot dopamine agonists, oral levodopa preparations, selegiline, and rasagiline are clinically useful.
- For adjunct therapy in early/stable PD, non-ergot dopamine agonists, rasagiline, and zonisamide are clinically useful.
- For adjunct therapy in optimized PD for general or specific motor symptoms including gait, rivastigmine is possibly useful and physiotherapy is clinically useful.
- For treating motor fluctuations, most nonergot dopamine agonists, pergolide, levodopa ER, levodopa intestinal infusion, entacapone, opicapone, rasagiline, zonisamide, safinamide, and bilateral STN and GPi DBS are clinically useful.
- For dyskinesia, amantadine, clozapine, and bilateral STN DBS and GPi DBS are clinically useful.
- For patients with motor fluctuations, international guidelines recommend a new levodopa ER formulation which they deem "efficacious" and "clinically useful" with no safety concerns. Duopa, a levodopa/carbidopa intestinal gel infusion, indicated for motor fluctuations in patients with advanced Parkinson's disease, is also noted to be "efficacious" and "clinically useful." However there are safety concerns due to possible pump complications with the conclusion being that it carries an "acceptable risk with specialized monitoring."
- International guidelines list (see chart below) dopamine agonists, COMT inhibitors, and MAO-B inhibitors as "efficacious" and "clinically useful" interventions. Istradefylline is listed as "likely efficacious" and "possibly useful."

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TABLE 5a. Treatments for motor fluctuations

Class	Intervention	Efficacy conclusions	Safety[a]	Implications for clinical practice
Dopamine agonists	**Pramipexole IR**	Efficacious		Clinically useful
Nonergot	**Pramipexole ER**	***Efficacious***		***Clinically useful***
	Ropinirole	Efficacious		Clinically useful
	Ropinirole PR	Efficacious		Clinically useful
	Rotigotine	Efficacious		Clinically useful
	Apomorphine Intermittent s.c.	Efficacious		Clinically useful
	Apomorphine infusion	Likely efficacious	Acceptable risk with specialized monitoring	Possibly Useful
	Piribedil	Insufficient evidence		Investigational
Ergot	Pergolide	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bromocriptine	Likely efficacious		Possibly useful
	Cabergoline	Likely efficacious		Possibly useful
	DHEC	Insufficient evidence		Investigational
Levodopa/peripheral decarboxylase inhibitor	Standard formulation	Efficacious		Clinically useful
	Controlled release	Insufficient evidence		Investigational
	Rapid onset	Insufficient evidence		Investigational
	Extended release	***Efficacious***		***Clinically useful***
	Intestinal Infusion	***Efficacious***	***Acceptable risk with specialized monitoring***	***Clinically useful***
COMT inhibitors	**Entacapone**	Efficacious		Clinically useful
	Tolcapone	Efficacious	Acceptable risk with specialized monitoring	Possibly useful
	Opicapone	***Efficacious***		***Clinically useful***
MAO-B inhibitors	**Rasagiline**	Efficacious		Clinically useful
	Selegiline	Insufficient evidence		Investigational
	Oral disintegrating selegiline	Insufficient evidence		Investigational
MAO-B inhibitor plus Channel blockers	**Zonisamide**	***Efficacious***		***Clinically useful***
	Safinamide	***Efficacious***		***Clinically useful***
Others	***Istradefylline***	***Likely efficacious***		***Possibly useful***
	Amantadine	Insufficient evidence		Investigational
Surgery	**Bilateral STN DBS**	Efficacious	Acceptable risk with specialized monitoring	Clinically useful
	Bilateral GPi DBS	Efficacious		Clinically useful
	Unilateral pallidotomy	Efficacious		Clinically useful
	Unilateral thalamotomy	Insufficient evidence		Investigational
	Thalamic stimulation (uni or bilateral)	Insufficient evidence		Investigational
	Subthalamotomy	Insufficient evidence		Investigational
	Human fetal transplantation	Nonefficacious	Unacceptable risk	Investigational

DHEC, dihydroergocryptine; MAO-B, monoamine oxidase B; IR, immediate release; PR, prolonged release; ER, extended release; CR, controlled release; s.c., subcutaneous.
Bolded text indicates interventions where **new studies** have been published since January 2011, or prior to this date in the case of newly identified interventions not previously reviewed: *Italicized* indicates *changes in conclusions* since last publication.
[a]Unless otherwise stated, the conclusion for safety is acceptable risk without specialized monitoring.

Parkinson's disease in adults. National Institute for Health and Excellence (NICE). 2017:1-30.

- Pharmacological management of motor symptoms (first-line)
  - Offer levodopa to people in the early stages of Parkinson's disease whose motor symptoms impact on their quality of life.
  - Consider a choice of dopamine agonists, levodopa or monoamine oxidase B (MAO-B) inhibitors for people in the early stages of Parkinson's disease whose motor symptoms do not impact on their quality of life.
  - Do not offer ergot-derived dopamine agonists as first-line treatment for Parkinson's disease.
- Pharmacological management of motor symptoms (adjuvant)
  - If a person with Parkinson's disease has developed dyskinesia and/or motor fluctuations, including medicines 'wearing off', seek advice from a healthcare professional with specialist expertise in Parkinson's disease before modifying therapy.

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- Offer a choice of dopamine agonists, MAO-B inhibitors or catechol-O-methyl transferase (COMT) inhibitors as an adjunct to levodopa for people with Parkinson's disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy.
- Choose a non-ergot-derived dopamine agonist in most cases, because of the monitoring that is needed with ergot-derived dopamine agonists.
- Only consider an ergot-derived dopamine agonist as an adjunct to levodopa for people with Parkinson's disease who have developed dyskinesia or motor fluctuations despite optimal levodopa therapy AND whose symptoms are not adequately controlled with non-ergot-derived dopamine agonists.
- If dyskinesia is not adequately managed by modifying existing therapy, consider amantadine.
- Do not offer anticholinergics to people with Parkinson's disease who have developed dyskinesia and/or motor fluctuations.

Ferreira JJ, Katzenschlager R, Bloem BR, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease. European Journal of Neurology. 2013;20:5-15.

- Interventions for the management of early (uncomplicated) PD for symptomatic control and the prevention of motor complications

	Level of recommendation	
Therapeutic interventions	Symptomatic control of parkinsonism	Prevention of motor complications
Levodopa	Effective (level A)	Not applicable
Levodopa CR[e]	Effective (level A)	Ineffective (level A)
Apomorphine	Not used[a]	Not used[a]
Bromocriptine[b]	Effective (level B)	Effective (level B)
Cabergoline[b]	Effective (level B)	Effective (level A)
Dihydroergocryptine[b]	Effective (level A)	No recommendation[c]
Lisuride[b]	Effective (level B)	Effective (level C)
Pergolide[b]	Effective (level A)	Effective (level B)
Piribedil	Effective (level C)	No recommendation[c]
Pramipexole	Effective (level A)	Effective (level A)
Pramipexole CR[e]	Effective (level A)	Not available
Ropinirole	Effective (level A)	Effective (level A)
Ropinirole CR[e]	Effective (level A)	No recommendation[c]
Rotigotine[d]	Effective (level A)	No recommendation[c]
Selegiline	Effective (level A)	Ineffective (level A)
Rasagiline	Effective (level A)	No recommendation[c]
Entacapone[f]	No recommendation[c]	Ineffective (level A)
Tolcapone[f]	No recommendation[c]	No recommendation[c]
Amantadine	Effective (level B)	No recommendation[c]
Anticholinergics	Effective (level B)	No recommendation[c]
Rehabilitation	No recommendation[c]	No recommendation[c]
Surgery	Not used	Not used

[a]Subcutaneous apomorphine is not used in early PD.
[b]Ergot derivates cannot be recommended as a first-line treatment because of the risk of valvular heart disorder.
[c]No recommendation can be made because of insufficient data.
[d]Transdermal patch.
[e]Controlled release.
[f]*Entacapone* and *tolcapone* should always be given with levodopa. Because of hepatic toxicity, *tolcapone* is not recommended in early PD.

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- Recommendations for the treatment of motor complications in PD
    - Motor fluctuations
        - Add COMT or MAO-B inhibitors: no recommendations can be made on which should be chosen first – all reduce OFF time by about 1–1.5 h/day. The only direct comparison (Level A) showed no difference between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic and only recommended in patients failing on other medications.
        - Add dopamine agonists: non-ergot dopamine agonists are first-line compounds. Dopamine agonists reduce OFF time. None has proven superior, but switching from one agonist to another can be helpful. (Level B/C)
        - CR levodopa: may improve wearing-off (Level C) and night-time akinesia (GPP)
        - Add amantadine or an anticholinergic: the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms. (GPP)

Recommendation Definitions

Level of Recommendation	Definition
Level A	Established as effective, ineffective, or harmful. Requires at least one convincing class I study or at least two consistent, convincing class II studies.
Level B	Probably effective, ineffective, or harmful. Requires at least one convincing class II study or overwhelming class III evidence.
Level C	Possibly effective, ineffective, or harmful. Requires at least two convincing class III studies.
GPP (good practice points)	Such good practice points should not imply that they are based on more than class IV evidence which implies large clinical uncertainty. No impression is intended that a randomized trial to test the intervention can be avoided by assigning such points to a specific recommendation.
Class of Evidence	**Definition**
Class I	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) randomization concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e.
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion.

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Clinical Trials/Systematic Reviews/Meta-Analyses

Citation	Design	Endpoints
A Study of Istradefylline (KW-6002) for the Treatment of Parkinson's Disease in Patients Taking Levodopa Nourianz [prescribing information]. Kyowa Kirin Inc., Bedminster, NJ; August, 2019.	Phase III, 12-week, double blind, placebo-controlled, randomized, parallel group, multicenter, fixed dose study to evaluate the efficacy and safety of a 20 mg/d oral dose of KW-6002 (istradefylline) as treatment for Parkinson's disease in patients with motor response complications on levodopa/carbidopa therapy. N = 225, patients had a mean duration of Parkinson's disease (PD) of 9 years. Patients were experiencing at least 2 hours (mean approximately 6 hours) of "off" time per day, and were treated with levodopa for at least one year, with stable dosage for at least 4 weeks before screening (mean total daily dosage range: 416 to 785 mg). Patients continued levodopa treatment with or without concomitant PD medications, including dopamine agonists (85%), COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%), provided the medications were stable for at least 4 weeks before screening and throughout the study period. The arms were: Istradefylline 20 mg once daily (N=112) and placebo once daily (N=113)	• Primary Endpoint: To establish the efficacy of a 20 mg/d dose of istradefylline for reducing the percentage of "off" time in patients with advanced Parkinson's disease treated with levodopa/carbidopa • Secondary Endpoints: To evaluate the efficacy of a 20 mg/d dose of istradefylline for reducing the total hours of "off" time, to evaluate the change in percentage of "on" time (without troublesome dyskinesia)
Results: Patients treated with placebo at baseline had 37.2% (SD: ± 13.8) of awake "off" hours, while patients treated with istradefylline at baseline had 38.4% (± 16.2). The least squares mean difference (LSMD) in the change from baseline in the percentage daily awake "off" time for istradefylline vs. placebo was -4.57% (p=0.025). Compared with patients on placebo, patients treated with istradefylline experienced an additional increase from baseline in "on" time without troublesome dyskinesia of 0.55 hours (p=0.135) **Conclusion**: Istradefylline was shown to improve the percentage of daily awake "off" time compared to placebo.		
Citation	**Design**	**Endpoints**
Study of KW-6002 (Istradefylline) for the Treatment of Parkinson's Disease in Patients Taking Levodopa (6002-009)	Phase III, placebo-controlled, double-blind, parallel group, fixed dose study of KW-6002 (istradefylline) in the treatment of Parkinson's disease. N = 366, patients had a mean duration of Parkinson's disease (PD) of 9 years (range: 1 month to 37 years). Patients were experiencing at least 2 hours (mean approximately 6 hours) of "off" time per day, and were treated with levodopa for at least one year, with stable dosage for at least 4 weeks before screening (mean total daily dosage range: 416 to 785 mg). Patients continued levodopa treatment with or without concomitant PD medications, including dopamine agonists (85%), COMT inhibitors (38%), MAO-B inhibitors (40%), anticholinergics (13%), and/or amantadine (33%), provided the medications were stable for at least 4 weeks before screening and throughout the study period. Arms	• Primary Endpoints: Reducing the mean total hours of awake time per day spent in the "off" state • Secondary Endpoint: Reducing the mean percentage of awake time per day spent in the "off" state, mean change in the total hours and the percentage of awake time per day spent in the "on" state (without dyskinesia)

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Nourianz [prescribing information]. Kyowa Kirin Inc., Bedminster, NJ; August, 2019.	were: Istradefylline 20 mg once daily (N=120), Istradefylline 40 mg once daily (N=123), and placebo once daily (N=123).	
Results: Patients treated with placebo at baseline had 6.3 hours (SD: ± 2.5) of daily "off" time, while patients treated with istradefylline 20 mg had 6.6 hours (± 2.7) at baseline, and patients treated with istradefylline 40 mg had 6.0 hours (± 2.5). The least squares mean difference (LSMD) in the change from baseline in total daily "off" time was -0.76 hours (p=0.006) for istradefylline 20 mg vs. placebo. The LSMD in the change from baseline in total daily "off" time was -0.74 hours (p=0.008) for istradefylline 40 mg vs. placebo. The corresponding increases in "on" time without troublesome dyskinesia was 0.83 hours (p=0.008) for istradefylline 20 mg and 0.81 hours (p=0.008) for istradefylline 40mg. **Conclusion**: Istradefylline was shown to improve total daily "off" time compared to placebo.		
Citation	**Design**	**Endpoints**
Efficacy and Safety Study of CVT-301 In Parkinson's Disease Patients With OFF Episodes (SPAN-PD™) Inbrija [prescribing information]. Acorda Therapeutics, Inc. Ardsley, NY; December, 2018.	Randomized, parallel assignment, double blind, placebo-controlled, phase 3 trial with 351 participants. The demographic characteristics were: 26.5% female, 73.5% male; 49.3% <65 years old 50.7% ≥65 years old; 5.9% from Canada, 73.2% from the United States, 19.5% from Poland, 1.5% from Spain; mean UPDRS Part III scores at screening in the ON state were 14.9 for Inbrija group and 16.1 for placebo. The arms were: Inbrija 84 mg or low dose (unspecified) up to 5 times per day for OFF episodes for 3 months vs. placebo.	• Primary Endpoint: Change from pre-dose in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III Score at 30 minutes post-dose at week 12 for CVT-301 (Inbrija) high dose versus placebo • Secondary Endpoints: Proportion of patients achieving resolution of an OFF to an ON state within 60 minutes, change from pre-dose in the UPDRS part III score at 20 and 10 minutes post-dose at week 12 for CVT-301 high dose versus placebo (ITT Population) and CVT-301 low dose versus placebo, patient global impression of change at treatment visit 4 (week 12) by improvement category, seven point Likert scale ranging from 1=much worse to 7= much better, and change in total daily OFF times for 3 consecutive days prior to week 12 visit compared to 3 consecutive days prior to baseline visit

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Results: Patients in the Inbrija group had an average UPDRS score of 29.0 predose and a 30 minute post dose score of 19.3, the placebo groups scores were 32.1 and 25.3, respectively which was statistically significant (p=0.009). A significant difference was also found between the groups, with an ON state sustained for 60 minutes post-dose in 58% of the Inbrija group and 36% for the placebo (p=0.003).
Conclusion: Inbrija appears to help those experiencing OFF symptoms, reducing the UPDRS score by 9.8 points which can be a large benefit to those who do experience these symptoms which can be debilitating. Over half of participants reported feeling less symptoms for at least an hour after the dose which brings them much closer to their next oral dose of levodopa which is often prescribed at an interval of 6 to 8 hours.

Citation	Design	Endpoints
Randomized Safety Study of CVT-301 Compared to an Observational Control Group Inbrija [prescribing information]. Acorda Therapeutics, Inc. Ardsley, NY; December, 2018.	Randomized, parallel assignment, open label, phase 3 trial with 408 participants. The demographic characteristics were: 39.9% female, 60.1% male; 49.2% <65 years old, 50.8% ≥ 65 years old; 23.4% of participants came from Poland, 22.4% from Romania, 6.8% from The United States, and the rest from Hungary, Czechia, the United Kingdom, Spain, Austria, Belgium, Israel, France, Serbia, and Germany. 271 patients were sorted into the Inbrija cohort and the observational cohort had 127 participants. 54 weeks after the trial began FEV1, FVC and FEV1/FVC were measured and compared between the groups.	• Primary Endpoints: Pulmonary safety assessed by forced expiratory volume in 1 second [FEV1], pulmonary safety assessed by forced vital capacity [FVC], and pulmonary Safety assessed by forced expiratory volume in 1 second/forced vital capacity ratio. [FEV1]/[FVC] • Secondary Endpoint: Diffusion Capacity of the Lungs for Carbon Monoxide

Results: The experimental cohort had an average FEV1 of 2.778L (SD: 0.7309L) and the observational cohort had an average of 2.767L (SD: 0.8419). The experimental cohort had an average FVC of 3.558 (SD: 0.8987L) and the observational cohort had an average of 3.642 (SD: 1.0687). The experimental cohort had an average FEV1/FVC of 78.1% (SD: 6.04%) and the observational cohort had an average of 76.1% (SD: 6.4%). Overall, both groups had an average reduction in FEV1 of 0.1L from the start of the trial, indicating no difference between the groups.
Conclusion: The results of the trial show very little difference, if any, between the two cohorts however no p-value was reported so the statistical significance is still unknown. It does appear that although this is an inhaled medication not being used to treat a pulmonary disorder it is safe to use in those with healthy lungs.

Citation	Design	Endpoints
Zhuo C, Zhu X, Jiang R, et al. Comparison for Efficacy and Tolerability among Ten Drugs for Treatment of Parkinson's Disease: A Network Meta-Analysis. Sci Rep. 2017;8:45865.	A systematic literature review to assess the efficacy among ten drugs used in the treatment of PD. Efficacy was assessed by various Unified Parkinson's Disease Rating Scales (UPDRS). Cluster analysis was performed and determined the drugs surface under the cumulative ranking curve. N = 24,846. 110 publication reviewed randomized controlled trials (RCTs). Patients were diagnosed with early or advanced PD.	• Pairwise comparisons: (mean differences (MD), 95% confidence intervals (CI)) ○ UPDRS II ○ UPDRS III ○ UPDRS total • Withdrawals (odds ratio (OR)/95% CI)

Results: Selegiline had a higher total in in UPSRS II, UPDRS III, and UPDRS scores when compared to bromocriptine and levodopa; selegiline was more tolerable than bromocriptine (OR= 0.62, 95 % CI: 0.39-0.98) and pramipexole was less tolerable than levodopa (OR = 1.43, 95% CI: 1.00 to 2.04). Patients taking levodopa, pramipexole, ropinirole, and selegiline significantly improved UPDRS III scores when compared to lazabemide.

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Conclusion: The study was designed to compare efficacy and tolerability among ten drugs used in PD, and levodopa, pramipexole, ropinirole, and selegiline, ropinirole and rotigotine are recommended for treatment.

Citation	Design	Endpoints
Li B-D, Bi Z-Y, Liu J-F, et al. Adverse effects produced by different drugs used in the treatment of Parkinson's disease: A mixed treatment comparison. CNS Neurosci Ther. 2017;23:827–842.	Meta-analysis from PubMed, EMBASE, Cochrane Library (inception-December 2015). Compared the incidences of different adverse effects of PD treatment (ropinirole, rasagiline, rotigotine, entacapone, apomorphine, pramipexole, sumanirole, bromocriptine, piribedil, pergolide, levodopa). 23 RCTs evaluated.	• Adverse events • merging OR; surface under the cumulative ranking curves (SUCRA)

Results:

Direct Comparison Results (vs. placebo)

- Higher nausea incidence in patients administered ropinirole, rotigotine, entacapone, sumanirole (OR = 0.44, 95% CI = 0.25-0.78; OR = 0.51, 95% CI = 0.29-0.87; OR = 0.51, 95% CI = 0.30-0.88; OR = 0.43, 95% CI = 0.30-0.63, respectively)
- Higher dyskinesia incidence in patients administered ropinirole, rotigotine, pramipexole, sumanirole, and pergolide (OR = 0.30, 95% CI = 0.15-0.61; OR = 0.44, 95% CI = 0.22-0.88; OR = 0.18, 95% CI = 0.06-0.56; OR = 0.37, 95% CI = 0.17-0.82; OR = 0.30, 95% CI = 0.01-8.33, respectively),
- Higher hallucinations incidence in patients administered ropinirole, rotigotine, pramipexole, and sumanirole (OR = 0.38, 95% CI = 0.16-0.90; OR = 0.23, 95% CI = 0.07-0.82; OR = 0.17, 95% CI = 0.04-0.84; OR = 0.32, 95% CI = 0.13-0.82, respectively)

SUCRA – incidence of adverse reaction (vs. placebo)

- Pergolide (nausea: 83.5%; hallucinations: 79.8%)
- Ropinirole (dyskinesia: 80.5%; somnolence: 69.4%)
- Piribedil: (dizziness: 67.0%)
- Bromocriptine: (constipation: 62.3%)

Conclusion: The highest incidence rates of nausea, dyskinesia, hallucinations, dizziness, constipation, and somnolence was seen in ropinirole, bromocriptine and piribedil. Therefore, these three drugs are not recommended for the treatment of PD.

Citation	Design	Endpoints
Sako W, Murakami N, Motohama K, et al. The effect of istradefylline for Parkinson's disease: A meta-analysis. Sci Rep. 2017 Dec 21;7(1):18018.	Meta-analysis with a systematic literature search of PubMed, Web of Science and Cochrane Library. Calculated the pooled standardized mean difference and risk ratio for continuous and dichotomous variables. 6 studies satisfied the inclusion criteria	• Off time and motor symptoms

Results: Istradefylline 40mg/day could improve off time and motor symptoms. They failed to provide robust evidence for the 20mg/day for off time or UPDRS III using a sensitivity analysis.

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Conclusion: Istradefylline 20mg/day improves UPDRS III and 40mg/day improves both off time and UPDRS III. The drug was well tolerated. The 40mg/day is the only drug to have meta-analysis based evidence and is recommended for administration in the early phases of PD, or at least before the onset of motor complications.		
Citation	**Design**	**Endpoints**
Binde CD, Tvete IF, Gasemyr J, et al. A multiple treatment comparison meta-analysis of monoamine oxidase type B inhibitors for Parkinson's disease. Br J Clin Pharmacol 2018;84:1917–27.	Meta-analysis with a systematic literature search to identify randomized controlled trials assessing the efficacy of MAO-B inhibitors inpatients with Parkinson's disease. MAO-B inhibitors were evaluated either as monotherapy or in combination with levodopa or dopamine agonists. We estimated the relative effect of each MAO-B inhibit or versus the comparator drug by creating three networks of direct and indirect comparisons. For each of the networks, we considered a joint model	• Change in the Unified Parkinson's Disease Rating Scale (UPDRS) score • Serious adverse events.
Results: The systematic literature search and study selection process identified 27 publications eligible for our three network analyses. We found the relative effects of rasagiline, safinamide and selegiline treatment given alone and compared to placebo in a model without explanatory variables to be 1.560 (1.409, 1.734), 1.449 (0.873, 2.413) and 1.532 (1.337, 1.757) respectively. We also found all MAO-B inhibitors to be efficient when given together with levodopa. When ranking the MAO-B inhibitors given in combination with levodopa, selegiline was the most effective and rasagiline was the second best. **Conclusion**: All of the included MAO-B inhibitors were effective compared to placebo when given as monotherapy. Combination therapy with MAO-B inhibitors and levodopa showed that all three MAO-B inhibitor s were effective compared to placebo, but selegiline was the most effective drug		
Citation	**Design**	**Endpoints**
Oertel W, et al. Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3).Mov Disord. 2017 Dec;32(12):1701-1709.	A phase 3, randomized, double-blind, placebo-controlled study (EASE LID 3 Study, Adamas Pharmaceuticals, Inc., ADS-AMT-PD304) was conducted at 39 sites in the United States and Western Europe (Germany, France, Spain, and Austria). Eligible patients were randomized on day 1 in a 1:1 ratio to receive placebo or ADS-5102. During the first week of dosing, patients randomized to ADS-5102 received a daily ADS-5102 dose of 137 mg (one ADS-5102–containing capsule and one placebo capsule, identical in appearance). During weeks 2 through 12, the daily ADS-5102 dose was 274 mg, administered as two 137-mg capsules. During the last week of dosing, the dose was reduced to 137 mg daily. Patients randomized to placebo received 2 placebo capsules for 13 weeks.	• Primary Endpoint: change from baseline to week 12 on the Unified Dyskinesia Rating Scale total score in the modified intent-to-treat population • Secondary Endpoints: change from baseline to week 12 in ON time without troublesome dyskinesia (ON time without dyskinesia plus ON time with non-troublesome dyskinesia) and OFF time, change from baseline to week 12 in MDS-UPDRS, ON time with troublesome dyskinesia, total ON time with dyskinesia, (non-troublesome plus troublesome), and the CGI-C.
Results: At week 12, least-squares mean change in the Unified Dyskinesia Rating Scale was 220.7 (standard error 2.2) for ADS-5102 and –6.3 (standard error 2.1) for placebo (treatment difference 214.4, 95% confidence interval 220.4 to 28.3, P < .0001), indicating improvement in levodopa-induced dyskinesia. OFF time decreased 0.5 hours (standard error 0.3) for ADS-5102 from a baseline mean of 2.6 hours and increased 0.6 hours (standard error 0.3) for placebo from a baseline mean of 2.0 hours (treatment		

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difference 21.1 hours, 95% confidence interval 22.0 to 20.2, P=.0199). The most common adverse events (ADS-5102 versus placebo) included dry mouth (13.5% versus 2.6%), nausea (13.5% versus 2.6%), decreased appetite (10.8% versus 0%), insomnia (10.8% versus 0%), orthostatic hypotension (10.8% versus 0%), constipation (8.1% versus 0%), falls (8.1% versus 5.3%), and visual hallucinations (8.1% versus 5.3%). Adverse events led to treatment discontinuation in 19% versus 8%, respectively.
Conclusion: ADS-5102 274 mg is an oral pharmacotherapy demonstrating a significant decrease in levodopa-induced dyskinesia and improving OFF time.

Citation	Design	Endpoints
Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. JAMA Neurol. 2017;74(8):941–949.	A randomized, double-blind, placebo-controlled clinical trial was conducted between May 7, 2014, and July 22, 2015, at 44 North American sites among patients with PD treated with levodopa who experienced at least 1 hour of troublesome dyskinesia per day with at least mild functional impact. Patients were randomized to receive placebo or 274 mg of ADS-5102 administered orally at bedtime for up to 25 weeks.	• Primary Endpoints: change from baseline to week 12 in the Unified Dyskinesia Rating Scale total score for ADS-5102 vs placebo • Secondary Endpoint: OFF time (amount of time the PD medication is not controlling motor symptoms)

Results: At week 12, the least-squares mean (SE) change in the Unified Dyskinesia Rating Scale score was –15.9 (1.6) for ADS-5102 (n = 63) and –8.0 (1.6) for placebo (n = 58) (treatment difference, –7.9; 95% CI, –12.5 to –3.3; P < .001). OFF time decreased by a mean (SE) of 0.6 (0.3) hours for ADS-5102 and increased by 0.3 (0.3) hours for placebo (treatment difference, –0.9 hours; 95% CI, –1.6 to –0.2; P = .02). Common adverse events for ADS-5102 vs placebo included visual hallucinations (15 [23.8%] vs 1 [1.7%]), peripheral edema (15 [23.8%] vs 0), and dizziness (14 [22.2%] vs 0). Adverse events led to treatment discontinuation for 13 patients receiving ADS-5102 (20.6%) vs 4 patients receiving placebo (6.9%).
Conclusion: ADS-5102, 274 mg at bedtime, may be an effective treatment for LID. An additional benefit is reduced OFF time. To our knowledge, this is the first demonstration of an oral treatment reducing both LID and OFF time in patients with PD with dyskinesia.

Citation	Design	Endpoints
Ferreira JJ, Lees A, Rocha JF, et al. Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomised, double-blind, controlled trial. Lancet Neurol. 2016;15(2):154-165.	Phase III, randomized, double-blind, placebo-controlled and active-controlled trial of opicapone as an adjunct to levodopa in patients with PD with end-of-dose motor fluctuations. N=600, the study enrolled patients with a mean duration of PD of approximately 7 years who were Hoehn and Yahr Stage III or less in the “on” state, and who were all receiving concomitant levodopa with a stable dose for at least 4 weeks before screening. Eighty-two percent of patients used concomitant PD medications in addition to levodopa; the most commonly used were dopamine agonists (68%), amantadine (23%), MAO-B inhibitors (20%), and anticholinergics (5%). The arms were: opicapone 5 mg (N=122), opicapone 25 mg (N=119), opicapone 50 mg (N=116), entacapone (N=122), and placebo (N=121).	• Primary Endpoint: Change in mean absolute “off” time, based on 24-hour patient diaries completed 3 days prior to each scheduled visits

Results: The mean change in “off” time was -56.0 min for placebo, -96.3 min for entacapone, -91.3 min for opicapone 5 mg, -85.9 min for opicapone 25 mg, and -116.8 min for opicapone 50 mg. Treatment with opicapone 50 mg was superior to placebo (mean difference in change from baseline -60.8 min, 95% CI -97.2 to -24.4; p=0.002) and non-

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inferior to entacapone (-26.2 min, -63.8 to 11.4; p=0.005). Treatment with opicapone 5 mg (p=0.056) or 25 mg (p=0.080) was not significantly different from treatment with placebo. Most common adverse events were dyskinesia, insomnia, and constipation.
Conclusion: The addition of opicapone 50 mg to levodopa treatment in patients with Parkinson's disease and end-of-dose motor fluctuations could enable a simplified drug regimen that allows physicians to individually tailor the existing levodopa daily regimen, by potentially reducing the total daily levodopa dose, increasing the dosing interval, and ultimately reducing the number of intakes, thereby maximizing its benefit.

Citation	Design	Endpoints
Wirdefeldt K, Odin P, Nyholm D. Levodopa-Carbidopa Intestinal Gel in Patients with Parkinson's Disease: A Systematic Review. CNS Drugs. 2016;30(5):381-404	This review focuses on infusion of levodopa/carbidopa intestinal gel (LCIG). Authors identified articles form PubMed and EMBASE up to March 2016. Of the 353 studies found, 25 studies were evaluated. Only 3 studies were RCTs and the remaining studies were open-label.	• Outcome measures included UPDRS, 'off' time, 'on' time with dyskinesia, Parkinson's disease Questionnaire, and Non-Motor Symptom Scale (NMSS).

Results: All studies that reported motor outcomes consistently showed that LCIG increased 'on' time without dyskinesias. Severe dyskinesias were unchanged or reduced and 'off' time was reduced. UPDRS motor examination was mostly unchanged. In levodopa-responsive patients, levodopa is expected to give major symptom relief independent of how it is delivered. LCIG is not expected to have greater maximal effect on PD symptoms than oral levodopa. Quality of evidence is moderate. Studies that assessed quality of life reported improvement following LCIG, but evidence is moderate. The most common adverse events related to the device or procedure: dislocation of tube, complication of device insertion, abdominal pain, irritation, granulation, or erythema at stoma, etc. Most common adverse events related to LCIG infusion were: nausea, falls, sleep disturbance, neuropathy, weight loss, hallucinations, troublesome dyskinesia, and mood disturbance.
Conclusion: Quality of evidence that LCIG reduces motor symptoms and improves quality of life is moderate. Motor examination reported no changes. In levodopa-responsive patients, LCIG is not expected to have a greater effect on PD symptoms than oral levodopa. LCIG might be useful in patients with PD who have severe motor fluctuations.

Citation	Design	Endpoints
Xie CL, Zhang YY, Wang XD, et al. Levodopa alone compared with levodopa-sparing therapy as initial treatment for Parkinson's disease: a meta-analysis. Neurol Sci. 2015;36(8):1319-29.	This review aims to assess whether L-dopa alone or L-dopa-sparing therapy should be used as first line treatment in patients with early PD. The meta-analysis pools relevant data from all published randomized controlled trials (RCTs) comparing the two therapies and assessing the benefits and risks. PubMed, Google scholar, Cochrane, and the Web of Science databases were searched from January 1990 to August 2014. Of the 481 references found only 11 studies (n=3,584) met the inclusion criteria.	• Outcomes measures included, unified Parkinson's disease rating scale (UPDRS), Parkinson's disease questionnaire (PDQ-39), EuroQol (EQ-5D), motor complications (dyskinesia, wearing-off phenomenon and on-off fluctuation) and withdrawal rates.

Results: The studies show that L-dopa alone could improve the UPDRS score compared with L-dopa-sparing therapy. L-dopa therapy had a significant difference in withdrawal rates reduction. The studies also confirmed that patients starting with dopamine agonists are less likely to develop motor complications (including dyskinesia and wearing-off) compared to those on L-dopa. Patients on L-dopa-sparing therapy were more likely to discontinue treatment due to adverse events.
Conclusion: L-dopa monotherapy provides the greatest symptomatic benefit for PD and is associated with less somnolence, edema, freezing, hallucinations, and risk of impulse control disorders. Dopamine agonists are more efficacious in early PD and are less likely to cause dopaminergic motor complications

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More patients on dopamine agonists or MAOB inhibitors were more likely to discontinue suggesting that non-motor side-effects or lack of efficacy appear clinically important as motor complications. L-dopa is the most effective medication for treating motor symptoms associated with PD.		
Citation	**Design**	**Endpoints**
Cai JP, Chen WJ, Lin Y, et al. Safety and efficacy of rasagiline in addition to levodopa for the treatment of idiopathic Parkinson's disease: a meta-analysis of randomised controlled trials. Eur Neurol. 2015;73(1-2):5-12.	The objective of this meta-analysis is to pool the existing evidence form published RCTs comparing any dose of rasagiline with placebo or no treatment in patients with PD who are receiving levodopa. The authors searched various databases including MEDLINE, Cochrane Library, PsychINFO, and EMBASE with dates ranging from 1946 to January 2013. Of the 709 articles retrieved, only three were found eligible to be included in this review.	• Primary outcome measure was improvement in motor functions. • Secondary outcome measures included symptomatic improvement, QoL improvement, adverse effects, motor symptoms, any disease-modifying effects, additional medication/change in dose, death, and leaving study early
Results: The results of the trials suggest that 0.5 – 2 mg/day rasagiline is safe and well-tolerated in PD patients receiving levodopa. The trials found that rasagiline was associated with significant improvements in daily "on" time without dyskinesia, significant improvement in UPDRS motor performance during "on" time, significant improvements in daily "off" time, and significant improvements in activities of daily living. There were no significant differences in adverse effects between the two groups. **Conclusion**: 0.5 to 1 mg/day rasagiline as adjunct therapy to levodopa is safe and well tolerated.		
Citation	**Design**	**Endpoints**
Zhou CQ, Zhang JW, Want M, Peng GG. Meta-analysis of the efficacy and safety of long-acting non-ergot dopamine agonists in Parkinson's disease. J Clin Neurosci. 2014;21(7):1094-101.	This meta-analysis pools all the available RCT results for long-acting non-ergot dopamine agonists (NEDA; rotigotine transdermal patch, pramipexole extended-release, and ropinirole prolonged-release) versus placebo in patients with PD. Authors conduct a comprehensive review to assess efficacy, tolerability, and safety. Databases including PubMed, Cochrane Library, and EMBASE were searched up to February 2013. The literature search identified 105 potential articles of which 9 large-scale RCTs (n=2,857) were included in the analysis.	• Main outcomes assessed were UPDRS activities of daily living (ADL), UPDRS motor scores, Off-On times, and adverse events
Results: The trial results showed that long-acting NEDA achieved greater improvements compared to placebo in UPDRS ADL (WMD -4.18, 95% CI -4.97 to -3.43), motor score (WMD -4.18, 95% CI -4.94 to -3.43), reduction in "off" time (WMD -1.29, 95% CI -1.64 to -0.93), and in increase in "on" time (WMD 1.55, 95% CI 1.06, 2.04). Patients with early PD had higher risk of nausea, dizziness, somnolence, constipation, vomiting, and insomnia. Advanced PD had higher risks of dyskinesia and hallucination. Long-acting NEDA were associated with a higher rate of withdrawals due to adverse events. **Conclusion**: Long-acting NEDA can reduce the symptoms of PD patients. They are associated with higher incidence of adverse events in early PD patients.		
Citation	**Design**	**Endpoints**
Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of	The authors conducted a systematic search for relevant literature in the MEDLINE database from January 1975 to November 2008. After the search yielded a total of 999 articles, the authors selected 40 RCT to be included in the meta-analysis.	• Twelve adverse events were assessed in each trial (nausea, dizziness, somnolence, dyskinesia, insomnia, headache, orthostatic hypotension,

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Parkinson's disease: meta-analysis of randomized controlled trials. Drug Saf. 2010;33(2):147-61.		vomiting, hallucinations, confusion, constipation, and abdominal pain) and the relative risk (RR) was calculated.
Results: Ropinirole vs bromocriptine = lower constipation with ropinirole (RR 0.55, 95% CI 0.35, 0.89); levodopa vs ropinirole = lower dyskinesia for ropinirole (RR 0.25, 95% CI 0.09, 0.71); no significant difference for dyskinesia or constipation for ropinirole vs rotigotine. Ropinirole, pergolide, and rotigotine demonstrated similar RRs for nausea. When compared with pramipexole, ropinirole showed higher RR for nausea, dizziness, somnolence, and dyskinesia. Pramipexole, pergolide, ropinirole, and rotigotine had higher RR for hallucinations. Pramipexole showed higher RR of confusion and constipation. **Conclusion**: There are no clear comparisons of efficacy for dopamine agonists. Choice of dopamine agonists depends on patient preference and tolerability of side-effects. Adverse events may cause a patient to switch therapy. Clinician can individualize treatment based on the adverse event profile of each agent.		
Citation	**Design**	**Endpoints**
Stowe R, Ives N, Clarke C, et al. Evaluation of the efficacy and safety of adjuvant treatment to levodopa therapy in Parkinson´s disease patients with motor complications. Cochrane Database Syst Rev. 2010;(7).	The objective of this review is to assess the benefits and risks of dopamine agonists, COMT inhibitors and MAO-B inhibitors as adjunctive treatment to levodopa in PD patients and to conclude whether one class provides better symptomatic control than another. The authors searched the Cochrane library, MEDLINE, EMBASE, PubMed, LILACS, Web of Science, abstract book, conference proceedings, and major journals in the field up to 2008. Indirect comparisons tests for heterogeneity were used to investigate treatment effects across the drug classes. The search yielded 78 trials of which 44 trials (n=8436) were used in the review.	• Outcomes measures used were time spent in “off”, levodopa dose, UPDRS score, incidence of dyskinesia and dystonia, frequency of adverse events, mortality, withdrawals, QoL, and health economic data.
Results: Compared to placebo, adjuvant therapy significantly improved UPDRS score (-3.26, 95% CI -4.52, -2.00), reduced off-time, and reduced levodopa dose. Dyskinesia, constipation, dizziness, dry mouth, hallucinations, hypotension, insomnia, nausea, somnolence, and vomiting increased with adjuvant therapy. Indirect comparisons of the three classes suggest that dopamine agonists were more efficacious than COMT and MAO-B inhibitors, but also had more adverse effects. **Conclusion**: Add-on therapy of dopamine agonists, COMT, or MAO-B inhibitors, to levodopa significantly reduces patient “off” time, reduces required levodopa dose, and improves UPDRS. Dyskinesias and other side-effects are common with adjuvant therapy. Dopamine agonists may provide more effective symptom control than COMT and MAO-B inhibitors. COMT and MAO-B inhibitors have comparable efficacy.		
Citation	**Design**	**Endpoints**
Talati R, Reinhart K, Baker W, et al. Pharmacologic treatment of advanced Parkinson's disease: a meta-analysis of COMT inhibitors and MAO-B inhibitors. Parkinsonism Relat Disord. 2009;15(7):500-5.	Authors sought to show the true effect of COMT and MAO-B inhibitors in advanced PD by pooling several studies. A systematic literature search of MEDLINE, EMBASE, CINAHL, Web of Science, and the Cochrane Database between 1990 and October 2007 yielded 678 articles of which 13 trials (n=3,775) were included for review.	• Efficacy outcomes assessed were UPDRS score, ADL, motor scores, “on” and “off” time, and safety.

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Results: For UPDRS total score, COMT inhibitor (WMD -2.13, 95% CI -0.46, -0.20) and MAO-B inhibitor (WMD -5.03, 95% CI -2.13, -0.83) showed greater improvement. Also, the COMT and MAO-B inhibitor exhibited significant improvements in ADL, motor scores, increase in "on" time, reduction in "off" time and decreased need in levodopa dose compared to placebo. Patients also had greater risk of developing dyskinesias with both COMT and MAO-B. **Conclusion**: Use of COMT and MAO-B inhibitor plus levodopa is superior to levodopa monotherapy at reducing PD symptoms in advanced PD. Benefits of this combination need to be weighed against the risk of developing adverse events.		
Citation	**Design**	**Endpoints**
Talati R, Baker WL, Patel AA, et al. Adding a dopamine agonist to preexisting levodopa therapy vs. levodopa therapy alone in advanced Parkinson's disease: a meta-analysis. Int J Clin Pract. 2009;63(4):613-23.	The objective of this meta-analysis was to evaluate the role of adjunctive dopamine agonist therapy (as a group and then as ergot and non-ergot subgroups) in advanced PD. The authors conducted a systematic literature search of MEDLINE, EMBASE, CINAHL, Web of Science, and Cochrane between 1990 and July 2007. The search yielded 688 articles of which 15 trials (n=4,391) were analyzed.	• Clinically important efficacy outcomes included UPDRS activities of daily living (ADL) and motor scores. Safety outcomes assessed included withdrawal rates, dyskinesias, hallucinations and mortality.
Results: Adjunctive DA resulted in improvement of UPDRS ADL scores (WMD -2.20 95% CI -2.64, -1.76) and motor score reduction (WMD -5.56, 95% CI-6.82, -4.31). Adjunctive DA also reduced "off" time (measured in hours/day) and reduced levodopa dose. Dyskinesias and hallucination incidence was higher with dopamine agonists. Ergot and non-ergot dopamine agonists provided beneficial effects on efficacy outcomes. Safety concerns with ergots discourage its use. **Conclusion**: Adjunctive use of dopamine agonists (preferably non-ergots) with levodopa provides significant improvements in patient function and motor symptoms and is especially helpful with wearing-off phenomenon. Benefits and risks of adverse effects must be considered.		

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Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Decarboxylase Inhibitors								
Carbidopa (Lodosyn®) 25 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dopamine Replacement								
Carbidopa/Levodopa (Sinemet®, Dhivy®) 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg tablets	4	3	$286.32	$71.58	0	0 (0%)	F	No change
Carbidopa/Levodopa 10 mg/100 mg, 25 mg/100 mg, 25 mg/250 mg disintegrating tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Carbidopa/Levodopa 25 mg/100 mg, 50 mg/200 mg ER tablets	1	1	$167.82	$167.82	0	0 (0%)	F	No change
Rytary® (carbidopa/levodopa) 23.75 mg/95 mg, 36.25 mg/145 mg, 48.75 mg/195 mg, 61.25 mg/245 mg ER capsules	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Crexont® (carbidopa/levodopa) 35 mg/140 mg, 52.5 mg/210 mg, 70 mg/280 mg, 87.5 mg/350 mg ER capsules	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Duopa™ (carbidopa/levodopa) 4.63 mg-20 mg/ml enteral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Vyalev™ (foscarbidopa/foslevodopa) 120 mg-2400 mg/10 ml SQ infusion vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Inbrija® (levodopa) 42 mg inhalation powder capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dopamine Agonists								
Ropinirole 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablets	2	2	$64.24	$32.12	0	0 (0%)	F	No change
Ropinirole 2 mg, 4 mg, 6 mg, 8 mg, 12 mg ER tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Bromocriptine (Parlodel®) 2.5 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Bromocriptine (Parlodel®) 5 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pramipexole 0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1 mg, 1.5 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Pramipexole 0.375 mg, 0.75 mg, 1.5 mg, 2.25 mg, 3 mg, 3.75 mg, 4.5 mg ER tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Apomorphine (Apokyn®) 10 mg/ml SQ injection	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Neupro® (rotigotine) 1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg transdermal patches	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change

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Monoamine Oxidase-B (MAO-B) Inhibitors								
Selegiline 5 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Selegiline 5 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Zelapar® (selegiline) 1.25 mg disintegrating tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Rasagiline (Azilect®) 0.5 mg, 1 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Xadago® (safinamide) 50 mg, 100 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Catechol-O-Methyltransferase (COMT) Inhibitors								
Entacapone 200 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-ST (prior use of carbidopa-levodopa)	No change
Tolcapone (Tasmar®) 100 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Ongentys® (opicapone) 50 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Dopamine Replacement/COMT Inhibitor Combination								
Carbidopa/Levodopa/Entacapone 12.5 mg/50 mg/200 mg, 18.75 mg/75 mg/200 mg, 25 mg/100 mg/200 mg, 31.25 mg/125 mg/200 mg, 37.5 mg/150 mg/200 mg, 50 mg/200 mg/200 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	F-ST (prior use of carbidopa-levodopa)	No change
Anticholinergics								
Benztropine 0.5 mg, 1 mg, 2 mg tablets	2	1	$5.96	$2.98	0	0 (0%)	F	No change
Benztropine 2 mg/2 ml injection vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Trihexyphenidyl 2 mg, 5 mg tablets	2	1	$14.76	$7.38	0	0 (0%)	F	No change
Trihexyphenidyl 0.4 mg/ml oral elixir	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Other								
Amantadine 100 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Amantadine 100 mg tablet	1	1	$91.57	$91.57	0	0 (0%)	F	No change
Amantadine 50 mg/5 ml oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Gocovri® (amantadine) 68.5 mg, 137 mg ER capsules	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Nourianz® (istradefylline) 20 mg, 40 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**12**	**9**	**$630.67**	**$52.56**	0	0 (0%)		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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Prior Authorization Criteria

Recommendation: No changes

Parkinson's Disease Agents	
Therapeutic Classes (AHFS)	DOPAMINE PRECURSORS
Medications	**Formulary, Step Therapy Required** Carbidopa-levodopa-entacapone (Stalevo) oral tablet Entacapone (Comtan) oral tablet **Formulary, Prior Authorization** Tolcapone (Tasmar) Ongentys (opicapone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 1 month for tolcapone (Tasmar)), 12 months for all other medications in this policy **Later Approvals** 12 months If criteria are not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	Formulary, step therapy required medications require trial and failure of carbidopa-levodopa INITIAL CRITERIA FOR AUTHORIZATION • Diagnosis of Parkinson's disease AND • Documentation patient is currently taking carbidopa and levodopa AND currently experiencing symptom fluctuations or "off" episodes AND not responding to or are not candidates for other adjunctive therapies (such as dopamine agonists [e.g., pramipexole or ropinirole] or monoamine oxidase B inhibitors [e.g., selegiline]) AND • Documented trial and failure, contraindication or intolerance to carbidopa-levodopa-entacapone (Stalevo). RENEWAL CRITERIA • Documentation of positive clinical response ○ If clinical improvement is not seen with tolcapone (Tasmar) after 3 weeks of use, tolcapone (Tasmar) should be discontinued. • Dosing is appropriate as per labeling or is supported by compendia or standard of care guidelines
Criteria Statement	Carbidopa-levodopa-entacapone and entacapone are reserved for members who are using carbidopa and levodopa and are still experiencing symptoms.

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	Tolcapone (Tasmar) or Ongentys are reserved for members who are using carbidopa and levodopa and are still experiencing symptoms and have used (or cannot/should not use) carbidopa-levodopa-entacapone (Stalevo) and also other adjunctive therapies (such as dopamine agonists [e.g., pramipexole or ropinirole] or monoamine oxidase B inhibitors [e.g., selegiline])
Last P&T Review Date	~~3/2025~~6/2025

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Recommendation: No changes

Vyalev	
Therapeutic Classes (AHFS)	Dopamine Precursors
Medications	Vyalev (foscarbidopa and foslevodopa)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Concurrent use with a nonselective monoamine oxidase (MAO) inhibitor (such as phenelzine or tranylcypromine)
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be a neurologist or in consultation with a neurologist
Coverage Duration	If all of the criteria are met, the initial and reauthorization requests will be approved for 12 months. If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review

PA Review Criteria	**Initial Authorization:**
	• Diagnosis of advanced Parkinson's Disease
	• Medication is prescribed at an FDA approved dose
	• Prescriber attestation or documentation that the patient is experiencing persistent motor fluctuations despite optimized carbidopa/levodopa therapy (including a minimum of 2.5 hours of "off" time per day)
	• Patient is taking ≥400 mg of levodopa/day
	• Documented trial and failure (or contraindication) to **at least two** of the following adjunctive medication classes:
	  ○ COMT-inhibitors (e.g., entacapone)
	  ○ Dopamine agonists (e.g., ropinirole, pramipexole)
	  ○ MAO-B inhibitors (e.g., rasagiline, selegiline)
	
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response (i.e. increase in "on" time without troublesome dyskinesia, decreased "off" time)
	• Medication is prescribed at an FDA approved dose

Criteria Statement	Vyalev is reserved for members who have a diagnosis of advanced Parkinson's disease, who experience persistent motor fluctuations despite optimized carbidopa/levodopa therapy, are taking at least 400 mg of levodopa per day, and who have used (or cannot/should not use) at least two of the following medication classes: COMT-inhibitors, dopamine agonists, and MAO-B inhibitors.
Last P&T Review Date	~~3/2025~~6/2025

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Potassium Removing Agents

Executive Summary

Class Overview

Hyperkalemia is most frequently a chronic condition that does not necessitate urgent treatment. In cases where treatment is a medical emergency, the potassium (K+) binders included in this review are not indicated. Potassium binders may be indicated in the following settings: when prompt (e.g. within 6-12 hours) reduction of K+ is required or where non-urgent K+ reduction is required and treatment of the underlying cause of hyperkalemia is insufficient.

Hyperkalemia most commonly occurs secondary to underlying diseases such as chronic kidney disease (CKD) and iatrogenically (i.e. use of renin angiotensin aldosterone system inhibitors [RAASis] to treat conditions such as diabetes mellitus [DM] and heart failure [HF]). Severe hyperkalemia (e.g. > 6.0 mEq/L) is associated with arrhythmia, cardiac arrest, and death. Treatment of chronic, mild to moderate hyperkalemia is primarily aimed at dietary modification, discontinuing offending medications when possible, and increasing K+ excretion with loop diuretics and K+ binders.

This review covers K+ removing agents including Kionex (sodium polystyrene sulfonate [SPS]), Veltassa (patiromer sorbitex calcium [PSC]) and Lokelma (sodium zirconium cyclosilicate [SZC]) all of which are indicated for the non-emergent treatment of hyperkalemia.

SPS is available in multiple formulations including powder and oral and rectal suspension; some formulations contain sorbitol. Because of the possible association between sorbitol and intestinal necrosis, FDA recommends against use of sorbitol-containing SPS formulations. International agencies recommend against SPS with or without sorbitol for the same reason. Despite use in practice for decades, there is lack of conclusive studies demonstrating efficacy of SPS, and its value for treatment of chronic hyperkalemia has been questioned.

Utilization Findings

There was 1 claim for 1 member, for a total cost of $828.62 and an average cost per claim of $828.62. There were no prior authorization requests.

Recommendations

- No changes

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Clinical Summary

Hyperkalemia is most frequently a chronic condition that does not necessitate urgent treatment. Potassium binders may be indicated in the following settings: when prompt (e.g. within 6-12 hours) reduction of K+ is required or where non-urgent K+ reduction is required and treatment of the underlying cause of hyperkalemia is insufficient. In practice, hyperkalemia is commonly treated first line with dietary modification, discontinuation of offending medications (i.e. NSAIDs) when possible, and diuretics (i.e. thiazide or loop) particularly for patients with hypertension (HTN) and/or hypervolemia. Potassium binders are typically reserved for therapy refractory to these interventions. SPS is generally not used due to risk of severe GI adverse events (AEs) with chronic use.

There are no upcoming outcome studies or anticipated new drug approvals within the next 6 months.

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Indications, Dosing and Administration

Medication	Indications	Dosing/Administration
Kionex® (sodium polystyrene sulfonate)	Hyperkalemia	• Oral: 15 g 1 to 4 times daily • Rectal: 30 to 50 g every 6 hours
Veltassa® (patiromer sorbitex calcium)		• Initial: 8.4 g once daily (QD) • Maintenance: adjust dose at ≥1-week intervals in increments of 8.4 g (maximum dose: 25.2 g/day)
Lokelma® (sodium zirconium cyclosilicate)		• Initial: 10 g 3 times daily (TID) for up to 48 hours; adjust dose by 5 g daily at 1-week intervals • Maintenance: 10 g QD (range: 5 g every other day to 15 g QD) (maximum maintenance dose: 15 g/day)

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Boxed Warnings and Contraindications

Medication	Boxed Warnings	Contraindications
Kionex® (sodium polystyrene sulfonate)	None	• Hypersensitivity to SPS, polystyrene sulfonate resins or any component of the formulation • Hypokalemia (excluding Kayexalate) • Obstructive bowel disease • Neonates: ○ with reduced gut motility ○ oral administration ○ rectal administration (sorbitol-containing formulations)
Veltassa® (patiromer sorbitex calcium)		Hypersensitivity to PSC or any component of the formulation
Lokelma® (sodium zirconium cyclosilicate)		None

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Warnings/Precautions

Medication	Warnings/Precautions
Kionex® (sodium polystyrene sulfonate)	• Concerns related to adverse effects (AEs): aspiration, electrolyte disturbances, fecal impaction (large doses in elderly, rectal administration in children), intestinal necrosis and other serious gastrointestinal (GI) events • Disease related concerns: caution in severe HF and/or HTN, edema, and renal impairment • Concurrent drug therapy issues: potentially significant drug-drug interactions may exist • Special populations: caution in premature or low birth weight infants • Dosage form specific issues: some formulations may contain propylene glycol large amounts of which are potentially toxic and have been associated with hyperosmolality, lactic acidosis, seizures and respiratory depression • Other: effective lowering of K+ may take hours to days, alternative measures or concomitant therapy may be warranted when rapid correction of severe hyperkalemia is required; enema will reduce K+ more rapidly than oral but oral will result in a greater reduction over several hours
Veltassa® (patiromer sorbitex calcium)	• Concerns related to AEs: may be ineffective and may worsen GI conditions (e.g. constipation, bowel obstruction or impaction, bowel motility disorders) • Special populations: elderly patients may experience more GI AEs
Lokelma® (sodium zirconium cyclosilicate)	• Concerns related to AEs: mild to moderate edema has been reported more commonly at higher doses; may be ineffective and may worsen GI conditions (e.g. constipation, bowel obstruction or impaction, bowel motility disorders) • Disease-related concerns: avoid use in patients with GI motility disorders (e.g. severe constipation, bowel obstruction or impaction, including abnormal postoperative bowel motility disorders) • Special populations: Hemodialysis (HD) patients may be at increased risk of hypokalemia due to associated conditions (e.g. diarrhea, decreased oral intake) • Dosage form specific issues: each 5 g dose contains ~ 400 mg sodium; dietary sodium intake may require adjustment • Other warnings or precautions: Abdominal x-rays: Sodium zirconium cyclosilicate has radio-opaque properties; may appear as an imaging agent on abdominal x-ray.

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Practice Guidelines

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024 Apr;105(4S):S117-S314.

- The concept that chronic hyperkalemia can be alleviated in people with normal or reduced estimated GFR is supported by randomized trial evidence, with durations of up to 1 year for the newer agents, patiromer and sodium zirconium cyclosilicate (SZC), with less compelling evidence from short-term studies (up to a week) for sodium polystyrene sulfonate (SPS)
- If available, SZC is generally preferred over patiromer because of its more rapid onset of action. Both SZC and patiromer can acutely reduce serum potassium in patients with hyperkalemic emergency, although data are somewhat limited.
- We do not use SPS if patiromer or SZC are available. If necessary, SPS can lower the serum potassium in patients presenting with a hyperkalemic emergency.

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Clinical Trials/Systematic Reviews/Meta-Analyses

Citation	Design	Endpoints
Lepage L, Dufour AC, Doiron J, et al. Randomized Clinical Trial of Sodium Polystyrene Sulfonate for the Treatment of Mild Hyperkalemia in CKD. Clin J Am Soc Nephrol. 2015 Dec 7;10(12):2136-42. doi: 10.2215/CJN.03640415. Epub 2015 Nov 17.	Double-blind, randomized (1:1) clinical trial N = 33 Arms: SPS 30 g by mouth daily or placebo (PBO) for 7 days Inclusion criteria: adult outpatients with CKD and mild hyperkalemia Exclusion criteria: patients on dialysis; with a medication change affecting K+ within prior 30 days (excepting insulin); with dose change in ACEi, ARB or aliskiren within prior 60 days; with decompensated HF within prior 30 days	Primary: • Mean difference between study groups of serum K+ levels between baseline and the day after the last dose of treatment Secondary: • Safety
Results: SPS was superior to PBO in reducing serum K+ levels (mean difference between groups, -1.04 mEq/L; 95% confidence interval [CI], -1.37 to -0.71). While a higher proportion of patients in the SPS group were normokalemic at the end of their treatment compared to the PBO group, the difference was not statistically significant (73% versus 38%; P=0.07). There was a trend toward higher rates of electrolytic disturbances and an increase in GI side effects in the SPS group. **Conclusion**: In patients with mild hyperkalemia and CKD, SPS reduced serum K+ to a statistically significant extent compared to PBO.		

Citation	Design	Endpoints
Weir MR, Bakris GL, Bushinsky DA, et al; for OPAL-HK Investigators. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med. 2015;372(3):211-221.	Phase 3, 2-part, 12 week multi-center study consisting of 4-week single-group, single-blind initial treatment phase and an 8-week, PBO-controlled, single-blind, randomized (1:1) withdrawal phase N = 243 (initial 4-week treatment phase); 109 (randomized withdrawal phase) Arms: • Initial treatment phase – patients with mild hyperkalemia received initial dose of 8.4 g/day and those with moderate-severe received 16.8 g/day; doses could be adjusted to reach and maintain a target K+ per a pre-specified algorithm • Randomized withdrawal phase – patients continued with the treatment dose at week 4 of the initial phase or received PBO Inclusion criteria: • Initial treatment phase – adults with CKD stage 3 or 4, serum K+ of 5.1 to < 6.5 mmol/L, receiving stable dose of RAASi	Primary: • Initial treatment phase: mean change in serum K+ from baseline • Randomized withdrawal phase: difference between PSC and PBO groups in estimated median change in serum K+ from randomized withdrawal phase baseline Secondary: • Initial treatment phase: proportion of patients who had a serum K+ level of 3.8 to < 5.1 mmol/L at week 4 • Randomized withdrawal phase: proportion of patients with a recurrence of hyperkalemia according to two

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	• Randomized withdrawal phase – serum K+ ≥ 5.5 mmol/L at baseline of the initial treatment phase and K+ level at the end of the initial treatment phase within the target range (3.8 to <5.1 mmol/L) while receiving PSC and RAASis Exclusion criteria: • Potassium-related electrocardiographic changes; severe GI disorders; uncontrolled or unstable arrhythmias or clinically significant ventricular arrhythmias; recent cardiac surgery; kidney or heart transplantation; acute coronary syndrome; transient ischemic attack or stroke within the previous 2 months; confirmed systolic blood pressure (BP) ≥ 180 mm Hg or < 110 mm Hg or diastolic BP of ≥ 110 mm Hg or < 60 mm Hg; type 1 DM; emergency treatment for type 2 DM or exacerbation of acute HF within the previous 3 months; and New York Heart Association (NYHA) class IV HF	definitions: a serum K+ level of ≥ 5.1 mmol/L and a serum K+ level of ≥ 5.5 mmol/L • Safety

Results:

Primary:

- Initial treatment phase – Mean change in serum K+ at 4 weeks:
  - -1.01 ± 0.03 mmol/L (95% CI, -1.07 to -0.95; P<0.001)
- Randomized withdrawal phase – Median change in serum K+ at 8 weeks:
  - PSC group: 0.0
  - PBO group: 0.72
  - Between-group difference of 0.72 mmol/L (95% CI, 0.46 to 0.99; P<0.001)

Secondary:

- Initial treatment phase – Proportion of patients who had a serum K+ level of 3.8 to < 5.1 mmol/L: 76% (95% CI, 70 to 81)
- Randomized withdrawal phase – Proportion of patients with a recurrence of hyperkalemia at
  - a serum K+ level of ≥ 5.1 mmol/L: 91% (95% CI, 83 to 99) of the patients in the PBO group as compared with 43% (95% CI, 30 to 56) in the PSC group had at least one K+ value of ≥ 5.1 mmol/L (P<0.001 for the between-group difference)
  - a serum K+ level of ≥ 5.5 mmol/L: 60% (95% CI, 47 to 74) of the patients in the PBO group as compared with 15% (95% CI, 6 to 24) in the PSC group had at least one K+ value of ≥ 5.5 mmol/L through week 8 (P<0.001)
- Safety
  - Initial treatment phase – AEs were reported in 47% of the patients overall at rates similar in both groups of patients (with mild hyperkalemia and moderate-severe hyperkalemia); mild-moderate constipation was the most common AE (11% of patients).
  - Randomized withdrawal phase – the proportion of patients with ≥ 1 AE was similar in PBO and the PSC groups (50% and 47%, respectively). Mild-to-moderate constipation, diarrhea, and nausea were the most common GI events reported with PSC (each in 4% of the patients); these events occurred in none of the patients in the PBO group.

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Conclusion: PSC treatment is associated with decreased serum K+ levels and, as compared with PBO, a reduced recurrence of hyperkalemia in patients with CKD and hyperkalemia receiving treatment with RAASis.

Citation	Design	Endpoints
Bakris GL, Pitt B, Weir MR, et al; for AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA. 2015;314(2):151-161.	Phase 2, open-label, randomized (1:1:1), 52-week, dose-ranging clinical trial N = 306 Arms: • Patients with mild hyperkalemia (baseline K+ > 5-5.5 mEq/L) received initial dose of PSC 4.2 g, 8.4 g, or 12.6 twice daily (BID) • Patients with moderate hyperkalemia (baseline K+ > 5.5-6 mEq/L) received initial dose of PSC 8.4 g, 12.6 g, or 16.8 g BID • Dose could be titrated in a stepwise fashion to the individualized effective dose to maintain control of serum K+ Inclusion criteria: Patients age 30 to 80 years with CKD and type 2 DM; baseline serum K+ > 5.0 mEq/L at randomization; receiving ACEi or ARB therapy Exclusion criteria: A1c > 12%, NYHA class III or IV HF	Primary: • Mean change in serum K+ from baseline to week 4 • Safety – frequency and severity of AEs through week 52 Secondary: • Mean changes in serum K+ from baseline to other post-baseline visits

Results:

Primary:

- Least squares mean reduction in serum K+ from baseline to week 4:
  - Mild hyperkalemia:
    - 8.4 g/d group – 0.35 (95% CI, 0.22-0.48) mEq/L
    - 16.8 g/d group – 0.51 (95% CI, 0.38-0.64) mEq/L
    - 25.2 g/d group – 0.55 (95% CI, 0.42-0.68) mEq/L
    - P < 0.001 for all
  - Moderate hyperkalemia:
    - 16.8 g/d group – 0.87 (95% CI, 0.60-1.14) mEq/L
    - 25.2 g/d group – 0.97 (95% CI, 0.70-1.23) mEq/L
    - 33.6 g/d group – 0.92 (0.67-1.17) mEq/L
    - P < 0.001 for all
- Safety – 69% of patients reported at least 1 treatment-emergent adverse event (TEAE), with 20% reporting an AE considered by the investigator to be related to PSC; the most frequently reported TEAEs were hypomagnesemia (7.2%), constipation (4.6%), and diarrhea (2.7%).

Secondary:

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- Mean changes in serum K+ from baseline to other post-baseline visits: From week 4 through week 52, significant (P < 0.001) mean decreases from baseline in serum K+ levels were observed at each monthly time point in patients with mild and moderate hyperkalemia.

Conclusion: PSC doses of 4.2 - 16.8 g BID are associated with statistically significant decreases in serum K+ levels beginning at 4 weeks of treatment and lasting through 52 weeks in patients with DM, CKD, and hyperkalemia taking RAASis.

Citation	Design	Endpoints
Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. JAMA. 2014 Dec 3;312(21):2223-33. doi: 10.1001/jama.2014.15688.	Phase 3, randomized (4:4:4:7), double-blind, 28 day, PBO-controlled trial N = 237 patients who achieved normokalemia (serum K+ 3.5 - 5.0 mEq/L) in the 48-hour open-label phase were randomized to receive active treatment or PBO Arms: SZC 5 g, 10 g or 15 g QD or PBO Inclusion criteria: adults with documented hyperkalemia (2 consecutive K+ values, measured 60 minutes apart, both ≥ 5.1 mEq/L) Exclusion criteria: pseudohyperkalemia, dialysis requirement, life expectancy < 3 months, pregnancy, cardiac arrhythmias requiring immediate treatment, diabetic ketoacidosis (DKA), active treatment with SPS or lactulose	Primary: • Mean serum K+ level in each SZC group vs PBO during days 8-29 Secondary: • Proportion of patients who were normokalemic at end of study • Safety

Results:

Primary:

- Mean serum K+ level in each SZC group vs PBO during days 8-29: Serum K+ was significantly lower with all three SZC doses vs PBO (5 g dose: 4.8 mEq/L [95% CI, 4.6-4.9]; 10 g dose: 4.5 mEq/L [95% CI, 4.4-4.6]; 15 g dose: 4.4 mEq/L [95% CI, 4.3-4.5]; PBO: 5.1 mEq/L [95% CI, 5.0-5.2]; P < 0.001 for all comparisons).

Secondary:

- Proportion of patients who were normokalemic at end of study: Significantly higher in each of the three SZC groups compared with PBO and numerically greater with higher doses (71%, 76%, and 85% for 5 g, 10 g, and 15 g groups, respectively, vs 48% with placebo; P = 0.01 for 5-g, P = 0.002 for 10-g, P < 0.001 for 15-g dose of SZC vs PBO).
- Safety: Edema was more common in the 15 g SZC group (incidence 14%) compared to a range of 2% - 6% in the PBO, 5 g, and 10 g groups. Hypokalemia developed in 10% and 11% in the 10 g and 15 g SZC groups but did not develop in 5 g and PBO groups.

Conclusion: Among outpatients with hyperkalemia, open-label SZC reduced serum K+ to normal levels within 48 hours. Compared with PBO, SZC resulted in statistically significantly lower K+ levels for up to 28 days.

Citation	Design	Endpoints
Packham DK, Rasmussen HS, Lavin PT. Sodium zirconium cyclosilicate in hyperkalemia. N Engl J Med. 2015 Jan 15;372(3):222-31. doi:	Phase 3, two-stage, 14-day study consisting of 48 hour, single-group, open-label, initial treatment phase and a 12-day, PBO-controlled, double-blind, randomized (1:1) withdrawal phase	Primary: • The between group difference in the mean serum K+ level during the 12-day treatment interval

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10.1056/NEJMoa1411487. Epub 2014 Nov 21.	N = 543 patients who achieved normokalemia (serum K+ 3.5 - 4.9 mmol/L) in the 48 hour open-label phase Arms: SZC 1.25 g, 2.5 g, 5 g, or 10 g TID or PBO Inclusion criteria: adults with a serum K+ of 5.0 to 6.5 mmol/L Exclusion criteria: patients receiving dialysis, with DKA, with K+ > 6.5 mmol/L, with cardiac arrhythmia that required immediate treatment, or patients who had received organic polymer resins or phosphate binders within 1 week before enrollment	Secondary: • Safety
Results: Primary: • During the maintenance phase, serum K+ levels were maintained at 4.7 mmol/L in the 5 g group and 4.5 mmol/L in the 10 g group, respectively, as compared with a level of > 5.0 mmol/L in the PBO group (P<0.01 for all comparisons). *(Note: the published study did not report on the between group difference in the mean serum K+ during the maintenance phase.)* Secondary: • Safety: Rates of adverse events were similar in the SZC (12.9%) and PBO (10.8%) groups during both initial an maintenance phases with diarrhea being the most common complication in the study groups. **Conclusion**: Patients with hyperkalemia who received SZC had a significant reduction in K+ levels at 48 hours, with normokalemia maintained during 12 days of maintenance therapy when compared to PBO therapy.		

Citation	Design	Endpoints
Meaney CJ, Beccari MV, Yang Y, Zhao J. Systematic Review and Meta-Analysis of Patiromer and Sodium Zirconium Cyclosilicate: A New Armamentarium for the Treatment of Hyperkalemia. Pharmacotherapy. 2017 Apr;37(4):401-411. doi: 10.1002/phar.1906. Epub 2017 Mar 10.	A systematic review and meta-analysis according to a standardized, pre-specified protocol and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines N = 6 studies – 3 studies of PSC (N=654 participants) and 3 studies of SZC (N=1,102 participants) Inclusion criteria: phase 2 and 3 clinical trials of PSC and SZC published in English Exclusion criteria: none listed	Primary: • PSC – change in K+ at 4 weeks • SZC – change in K+ at 48 hours Secondary: • PSC – change in K+ at 3 days • SZC – change in K+ at 1 hour • Safety
Results: Primary: • PSC – change in K+ at 4 weeks: -0.7 mEq/L (95% CI -0.48 to -0.91 mEq/L) • SZC – change in K+ at 48 hours: -0.67 mEq/L (95% CI -0.45 to -0.89 mEq/L)		

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Secondary:

- PSC – change in K+ at day 3: -0.36 mEq/L (range of standard deviation: 0.07 to 0.30 mEq/L)
- SZC – change in K+ at 1 hour: -0.17 mEq/L (95% CI -0.05 to -0.30 mEq/L)
- Safety: Adverse effects: PSC was associated with more GI upset (7.6% constipation, 4.5% diarrhea) and electrolyte depletion (7.1% hypomagnesemia), while SZC was associated urinary tract infections (1.1%) and edema (0.9%).

Conclusion: Both PSC and SZC reduced K+ to statistically and clinically significant extents for the primary endpoint. SZC may prove preferred in the treatment of acute hyperkalemia as a result of the improved adverse effect profile and demonstrated onset of action.

Citation	Design	Endpoints
Natale P, Palmer SC, Ruospo M, Saglimbene VM, Strippoli GF. Potassium binders for chronic hyperkalaemia in people with chronic kidney disease. Cochrane Database Syst Rev. 2020 Jun 26;6(6):CD013165. doi: 10.1002/14651858.CD013165.pub2.	Meta-analysis of K+ binders for chronic hyperkalemia in renal disease N = 15 studies, 1,849 patients Inclusion criteria: Randomized controlled trials (RCTs) and quasi-RCTs; adults and children; CKD and chronic hyperkalemia or at risk of chronic hyperkalemia or tubular renal disorders associated with hyperkalemia; people treated with dialysis (CKD stage 5D), those who had end-stage kidney disease (ESKD) treated with conservative care, recipients of a kidney transplant (CKD 5T), and those with earlier stages (1 to 4) of CKD; studies of K+ binders for hyperkalemia in people with several medical conditions (such as HF) if the study included people with CKD; studies that evaluated K+ binders; Exclusion criteria: studies that evaluated acute management of hyperkalemia using interventions such as salbutamol, calcium gluconate, insulin-dextrose, or sodium bicarbonate; studies of interventions for hyperkalemia within the hospital setting.	Primary: • Death from any cause • Cardiovascular death • Health-related quality of life (HRQoL) • GI symptoms Secondary: • Serum K+ levels • BP

Results:

Primary:

- Death from any cause: PSC or SZC may make little or no difference to death (any cause) (4 studies, 688 participants: RR 0.69, 95% CI 0.11, 4.32; I2 = 0%; low certainty evidence) in CKD.
- Cardiovascular death: There was no difference between PSC or SZC and PBO for cardiovascular death in CKD and HD.
- HRQoL: There was no evidence of a difference between PSC or SZC and PBO at the end of treatment (one study) in CKD or HD.
- GI symptoms: K+ binders had uncertain effects on nausea (3 studies, 229 participants: RR 2.10, 95% CI 0.65, 6.78; I2 = 0%; low certainty evidence), diarrhea (5 studies, 720 participants: RR 0.84, 95% CI 0.47, 1.48; I2 = 0%; low certainty evidence), vomiting (2 studies, 122 participants: RR 1.72, 95% CI 0.35 to 8.51; I2 = 0%; low certainty evidence), and constipation (4 studies, 425 participants: RR 1.58, 95% CI 0.71, 3.52; I2 = 0%; low certainty evidence) in CKD.

Secondary:

- Serum K+ levels: K+ binders may lower serum K+ levels (at the end of treatment) (3 studies, 277 participants: MD -0.62 mEq/L, 95% CI -0.97, -0.27; I2 = 92%; low certainty evidence) in CKD and HD.

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- BP: K+ binders may decrease systolic BP (2 studies, 369 participants: MD -3.73 mmHg, 95%CI -6.64 to -0.83; I2 = 79%; low certainty evidence) and diastolic BP (one study) at the end of the treatment.

Conclusion: The authors concluded "This review suggests the need for a large, adequately powered study of potassium binders versus placebo that assesses clinical outcomes of relevance to patients, clinicians and policy-makers."

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Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
SPS® (sodium polystyrene sulfonate) with sorbitol 15 gm/60 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
SPS® (sodium polystyrene sulfonate) with sorbitol 30 gm/120 mL enema suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Kionex® (sodium polystyrene sulfonate) 15 gm/60 mL oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
sodium polystyrene sulfonate oral powder	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Lokelma® (sodium zirconium cyclosilicate) 5 gram, 10 gram oral powder packet	1	1	$828.62	$828.62	0	0 (0%)	F-QL (34/30)	No change
Veltassa® (patiromer calcium sorbitex) 8.4 gram, 16.8 gram, 25.2 gram oral powder packet	0	0	$0.00	$0.00	0	0 (0%)	F-QL-ST (30/30) (Trial and failure of Lokelma)	No change
TOTAL	1	1	$828.62	$828.62	0	0 (0%)		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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Prior Authorization Criteria

Recommendation: No changes

Potassium-removing agents	
Therapeutic Classes (AHFS)	Potassium-removing agents
Medications	Formulary, quantity limit Lokelma (sodium zirconium cyclosilicate) Formulary, step therapy required, quantity limit Veltassa (patiromer) powder packets
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Step-therapy Criteria • For Veltassa, documented (consistent with pharmacy claims data), OR for new members to the health plan consistent with medical chart history) documentation of trial and failure, intolerance, or contraindication to Lokelma
Criteria Statement	Veltassa is reserved for members who have used (or cannot/should not use) Lokelma.
Last P&T Review Date	~~6/2024~~6/2025

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Potassium Supplements

Executive Summary

Class Overview

Hypokalemia is a common occurrence. It is most often caused by unreplenished urinary or gastrointestinal (GI) loss of potassium resulting from medical conditions, such as vomiting or diarrhea, or as a side effect of pharmacotherapy, such as with diuretics. It can also be precipitated by decreased potassium intake or redistribution of potassium into cells. In the latter case, supplementation with exogenous potassium is administered cautiously because translocation back out of cells typically occurs rapidly and can therefore precipitate hyperkalemia.

Optimal therapy in patients with hypokalemia due to potassium loss is dependent upon the severity of the potassium deficit. The most recent guidelines in the United States relating to the treatment of hypokalemia were published in 2000. Treatment options include various potassium salts (chloride, phosphate, bicarbonate or its precursors citrate or acetate, or gluconate) available by parenteral or enteral routes. There are both prescription and over-the-counter formulations of potassium supplements. Choice of therapy depends on the clinical setting. Potassium bicarbonate is preferred in the setting of metabolic acidosis (e.g. renal tubular acidosis or diarrhea) while potassium chloride is preferred in all other settings.

Utilization Findings

There were 33 claims for 27 members, for a total cost of $1,178.30 and an average cost per claim of $35.71. The most highly utilized medication was potassium chloride (Klor-Con M) ER tablets, with 16 claims, followed by potassium chloride (Klor-Con K-Tab) ER tablets with 13 claims. There were no prior authorization requests.

Recommendations

- No changes

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Clinical Summary

Hypokalemia is a common occurrence. It is most often caused by unreplenished urinary or GI loss of potassium resulting from medical conditions, such as vomiting or diarrhea, or as a side effect of pharmacotherapy, such as with diuretics. It can also be precipitated by decreased potassium intake or redistribution of potassium into cells. In the latter case, supplementation with exogenous potassium is administered cautiously because translocation back out of cells typically occurs rapidly and can therefore precipitate hyperkalemia. Optimal therapy in patients with hypokalemia due to potassium loss is dependent upon the severity of the potassium deficit. Treatment options include various potassium salts (chloride, phosphate, bicarbonate or its precursors citrate or acetate, or gluconate) available by parenteral or enteral routes. There are both prescription and over-the-counter formulations of potassium supplements.

Most hypokalemic patients are mildly to moderately so, having a serum potassium of 3.0 to 3.4 mEq/L. They are typically asymptomatic, with the exception of patients with heart disease or cirrhosis. The treatment of mild to moderate hypokalemia depends on the cause and acid-base status. Patients with GI losses are repleted with potassium chloride (in the setting of metabolic alkalosis or normal serum bicarbonate concentration) or potassium bicarbonate in the setting of metabolic acidosis. Treatment is usually started with 10 to 20 mEq of potassium given two to four times per day (20 to 80 mEq/day), depending upon the severity of the hypokalemia. By contrast, in patients with renal potassium wasting, a potassium sparing diuretic is more likely to be effective than potassium supplements. Severe (serum potassium < 2.5 to 3.0 mEq/L) or symptomatic (arrhythmias, marked muscle weakness, or rhabdomyolysis) hypokalemia requires rapid potassium repletion orally or intravenously. The choice of potassium salt depends on the clinical setting; potassium bicarbonate is preferred in the setting of metabolic acidosis (e.g. renal tubular acidosis or diarrhea) while potassium chloride is preferred in all other settings.

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Indications, Dosing and Administration

Medication	Indications	Dosing/Administration
Potassium chloride (Klor-Con®, K-Tab®, Klor-Con® M, Pokonza™)	Treatment or prevention of hypokalemia	Prevention: 10 to 80 mEq/day in 1 to 4 divided doses Treatment: 40 to 100 mEq/day in divided doses; limit single doses to 20 to 25 mEq/dose to avoid GI discomfort
Potassium bicarbonate/citric acid (Effer-K®, Klor-Con®/EF, K-Prime®)	Treatment or prevention of hypokalemia	Prevention: 10 to 80 mEq/day in 1 to 4 divided doses Treatment: 40 to 100 mEq/day in divided doses; limit single doses to 20 to 25 mEq/dose to avoid GI discomfort
Potassium gluconate	Dietary potassium supplement	One tablet daily
Potassium aspartate/magnesium aspartate	As a dietary supplement	Take one capsule with a meal

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Boxed Warnings and Contraindications

Medication	Boxed Warnings	Contraindications
Potassium chloride (Klor-Con®, K-Tab®, Klor-Con® M, Pokonza™)	None	Hypersensitivity, hyperkalemia, coadministration with potassium-sparing diuretics All solid oral dosage forms are contraindicated in patients in whom there is a structural, pathological, and/or pharmacologic cause for delay or arrest in passage through the GI tract
Potassium bicarbonate/citric acid (Effer-K®, Klor-Con®/EF, K-Prime®)		Hyperkalemia, coadministration with potassium-sparing diuretics or potassium supplements
Potassium gluconate		Hyperkalemia
Potassium aspartate/magnesium aspartate		None

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Warnings/Precautions

Medication	Warnings/Precautions
Potassium chloride (Klor-Con®, K-Tab®, Klor-Con® M, Pokonza™)	Concerns related to adverse effects: - Hyperkalemia may occur; use with caution or avoid use in patients with predisposing conditions for hyperkalemia (e.g., chronic or severe renal impairment, extensive burns or tissue injury, heart failure, acute dehydration, systemic acidosis, adrenal insufficiency, or the administration of potassium-sparing diuretics) Disease-related concerns: - Acid/base disorders: Use with caution in patients with acid/base alterations or acid/base correction; hyperosmolality or acidosis (or correction of alkalosis) is associated with hyperkalemia (shift of intracellular potassium to extracellular space); monitor serum potassium closely - Cardiovascular disease: Use with caution in patients with cardiovascular disease (e.g., heart failure, cardiac arrhythmias, atrioventricular block); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia - Hepatic impairment: Use with caution in patients with cirrhosis; monitor serum potassium more frequently - Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium closely Dosage form specific issues: - Oral formulations: May cause GI upset and irritation and lead to GI ulceration, bleeding, perforation, and/or obstruction
Potassium bicarbonate/citric acid (Effer-K®, Klor-Con®/EF, K-Prime®)	Concerns related to adverse effects: - GI effects: May cause GI upset (e.g., nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction - Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (e.g., heart block, ventricular arrhythmias, asystole) Disease-related concerns: - Acid/base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction, monitor closely - Cardiovascular disease: Use with caution in patients with cardiovascular disease (e.g., heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia - Metabolic acidosis: Patients with hypokalemia accompanied by metabolic acidosis should be treated with an alkalinizing potassium salt - Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (e.g., untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns) - Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely; avoid with severe impairment Concurrent drug therapy issues:

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Medication	Warnings/Precautions
	- Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations - Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (e.g., ACE inhibitors, potassium-sparing diuretics, potassium-containing salt substitutes)
Potassium gluconate	Concerns related to adverse effects: - GI effects: May cause GI upset (e.g., nausea, vomiting, diarrhea, abdominal pain, discomfort) and lead to GI ulceration, bleeding, perforation and/or obstruction - Hyperkalemia: Close monitoring of serum potassium concentrations is needed to avoid hyperkalemia; severe hyperkalemia may lead to muscle weakness/paralysis and cardiac conduction abnormalities (e.g., heart block, ventricular arrhythmias, asystole) Disease-related concerns: - Acid/Base disorders: Use with caution in patients with acid/base alterations; changes in serum potassium concentrations can occur during acid/base correction - Cardiovascular disease: Use with caution in patients with cardiovascular disease (e.g., heart failure, cardiac arrhythmias); patients may be more susceptible to life-threatening cardiac effects associated with hyper/hypokalemia - Potassium-altering conditions/disorders: Use with caution in patients with disorders or conditions likely to contribute to altered serum potassium and hyperkalemia (e.g., untreated Addison's disease, heat cramps, severe tissue breakdown from trauma or burns) - Renal impairment: Use with caution in patients with renal impairment; monitor serum potassium concentrations closely Concurrent drug therapy issues: - Digitalis: Use with caution in digitalized patients; may be more susceptible to potentially life-threatening cardiac effects with rapid changes in serum potassium concentrations - Potassium-altering therapies: Use with caution in patients receiving concomitant medications or therapies that increase potassium (e.g., ACE-inhibitors, potassium-sparing diuretics, potassium containing salt substitutes)
Potassium/magnesium aspartate	Keep out of reach of children

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Practice Guidelines

Cohn JN, Kowey PR, Whelton PK, Prisant LM. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. Arch Intern Med. 2000;160(16):2429-2436.

Consensus guidelines for the use of potassium replacement in clinical practice:

Low serum potassium concentration is perhaps the most common electrolyte abnormality encountered in clinical practice. Strategies aimed at achieving and maintaining normokalemia must take into account such factors as (1) baseline potassium values, (2) the presence of underlying medical conditions (e.g., CHF), (3) the use of medications that alter potassium levels (e.g., non–potassium-sparing diuretics) or that lead to arrhythmias in the presence of hypokalemia (e.g., cardiac glycosides), (4) patient variables such as diet and salt intake, and (5) the ability to adhere to a therapeutic regimen.

Because of the multiple factors involved, guidelines therefore should be directed toward patients with specific disease states, such as those with cardiovascular conditions, and toward the general patient population. The following list encompasses our general practices for the use of potassium. The guidelines were developed at a 1998 meeting of the National Council on Potassium in Clinical Practice. It is clear that controlled clinical studies are necessary to determine the specific recommendations.

General Guidelines

1. Dietary consumption of potassium-rich foods should be supplemented with potassium replacement therapy. Often, increasing dietary potassium intake is not completely effective in replacing the potassium loss associated with chloride depletion (e.g., that which occurs in diuretic therapy, vomiting, or nasogastric drainage) because dietary potassium is almost entirely coupled with phosphate, rather than with chloride. In addition, the consumption of potassium-rich foods in amounts that are sufficient to increase the level of serum potassium level to acceptable concentrations may be costly, and it may lead to weight gain.
2. Potassium replacement is recommended for individuals who are sensitive to sodium or who are unable or unwilling to reduce salt intake; it is especially effective in reducing blood pressure in such persons. A high-sodium diet often results in excessive urinary potassium loss.
3. Potassium replacement is recommended for individuals who are subject to nausea, vomiting, diarrhea, bulimia, or diuretic/laxative abuse. Potassium chloride has been shown to be the most effective means of replacing acute potassium loss.
4. Potassium supplements are best administered orally in a moderate dosage over a period of days to weeks to achieve the full repletion of potassium.
5. Although laboratory measurement of serum potassium is convenient, it is not always an accurate indicator of total body potassium. Measurement of 24-hour urinary potassium excretion is appropriate for patients who are at high risk (e.g., those with CHF).
6. Patient adherence to potassium supplementation may be increased with compliance-enhancing regimens. Microencapsulated formulations have no unpleasant taste and are associated with a relatively low incidence of gastrointestinal side effects.
7. Potassium supplementation regimens should be as uncomplicated as possible to help optimize long-term compliance.
8. A dosage of 20 mmol/d of potassium in oral form is generally sufficient for the prevention of hypokalemia, and 40 to 100 mmol/d sufficient for its treatment.

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Patients With Hypertension

1. Patients with drug-related hypokalemia (i.e., therapy with a non–potassium-sparing diuretic) should receive potassium supplementation.
2. In patients with asymptomatic hypertension, an effort should be made to achieve and maintain serum potassium levels of at least 4.0 mmol/L. Low serum potassium levels (e.g., 3.4 mmol/L) in asymptomatic patients with uncomplicated hypertension should not be regarded as inconsequential. Dietary consumption of potassium-rich foods and potassium supplementation should be instituted as necessary.

Patients With CHF

Potassium replacement should be routinely considered in patients with CHF, even if the initial potassium determination appears to be normal (e.g., 4.0 mmol/L). The majority of patients with CHF are at increased risk for hypokalemia. In patients with CHF or myocardial ischemia, mild-to-moderate hypokalemia can increase the risk of cardiac arrhythmia. In addition, diuretic-induced hypokalemia can increase the risk of digitalis intoxication and life-threatening arrhythmias.

In light of the above information and the potential for hyperkalemia to occur secondary to drug therapy with ACE inhibitors or angiotensin II receptor blockers, regular monitoring of the serum potassium level is essential in these patients. At any time, stress can trigger the secretion of aldosterone and the release of catecholamine in response to low cardiac output, thereby precipitating a fall in the serum potassium level.

Patients With Cardiac Arrhythmias

Maintenance of optimal potassium levels (at least 4.0 mmol/L) is critical in these patients and routine potassium monitoring is obligatory. Patients with heart disease are often susceptible to life-threatening ventricular arrhythmias. In particular, such arrhythmias are associated with heart failure, left ventricular hypertrophy (characterized by an abnormal QRS complex), myocardial ischemia, and myocardial infarction (both in the acute phase and after remodeling). The coadministration of magnesium should be considered to facilitate the cellular uptake of potassium.

Patients Prone to Stroke

It is prudent to maintain optimal potassium levels in patients at high risk for stroke (including those with a history of atherosclerotic or hemorrhagic cerebral vascular accidents). Although the effectiveness of potassium supplementation in reducing the incidence of stroke in humans has not been demonstrated in randomized controlled trials, prospective studies suggest that the incidence of fatal and nonfatal stroke correlates inversely with dietary potassium intake. In addition, the association of stroke with hypertension is well known.

Patients With Diabetes Mellitus

Potassium levels should be closely monitored in patients with diabetes mellitus and potassium replacement therapy should be administered when appropriate. Data underscore the adverse effects of glucose and insulin on potassium levels and the high incidence of cardiovascular and renal complications in patients with diabetes mellitus. These factors are specific to patients with type 2 diabetes who have poorly controlled serum glucose levels.

Patients With Renal Impairment

Data suggest a link between potassium levels and lesions of the kidneys in patients with renal disease or diabetes. Animal studies have demonstrated that potassium may offer a protective effect on the renal arterioles. The clinical implications of these findings are not yet clear.

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Clinical Trials/Systematic Reviews/Meta-Analyses

A search of the literature revealed no clinical studies, meta-analyses, comparative effectiveness trials or systematic reviews on the use of potassium to treat or prevent the indicated disease state, hypokalemia.

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Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Prescription								
Potassium chloride 8 mEq, 10 mEq ER capsules	3	2	$205.04	$68.35	0	0 (0%)	F	No change
Pokonza™ (potassium chloride) 10 mEq oral packet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Potassium chloride (Klor-Con®) 20 mEq oral packet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Potassium chloride 20 mEq/15 ml, 40 mEq/15 ml oral solution	1	1	$20.10	$20.10	0	0 (0%)	F	No change
Potassium chloride (Klor-Con®, K-Tab®) 8 mEq, 10 mEq, 15 mEQ, 20 mEq ER tablets	13	11	$357.64	$27.51	0	0 (0%)	F	No change
Potassium chloride (Klor-Con® M) 10 mEq, 15 mEq, 20 mEq ER PRT tablets	16	13	$595.52	$37.22	0	0 (0%)	F	No change
Effer-K® (potassium bicarbonate/citric acid) 10 mEq, 20 mEq effervescent tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Potassium bicarbonate/citric acid (Effer-K®, Klor-Con®/EF) 25 mEq effervescent tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
OTC								
Magnesium aspartate/potassium aspartate 250 mg/250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Potassium gluconate 500 (83) mg, 550 (90) mg, 595 (99) mg tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**33**	**27**	**$1,178.30**	**$35.71**	0	0 (0%)		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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Drug Name: Luxturna (voretigene neparvovec-rzyl)

Manufacturer: Spark Therapeutics, Inc.

Approval Date: 12/19/2017

Marketing Date: 1/12/2018

Recommendation

- No changes
  - The current formulary status is NF
  - There was no utilization of this medication and no prior authorization requests from 1/1/2025 to 3/31/2025

Prescribing Information

Indication

Luxturna (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

Patients must have viable retinal cells as determined by the treating physician(s).

Mechanism of Action

Luxturna is designed to deliver a normal copy of the gene encoding the human retinoid isomerohydrolase RPE65 (RPE65) to cells of the retina in persons with reduced or absent 10 levels of biologically active RPE65. The RPE65 is produced in the retinal pigment epithelial (RPE) cells and converts all-trans-retinol to 11-cis-retinol, which subsequently forms the chromophore, 11-cis-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in the RPE65 gene lead to reduced or absent levels of retinoid isomerohydrolase RPE65 activity, blocking the visual cycle and resulting in impairment of vision.

Dosage and Administration

The recommended dose of Luxturna for each eye is 1.5 x 1011 vector genomes (vg), administered by subretinal injection in a total volume of 0.3 ml to each eye on separate days within a close interval, but no fewer than 6 days apart.

Recommend systemic oral corticosteroids equivalent to prednisone at 1 mg/kg/day (maximum of 40 mg/day) for a total of 7 days (starting 3 days before administration of Luxturna to the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid dosing regimen applies for the administration of Luxturna to the second eye. If the corticosteroid taper following Luxturna administration to the first eye is not complete three days prior to the

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planned Luxturna administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.

Black Box Warning

None

Adverse Reactions

Most common: (incidence ≥ 5%): conjunctival hyperemia, cataract, increased intraocular pressure, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

Serious: endophthalmitis; permanent decline in visual acuity; retinal abnormalities (macular holes, foveal thinning, loss of foveal function, foveal dehiscence, retinal hemorrhage); increased intraocular pressure, irreversible visions loss (due to expansion of intraocular air bubbles); cataract.

Use in Specific Populations, Pregnancy

Adequate and well-controlled studies with Luxturna have not been conducted in pregnant women. Animal reproductive studies have not been conducted with Luxturna.

Drug Interactions

Unknown. No interaction studies have been performed.

How Supplied

Luxturna is a suspension for subretinal injection, supplied in a 0.5-mL extractable volume in a 2-mL single-dose vial; the supplied concentration (5 x 1012 vg/mL) requires a 1:10 dilution prior to administration.

Price

$913,750 (both eyes)

(Per one time treatment, based on WAC)

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Clinical Studies

Completed

Title	A Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301] NCT: 00999609 PMID: 28712537
Design	Phase 3, open-label, parallel assignment, randomized controlled trial
Population	N = 31 The average age of the 31 randomized subjects was 15 years (range 4 to 44 years), including 64% pediatric subjects (n=20, age from 4 to 17 years) and 36% adults (n=11). The 31 randomized subjects included 13 males and 18 females. Sixty-eight percent (68%) of the subjects were White, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were Black or African-American. Bilateral subretinal injections of LUXTURNA were administered sequentially in two separate surgical procedures with an interval of 6 to 18 days.
Arms	• Experimental: Subretinal administration of gene therapy vector to both eyes via surgical procedures on separate days • Control: no intervention
Endpoint(s)	Primary: • Multi-luminance mobility testing (MLMT) score change from Baseline to Year 1
Inclusion Criteria	• Diagnosis of LCA due to RPE65 mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-approved laboratory. • Age three years old or older. • Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes). • Sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Must have either: 1) an area of retina within the posterior pole of >100 µm thickness shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or 3) remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent. • Subjects must be evaluable on mobility testing (the primary efficacy endpoint) to be eligible for the study. Evaluable is defined as: 1) The ability to perform mobility testing within the luminance range evaluated in the study. Individuals must receive an accuracy score of ≤ 1 during screening mobility testing at 400 lux or less to be eligible; individuals with an accuracy

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	score of > 1 on all screening mobility test runs at 400 lux, or those who refuse to perform mobility testing at screening, will be excluded. (See Appendix 3 for a description of accuracy score.); 2) The inability to pass mobility testing at 1 lux. Individuals must fail screening mobility testing at 1 lux to be eligible; individuals that pass one or more screening mobility test runs at 1 lux will be excluded.
Exclusion Criteria	• Any prior participation in a study in which a gene therapy vector was administered. • Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who discontinue use of these compounds for 18 months may become eligible. • Prior intraocular surgery within six months. • Known sensitivity to medications planned for use in the peri-operative period. • Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study. • Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration. • Individuals incapable of performing mobility testing (the primary efficacy endpoint) for reason other than poor vision, including physical or attentional limitations
Results	At 1 year, mean bilateral MLMT change score was 1·8 (SD 1·1) light levels in the intervention group versus 0·2 (1·0) in the control group (difference of 1·6, 95% CI 0·72-2·41, p=0·0013). 13 (65%) of 20 intervention participants, but no control participants, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement. No product-related serious adverse events or deleterious immune responses occurred. Two intervention participants, one with a pre-existing complex seizure disorder and another who experienced oral surgery complications, had serious adverse events unrelated to study participation. Most ocular events were mild in severity.
Conclusion	Voretigene neparvovec gene replacement improved functional vision in RPE65-mediated inherited retinal dystrophy previously medically untreatable.

Table 2. Efficacy Results of Study 2 at Year 1, Compared to Baseline

Efficacy Outcomes	LUXTURNA n=21	Control n=10	Difference (LUXTURNA minus Control)	p-value
MLMT score change for bilateral eyes, median (min, max)	2 (0, 4)	0 (-1, 2)	2	0.001
MLMT score change for first-treated eye, median (min, max)	2 (0, 4)	0 (-1, 1)	2	0.003

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Interpretation	Questions exist as to whether the treatment will continue to be of benefit clinically to the patient long term, as the patients were only assessed after one year.

Ongoing

Title	A Long-Term Follow-Up Study in Subjects Who Received an Adenovirus-Associated Viral Vector Serotype 2 Containing the Human RPE65 Gene (AAV2-hRPE65v2, Voretigene Neparvovec-rzyl) Administered Via Subretinal Injection NCT: 03602820
Design	Multi-site, non-randomized, observational study, for up to 15 years after subretinal AAV2-hRPE65v2 administration for each subject. The study is a non-interventional, follow-up study of subjects who participated in previous AAV2-hRPE65v2 gene therapy clinical trials.
Completion Date	June 2030

Guidelines

Inherited Retinal Dystrophy (IRD) is a previously untreatable disorder. Available guidelines focus on clinical assessment rather than treatment.

Clinical Opinions

The approval of Luxturna for the treatment of IRD is a groundbreaking moment in gene-based therapy for previously untreatable genetic disorders. However, much is still to be discovered regarding long-term benefits and risks of this therapy. Currently Luxturna is approved as a one-time treatment, but the phase III study resulting in FDA approval of this medication only demonstrated clinical significance in this population at one year post treatment. It is unclear how long Luxturna provides significant clinical benefit for patients, and longer term follow up studies should assess this question as well as any long-term complications or if repeated administration of the product yields positive outcomes. Studies should also determine whether Luxturna arrests the progression of IRD, or merely slows its progression. Some studies performed in animal models point to the likelihood that IRD will nonetheless progress after Luxturna treatment, and that repeated therapy may be more beneficial than a single treatment over a patient's lifetime[8]. The matter of taking clinical significance and translating it into quality-of-life improvements for IRD patients is also important. The trial defined improved "functional vision" as improved ability to navigate a course in varying degrees of light, but no improvement in visual acuity was demonstrated.

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Considering the significant cost of Luxturna and limited treatment options, payers are tasked with the difficult decisions surrounding utilization management of this gene therapy. The observational follow-up study will provide additional information to navigate the product's place on formulary and anticipate financial impact. Of note, the Institute for Clinical and Economic Review (ICER) evidence report on the effectiveness and value of Luxturna (abbreviated in this report as VN) for eligible patients found this treatment in most cases to not be cost effective:

"A discount of up to 75%, would be necessary to reach a cost-effectiveness threshold of $150,000/QALY."

"The high cost makes this unlikely to be a cost-effective intervention at commonly used cost-effectiveness thresholds. However, if a societal perspective is used for a younger population, VN is likely to be cost-effective compared to standard of care at a threshold of $150,000/QALY."

Alternatives

None

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Drug Name: Provenge® (sipuleucel-T)

Manufacturer: Dendreon

Approval Date: 4/29/2010

Marketing Date: 5/14/2010

Recommendation

- No changes
  - The current formulary status is NF
  - There was no utilization of this medication and no prior authorization requests from 1/1/2025 to 3/31/2025

Prescribing Information

Indication

Asymptomatic or minimally symptomatic metastatic castration-resistant (hormone refractory) prostate cancer (mCRPC).

Mechanism of Action

The precise mechanism of action is unknown. However, sipuleucel-T is designed to induce an immune response targeted against PAP, an antigen expressed in most prostate cancers.

Dosage and Administration

- For autologous use only. For intravenous use only; do not use a cell filter
- Premedicate patients with oral acetaminophen and an antihistamine 30 minutes prior to administration to minimize acute infusion reactions such as chills, fever, nausea and joint ache.
- Recommended course of therapy for sipuleucel-T is 3 complete doses, infused over approximately 60 minutes, given at approximately 2-week intervals. If the patient is unable to receive a scheduled infusion of sipuleucel-T, the patient will need to undergo an additional leukapheresis procedure if the course of treatment is to be continued
- Do not infuse sipuleucel-T until confirmation of product release has been received from Dendreon. Dendreon will send a Cell Product Disposition Form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected), to the infusion site.

Black Box Warning

None

Adverse Reactions

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Most common: (incidence ≥ 15%) chills, fatigue, fever, back pain, nausea, joint ache, and headache
Serious: acute infusion reactions, cerebrovascular events, eosinophilia, rhabdomyolysis, myasthenia gravis, myositis, and tumor flare

Use in Specific Populations, Pregnancy

Not indicated for use in women.

Drug Interactions

None listed.

How Supplied

250 mL suspension containing a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF in Lactated Ringer's Injection, USP supplied in a sealed infusion bag, labeled for the specific recipient

Price

$62,500

(Per dose, based on WAC.)

Clinical Studies

Completed

Title	Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer NCT: 00005947 and 01133704 PMID: 19536890
Design	Two identical Phase 3 randomized (2:1), double-blind, placebo-controlled studies, intention to treat clinical trials evaluating the safety and efficacy of sipuleucel-T
Population	N = 225 Median age was 72 years in the sipuleucel-T group and 71 in the placebo group; >90% of patients were White; 77% of patients had an ECOG status of 0; only 7% of the sipuleucel-T group and 9% of the placebo group had received prior chemotherapy
Arms	Sipuleucel-T or placebo 3 doses administered approximately 2 weeks apart

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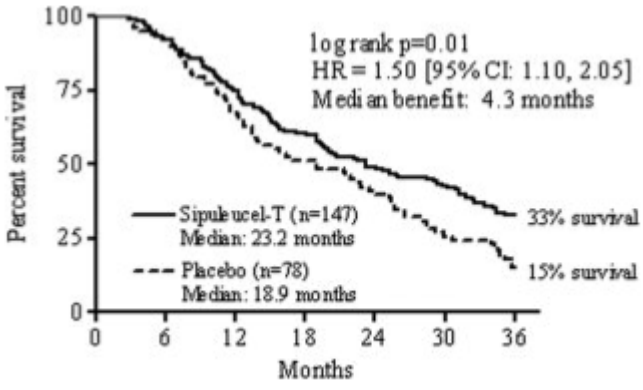
Endpoint(s)	Primary: • Time to objective disease progression Secondary: • Overall survival • Adverse events
Inclusion Criteria	• Evidence of progressive disease based on successive radiographic studies or PSA progression, as defined by PSA Consensus Criteria • An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and positive immunohistochemistry staining for PAP in ≥ 25% of tumor cells • Adequate hematologic, renal and hepatic functions • Prior investigational agents, hormonal agents (other than luteinizing hormone–releasing hormone [LHRH] agonists), herbal preparations, and radiation therapy were to be discontinued ≥ 4 weeks before registration. Radiopharmaceuticals could not have been administered within 1 year of treatment. • Concurrent bisphosphonate therapy was permitted provided therapy was initiated ≥ 30days before registration and was not discontinued (or initiated) during the study • Prior chemotherapy was permitted provided ≥ 6 months had elapsed, or ≥ 3 months had elapsed and the CD4+T-cell count was >400/µ
Exclusion Criteria	• Cancer-related bone pain, prior immunotherapy, requirement for systemic corticosteroids, requirement for opioid analgesics for cancer pain, and visceral metastases
Results	Primary: • Time to disease progression was not statistically different between the treatment groups (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.69-1.70; P = 0.72) Secondary: • Overall patient survival: 

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	• The median overall patient survival was 23.2 months for sipuleucel-T and 18.9 months for placebo, and the percentage of patients alive at 36 months was 33% and 15%. • Adverse events generally occurred soon after treatment and were low grade and transient. Less than 3% of patients were not able to receive all 3 infusions because of treatment-related adverse events. The overall incidence of adverse events was similar between patients treated with sipuleucel-T (98.6%) and patients treated with placebo (96.1%). The events occurring at a higher rate ($P \leq 0.05$) in those patients treated with sipuleucel-T compared with placebo were chills, pyrexia, headache, asthenia, dyspnea, vomiting, and tremor. Conclusions regarding the possible increased risk of cerebrovascular events could not be drawn at the time of study publication.
Conclusion	Sipuleucel-T may prolong overall survival. The modest toxicity profile, along with the survival benefit suggests a favorable risk-benefit ratio for sipuleucel-T in patients with asymptomatic, metastatic androgen independent prostate cancer.
Interpretation	The reduced risk of disease progression was not statistically significant in the integrated analysis. The reduced risk of death was. Separating out the results of the individual trials, one sees that the reduced risk of disease progression was statistically significant for NCT00005947 but not NCT01133704. The study authors hypothesize that this difference is attributable to the lower number of trial participants in NCT01133704, a number low enough that statistical significance calculations were compromised. An interdisciplinary critique of the studies appearing in JAMA in 2012 offered a different explanation, proposing flawed trial design or imbalanced risk as possible explanations.

Title	Sipuleucel-T immunotherapy for castration-resistant prostate cancer NCT: 00065442 PMID: 20818862
Design	Phase 3, randomized (2:1), double-blind, placebo-controlled
Population	N = 512 Median age was 71 years. All patients had received previous androgen-deprivation therapy; 82.0% reported having undergone combined androgen blockade. Previous therapies also included radiotherapy of the prostate or prostate bed (53.9% of patients), radical prostatectomy (35.2%), and chemotherapy (18.2%).
Arms	Sipuleucel-T (each dose containing a minimum of 40 million large cells expressing the costimulatory molecule CD54) or placebo administered intravenously every 2 weeks, for a total of three infusions
Endpoint(s)	Primary: • Overall survival

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	Secondary: • Time to objective disease progression • Adverse events
Inclusion Criteria	• Serum PSA ≥ 5 ng/mL • Serum testosterone < 50 ng/dL • Progressive disease on the basis of imaging studies or PSA measurements
Exclusion Criteria	• ECOG performance status ≥ 2, visceral metastases, pathologic long-bone fractures, spinal cord compression, and treatment within the previous 28 days with systemic glucocorticoids, external-beam radiation, surgery, or systemic therapy for prostate cancer (except medical or surgical castration) • Patients who had initiated or discontinued bisphosphonate therapy within the previous 28 days, had undergone previous treatment with > 2 chemotherapy regimens, or had undergone chemotherapy within the previous 3 months
Results	Primary: • Overall survival – By the study cut-off date, 331 patients had died, 61.6% from the sipuleucel-T group and 70.8% from the placebo group. For men in the sipuleucel-T group, as compared with those in the placebo group, the adjusted hazard ratio for death was 0.78 (95% CI, 0.61 to 0.98), representing a relative reduction in the risk of death of 22% (P = 0.03). The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months). Secondary: • Time to objective disease progression – 14.6 weeks (3.7 months) in the sipuleucel-T group and 14.4 weeks (3.6 months) in the placebo group (hazard ratio, 0.95; 95% CI, 0.77 to 1.17; P=0.63) • Adverse events – Ninety-eight percent of patients reported adverse events, 65.2% of whom experienced mild to moderate adverse events. Adverse events that were reported more frequently in the sipuleucel-T group than in the placebo group included chills (51.2%), fever (22.5%), headache (10.7%), influenza-like illness, myalgia, hypertension, hyperhidrosis, and groin pain. Except for groin pain, most of these events occurred within 1 day after infusion and resolved within 1-2 days.
Conclusion	Sipuleucel-T led to a significant improvement in overall survival for men with mCRPC. With a median follow-up of 34.1 months and complete survival follow-up data for 99% of patients, treatment with sipuleucel-T resulted in a 4.1-month improvement in median survival and an improvement in the rate of 3-year survival (31.7% for patients receiving sipuleucel-T, as compared with 23.0% for those receiving placebo). Overall, sipuleucel-T was well tolerated, and most patients received all three scheduled infusions. Adverse events that were more frequently reported for sipuleucel-T treatment than for placebo were generally consistent with the release of cytokines. There was no increased

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	incidence of cerebrovascular events, reports of anaphylaxis after administration, and no evidence of autoimmune sequelae observed. There was no significant effect on the time to objective disease progression observed.
Interpretation	According to the published study results, sipuleucel-T improved overall survival compared to placebo for men with mCRPC. As above, an interdisciplinary critique of the studies appearing in JAMA in 2012 offered a different explanation, proposing flawed trial design or imbalanced risk as possible explanations.

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Guidelines

NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Version 1.2025. December 4,2024.

Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2025
Prostate Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR M1 CRPC: ADENOCARCINOMA[f,fff,ggg,hhh,iii]

No prior docetaxel/no prior novel hormone therapy[lll]	Progression on prior novel hormone therapy/no prior docetaxel[lll]
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1 if no visceral metastases) ▸ Docetaxel[ddd] (category 1) ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 1) ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation (category 1) ▸ Pembrolizumab for MSI-high (MSI-H)/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] (category 1) ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 1) • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Docetaxel (category 1)[ddd] ▸ Olaparib for *BRCA* mutation[lll] (category 1) ▸ Rucaparib for *BRCA* mutation[lll] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation (category 2B) ▸ Olaparib for HRR mutation other than *BRCA1/2*[lll] ▸ Pembrolizumab for MSI-H/dMMR or TMB ≥10 mut/Mb[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] (category 2B) • Other recommended regimens ▸ Other secondary hormone therapy[z]
Progression on prior docetaxel/no prior novel hormone therapy[lll]	**Progression on prior docetaxel and a novel hormone therapy[lll]**
• Preferred regimens ▸ Abiraterone[z,kkk] (category 1) ▸ Cabazitaxel[ddd] ▸ Enzalutamide[z] (category 1) • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Niraparib/abiraterone[z,lll,mmm] for *BRCA* mutation ▸ Olaparib/abiraterone[z,kkk,lll] for *BRCA* mutation ▸ Pembrolizumab for MSI-H/dMMR[ddd] (category 2B) ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Sipuleucel-T[ddd,ooo] ▸ Talazoparib/enzalutamide for HRR mutation[z,lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]	• Preferred regimens ▸ Cabazitaxel[ddd] (category 1) ▸ Docetaxel rechallenge[ddd] • Useful in certain circumstances ▸ Cabazitaxel/carboplatin[ddd] ▸ Lutetium Lu 177 vipivotide tetraxetan (Lu-177–PSMA-617) for PSMA-positive metastases[ppp] (category 1) ▸ Mitoxantrone for palliation in symptomatic patients who cannot tolerate other therapies[ddd] ▸ Olaparib for HRR mutation[lll] (category 1 for *BRCA* mutation) ▸ Pembrolizumab for MSI-H/dMMR, or TMB ≥10 mut/Mb[ddd] ▸ Radium-223[s,nnn] for symptomatic bone metastases (category 1) ▸ Rucaparib for *BRCA* mutation[lll] • Other recommended regimens ▸ Other secondary hormone therapy[z]

Footnotes for Systemic Therapy for M1 CRPC: Adenocarcinoma (PROS-16A).

Note: All recommendations are category 2A unless otherwise indicated.

[yy]*Principles of Non-hormonal Systemic Therapy*
Immunotherapy

- *Patients with asymptomatic or minimally symptomatic mCRPC may consider immunotherapy*
- *Sipuleucel-T*
  o Sipuleucel-T is only for asymptomatic or minimally symptomatic, patients with no liver metastases, life expectancy > 6 months, ECOG performance status 0-1.
  o Sipuleucel-T is not recommended or patients with small cell/neuroendocrine prostate cancer (NEPC).
  o Sipuleucel-T has been shown in a phase 3 clinical trial to extend mean survival from 21.7 months in the control arm to 25.8 months in the treatment arm, which constitutes a 22% reduction in mortality risk.
  o Sipuleucel-T is well tolerated; common complications include chills, pyrexia, and headache.

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[mmm]*Sipuleucel-T is recommended only for asymptomatic or minimally symptomatic, no liver metastases, life expectancy > 6 mo, and ECOG performance status 0-1. Benefit with sipuleucel-T has not been reported in patients with visceral metastases and is not recommended if visceral metastases are present. Sipuleucel-T also is not recommended for patients with small cell/NEPC*

Lowrance WT, Breau RH, Chou R et al: Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline PART II. J Urol 2021; 205: 22.

- In mCRPC patients who are asymptomatic or minimally symptomatic, clinicians may offer sipuleucel-T. (Conditional Recommendation; Evidence Level: Grade B)

Virgo KS, Basch E, Loblaw DA, et al. Second-Line Hormonal Therapy for Men With Chemotherapy-Naïve, Castration-Resistant Prostate Cancer: American Society of Clinical Oncology Provisional Clinical Opinion [published correction appears in J Clin Oncol. 2017 Aug 1;35(22):2591] [published correction appears in J Clin Oncol. 2017 Dec 20;35(36):4096]. J Clin Oncol. 2017;35(17):1952-1964. doi:10.1200/JCO.2017.72.8030

- Enzalutamide or abiraterone should be offered; sipuleucel-T is an option.

Basch E, Loblaw DA, Oliver TK, et al. Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline. J Clin Oncol. 2014;32(30):3436-3448. doi:10.1200/JCO.2013.54.8404

- Sipuleucel-T may be offered to asymptomatic/minimally symptomatic men. (Benefit: moderate; harm: low; evidence strength: moderate; recommendation strength: weak.) The guidelines note that sipuleucel-T demonstrates improved survival although unclear impact on quality of life.

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Clinical Opinions

Androgen deprivation therapy (ADT) is considered the first-line treatment for patients with advanced or metastatic prostate cancer. However, over time, these patients may develop a decreased response to ADT resulting in castrate resistant prostate cancer (CRPC) or metastatic castrate resistant prostate cancer (mCRPC). Agents approved for use in patients with previously untreated mCRPC include: docetaxel, Provenge® (sipuleucel-T), abiraterone (Zytiga®), Xtandi® (enzalutamide) and Yonsa® (abiraterone). All have been shown to prolong overall survival, but only docetaxel, abiraterone and enzalutamide have been reported to improve quality of life (QOL) outcomes. For patients with mCRPC who received first-line therapy with docetaxel and progressed, there are a few treatment options that have been shown to improve overall survival: Zytiga®, Xtandi®, Jevtana® (cabazitaxel), and Provenge®. Xofigo® (radium Ra 223 Dichloride) and Pluvicto® (lutetium Lu 177 Vipivotide Tetraxetan) are radiopharmaceuticals that have also shown benefit. Jevtana® and Provenge® have been shown to improve overall survival only.

There are several potential disadvantages to sipuleucel-T compared to other therapies. Disadvantages include high cost, lack of QOL improvement, and questionable efficacy. With a lack of clinical trials demonstrating the superiority of one agent over the other, choice of therapy may be guided by the patient specific parameters, side effect profile, and cost.

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Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Xtandi® (enzalutamide)	NF	40 mg capsule 40 mg, 80 mg tablet	$14,880
Abiraterone (Zytiga®)	F-PA (250mg)	250 mg, 500 mg tablet	$901
Yonsa® (abiraterone)	NF	125 mg tablet	$10,457
Docetaxel	NF	20 mg/mL, 20 mg/2 mL, 80 mg/4 mL, 80 mg/8 mL, 160 mg/8 mL, 160 mg/16 mL	$11§
Jevtana® (cabazitaxel)	NF	60 mg/1.5 mL vial	$14,358+

^The manner in which the Drug Name is listed implies its availability. The generic name is listed first, with brand in parenthesis, if the product is available as a generic. The brand name is listed first, with the generic name in parenthesis, if the product is available as a brand only.

*Price per month unless otherwise noted. Pricing for multi-source generic medications based on National Average Drug Acquisition Cost (NADAC). Pricing for single-source branded medications and generic drugs without NADAC data based on Wholesale Acquisition Cost (WAC).

+Price per vial. Recommended dose is 20 mg/m2 once every 3 weeks.

§NADAC price not available. Maximum Acquisition Cost (MAC) price varies between vial size. Price based on dose for person with BSA = 1.83 m2.

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Drug Name: Ridaura (auranofin)

Manufacturer: Legacy Pharma

Approval Date: 4/24/1985

Marketing Date: 5/24/1985

Recommendation

- No changes
  - The current formulary status is NF
  - There was no utilization of this medication and no prior authorization requests from 1/1/2025 to 3/31/2025

Prescribing Information

Indication

Ridaura® (auranofin) is indicated in the management of adults with active classical or definite rheumatoid arthritis (RA) [per American Rheumatism Association (ARA) criteria] who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of full doses of one or more nonsteroidal anti-inflammatory drugs (NSAIDs).

Mechanism of Action

The mechanism of action of auranofin is not understood. In patients with adult RA, auranofin may modify disease activity as manifested by synovitis and associated symptoms and reflected by laboratory parameters such as erythrocyte sedimentation rate (ESR). There is no substantial evidence, however, that gold-containing compounds induce remission of RA.

Dosage and Administration

Two capsules (6 mg) by mouth daily. If response remains inadequate after 6 months increase to 9 mg (3 mg three times daily). If response to 9 mg dose remains inadequate after 6 months, discontinue. Transferring from Injectable gold: First discontinue injectable agent, then start oral therapy with auranofin 6 mg daily.

Black Box Warning

Auranofin contains gold and, like other gold-containing drugs, can cause gold toxicity, signs of which include: fall in hemoglobin, leukopenia below 4,000 WBC/cu mm, granulocytes below 1,500/cu mm, decrease in platelets below 150,000/cu mm, proteinuria, hematuria, pruritus, rash, stomatitis or persistent diarrhea. Therefore, the results of recommended laboratory work should be reviewed before writing each auranofin prescription. Like other gold preparations, auranofin is only indicated for use in selected patients with active RA. Physicians planning to use auranofin

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should be experienced with chrysotherapy and should thoroughly familiarize themselves with the toxicity and benefits of auranofin.

In addition, the following precautions should be routinely employed:

- The possibility of adverse reactions should be explained to patients before starting therapy.
- Patients should be advised to report promptly any symptoms suggesting toxicity.

Adverse Reactions

Reactions occurring in > 1% of auranofin-treated patients:

- Gastrointestinal: loose stools or diarrhea (47%), abdominal pain (14%), nausea with or without vomiting (10%), constipation, anorexia, flatulence, dyspepsia, dysgeusia
- Dermatological: rash (24%), pruritus (17%), hair loss, urticaria
- Mucous Membrane: stomatitis (13%), conjunctivitis, glossitis
- Hematological: anemia, leukopenia, thrombocytopenia, eosinophilia
- Renal: proteinuria, hematuria
- Hepatic: elevated liver enzymes

Use in Specific Populations, Pregnancy

Use of auranofin by pregnant women is not recommended. Furthermore, women of childbearing potential should be warned of the potential risks of auranofin therapy during pregnancy. There are no adequate and well-controlled auranofin studies in pregnant women.

Drug Interactions

In a single patient-report, there is the suggestion that concurrent administration of auranofin and phenytoin may have increased phenytoin blood levels.

How Supplied

Oral capsules: 3 mg

Price

$2,349

(Per month for maximum dosing, based on WAC.)

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Clinical Studies

Completed

Title	Auranofin is safe and superior to placebo in elderly-onset rheumatoid arthritis PMID: 9291856
Design	Two-year prospective double-blind placebo-controlled clinical trial
Population	N=65 Elderly-onset rheumatoid arthritis (EORA), defined as onset at age > 60 years
Arms	Auranofin 3 mg BID or placebo for 2 years Prednisolone starting at 7.5 or 20 mg daily was used as a rescue drug in patients with intolerable joint pain and stiffness and with C-reactive Protein (CRP) >= 20 (was tapered down according to guidelines)
Endpoint(s)	Primary – Efficacy of auranofin as compared to placebo measured by primary clinical variables: • Changes in joint pain • Number of swollen joints • Health Assessment Questionnaire score • Radiographic damage score of hands (Larsen-Dale index) Secondary – Evaluate safety of auranofin as compared to placebo measured by: • Total number of adverse events • Reasons for withdrawals and discontinuations
Inclusion Criteria	• RA, according to the American College of Rheumatology (ACR) 1987 criteria, or oligoarthritis (at least three swollen joints) associated with PMR-like symptoms
Exclusion Criteria	• Patients with temporal arthritis or polymyalgia rheumatica (PMR) without arthritis • Patients with major arthropathies other than EORA • Patients previously treated with gold-containing drugs • Patients on oral prednisolone for other reasons than EORA or doses > 20 mg daily within the 4 weeks preceding study • Chronic inflammatory bowel disease (IBD) • Liver or kidney disease
Results	Primary endpoint: • No statistically significant differences between the treatment groups could be demonstrated during the treatment period. • The auranofin group consumed significantly less prednisolone 2.64 (0-11.85) mg/day, compared to 5.0 (0-18.33) mg/day in the placebo group (P=0.006) Secondary endpoint:

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	• The total number of adverse events tended to be higher in the auranofin group: 8.5 events per patient compared with 7.5 events per patient in the placebo group. • 10% of patients on auranofin and 41% of patients on placebo withdrew due to adverse events • Additionally, 16% on auranofin and 29% on placebo treatment withdrew due to lack of effect
Conclusion	Auranofin is safe, superior to placebo and has steroid-sparing capacity in the treatment of elderly-onset RA (EORA).
Interpretation	Auranofin demonstrates clinical efficacy in patients with EORA when compared to placebo. It is unclear why there were more adverse events in the placebo group but the adverse effects due to auranofin are generally mild and tolerated. The steroid-sparing effect could prove useful for those who cannot tolerate steroids for the treatment of EORA.

Title	Efficacy and safety of auranofin in patients with active early rheumatoid arthritis PMID: 7758062
Design	Single-arm, non-randomized, non-blinded trial
Population	N=48; 35 completed the trial but all were used in the determination of adverse events 7 males, 28 females; majority aged 50-59 (Min 27-Max 71) 1:2 ratio having < 1 year to 1-5 year duration and Class 1 to 2 3:4 ratio having Stage I to Stage II
Arms	Auranofin 3 mg twice daily after morning and evening meals for 12 months + NSAIDs +/- prednisolone 5 mg or 2.5 mg (8 patients used oral steroids)
Endpoint(s)	On the first day of the trial and after 3, 6, and 12 months of treatment, clinical symptoms, modified Lansbury index, CRP, ESR, rheumatoid factor, and the patients' assessments of severity of pain, judged using a visual analog scale (VAS), were evaluated.
Inclusion Criteria	Diagnosis of RA that satisfied the diagnostic standards set in 1987 by the ACR, was of less than 5 years' duration, and was of stage I or II and class 1 or 2 according to the Steinbrocker system.
Exclusion Criteria	• Patients under 18 years of age • Women of childbearing potential
Results	Statistically significant improvement in clinical symptoms, modified Lansbury index, C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, and the patients' assessments of severity of pain, judged using a VAS after 12 months of treatment. Mean duration of morning stiffness and mean grip strength was statistically significantly lower from 6 months to the duration of the study. ESR, mean number of painful joints, was statistically significantly improved after 3 months and for the duration of the study. The modified Lansbury index (includes duration of morning stiffness, grip strength, ESR, and articular index) was statistically significantly improved after 6 months and for the duration of the study. The RA test result was positive for all patients at the

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	beginning of the study but became negative in 1, 2, and 4 patients after month 3, 6, and 12 respectively. The CRP test was positive for all patients in the beginning of the trial but showed improvement. Pain assessed using VAS was significantly reduced after 6 months of treatment, but statistical significance was lost at 12 months. Self-reported general impressions and the global improvement ratings were improved. No adverse events were observed during the treatment period.
Conclusion	Auranofin combined with NSAIDs and/or steroids shows significant improvement in both objective and subjective factors in the assessment of RA with no observable adverse events.
Interpretation	Although this study shows improvement with auranofin, it is important to observe the meaningful impact that NSAIDs and/or oral steroids (8 of 35 patients used steroids) have on an inflammatory condition like RA. Many of these improvements only occurred after 3 months of use and arguably the most important outcome, pain, lost statistical significance at 12 months. Other studies showed GI adverse events with auranofin, but this study did not. The small sample size (35 completed the study) implies low statistical power and poor study design (not randomized and single arm) reduces the value of this study. Larger, placebo-controlled trials are necessary to obtain an adequate conclusion.

Title	Comparison of auranofin, methotrexate, and the combination of both in the treatment of rheumatoid arthritis. A controlled clinical trial PMID: 1536666
Design	Prospective, controlled, double-blind, multicenter trial
Population	N=335 (211 completed trial) No baseline differences in age, sex, race, disease duration, or disease severity
Arms	• Auranofin 3 mg BID + placebo • Methotrexate (MTX) 2.5 mg q12 hours for 3 doses per week + placebo • Auranofin 3 mg BID + MTX 2.5 mg q12 hours for 3 doses per week Every patient was allowed to take aspirin and/or NSAID provided the dosage had been stable for 1 month and was kept constant for the duration of the trial. Prednisone therapy at a stable dose for 1 month prior to study entry was maintained if <=10 mg/day (or equivalent).
Endpoint(s)	• Response to treatment in all patients entering the trial • Response to treatment in patients completing the 48-week trial • Time to response • Patient withdrawals

Inclusion Criteria	• Patients ≥ 18 years old
	• Definite or classic RA of > 6 months duration with onset after age 16 with ≥ 6 swollen joints capable of responding to drug therapy and ≥ 2 of the following:
	  ○ 9 or more joints tender on pressure
	  ○ 45 minutes or more of AM stiffness
	  ○ ESR of ≥ 28 mm/hr

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	• Unsuccessful treatment with conventional doses of ≥ 2 NSAIDs and/or salicylates • No antimalarial agents, intraarticular corticosteroids or parenteral corticosteroids for the 2 months prior to study start and no phenylbutazone for the 1 month prior to study start • Patients never received treatment with gold, penicillamine, immunosuppressives or cytotoxic medications (including methotrexate) • Patients and sexual partners either had no childbearing potential or were practicing successful contraception for ≥ 3 months before the study start
Exclusion Criteria	• ACR exclusion criteria for RA • Seronegative spondylarthropathy, mixed connective tissue disease • Psoriasis • RA functional class IV • Concomitant treatment with another experimental drug • History or presence of malignancy • Acute or chronic infection • Active peptic ulcer disease (PUD) or IBD • Bone marrow hypoplasia • Concomitant treatment with an anticoagulant • Insulin-dependent diabetes mellitus (IDDM) • Regular alcohol intake of > 14 oz of 100-proof liquor or equivalent/week • Elevated hepatic enzymes, serum creatinine > normal • Positive Hep-B surface antigen • Proteinuria, thrombocytopenia, leukopenia
Results	Patients taking auranofin monotherapy had a slower onset of response than did patients taking MTX alone or in combination. Withdrawals because of adverse drug reactions were slightly more common for patients taking combination therapy, but the differences were not statistically significant. Withdrawals because of lack of response were more common for single-drug therapy, with the difference between auranofin and the combination group reaching statistical significance. No unexpected adverse drug effects were identified, and all reactions resolved without sequelae. Except for fewer withdrawals because of lack of response, combination therapy did not demonstrate any advantage in efficacy over single-drug treatment within the time frame of the study.
Conclusion	There was no difference in efficacy between combination MTX and auranofin versus single drug therapy, but withdrawal from the study was the smallest in the combination group. Both MTX and auranofin had similar efficacy but patients taking MTX alone or in combination had an earlier onset of benefit than patients taking auranofin. Adverse drug events were more common in the combination group, with the toxicities seeming additive and not synergistic.
Interpretation	This is one of the few randomized, controlled trials with a sufficient patient population that tests the safety and efficacy of auranofin. Auranofin and MTX have similar efficacy according to this study. However, the onset of benefit for auranofin is delayed at 8-12 weeks compared to MTX which had a 6-week onset. The combination therapy only increases the risks of additive adverse events and

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	therefore should be avoided. However, it is important to note that each drug has a unique set of risks (i.e., MTX more commonly increases liver enzymes and leukopenia while auranofin more likely increases the risk of GI distress, rash, and mucosal ulcers).

Title	Low-Dose Methotrexate Compared With Auranofin In Adult Rheumatoid Arthritis PMID: 2180405
Design	36-week double-blind, randomized, multicenter study
Population	N=281 Patients with adult-onset, definite, or classic RA of more than 6 months duration No statistically significant differences in demographic or clinical characteristics between groups
Arms	• MTX 7.5 mg once weekly + placebo for 36 weeks • Auranofin 3 mg BID + placebo for 36 weeks If inadequate response, dose was increased up to MTX 15 mg/week or auranofin 9 mg/day.
Endpoint(s)	Primary: • Physician global assessment of disease activity • Patient global assessment • Number of joints with tenderness and/or pain on pressure or passive motion • Number of joints with swelling Secondary: • Joint pain/tenderness index • Joint swelling index • ESR • Duration of morning stiffness • 50-foot unaided walk time • Grip strength
Inclusion Criteria	• Diagnosed with adult-onset, definite, or classic RA of more than 6 months • Inadequate response to at least 2 NSAIDs • Active disease, defined as the presence of at least 3 of the following: >=6 painful or tender joints, >=3 swollen joints, morning stiffness of >=45 minutes duration, and a Westergren ESR >=28 mm/hr.
Exclusion Criteria	• Patients who previously received therapy with either gold salts (oral or parenteral), D-penicillamine (DP), MTX, or cytotoxic drugs • Patients who had previously used antimalarial drugs or sulfasalazine which were discontinued due to factors other than toxicity or lack of efficacy • Active PUD or IDDM • Serum transaminase or bilirubin level greater than twice the upper limit of normal (ULN) • History of alcoholism or unwillingness to limit alcohol consumption to 2 drinks per week

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	• Serum creatinine > ULN or a creatinine clearance <50 mL/minute • Thrombocytopenia or leukopenia • Serious coexisting illness • Functional class I or IV • History of malignancy • Recent major surgery • Pulmonary fibrosis if the FEV1 or carbon monoxide diffusing capacity <60% of predicted • Women of childbearing potential including sexual partners of male patients were required to be practicing an accepted method of birth control
Results	There was a statistically significant improvement from baseline for all efficacy measures at weeks 12, 24, and 36 for both treatment groups, but mean improvement favored MTX. The response with MTX occurred earlier and was consistently greater than that with auranofin. Intent-to-treat analysis showed significantly greater improvement with MTX for painful and swollen joint counts and physician and patient global assessments of disease activity. There was a higher frequency of adverse events in the auranofin group and more auranofin-treated patients were withdrawn from the study.
Conclusion	Both MTX and auranofin demonstrated effectiveness in improving the standard measures of RA activity but the response with MTX was “superior” and occurred earlier. Auranofin has less tolerated adverse events leading to patient withdrawal from the study
Interpretation	MTX has both a safety and efficacy benefit over auranofin for patients who had not received prior treatment with other second-line agents. Although the study did not test for superiority, MTX had consistently better outcomes and the clinical benefit occurred earlier than auranofin, justifying MTX’s place in RA guidelines as a first line agent.

Ongoing

Title	Phase II Trial to Evaluate the Efficacy of Auranofin and Sirolimus in Serous Ovarian Cancer Patients With Recurrent Disease NCT: 03456700
Design	A single group, open label, phase II interventional trial with the primary objective to estimate the overall tumor response rate (ORR, that is, complete response [CR] + partial response [PR]) of the combination of auranofin and sirolimus in the setting of metastatic serous ovarian cancer across all patients.
Completion Date	6/30/2025

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Guidelines

Fraenkel L, Bathon JM, England BR, et al. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Care Res (Hoboken). 2021;73(7):924-939.

The 2021 American College of Rheumatology Guidelines for the Treatment of Rheumatoid Arthritis do not include any recommendations for gold compounds due to their infrequent use and/or lack of new data.

Clinical Opinions

Gold has demonstrated efficacy in controlling disease activity and radiographic progression of RA compared to placebo. However, two meta-analyses showed reduced efficacy of auranofin compared to MTX and sulfasalazine. Additionally, auranofin is less effective than gold sodium thiomalate (GST), the parenteral form of gold, but it also has fewer adverse effects. Infliximab has also demonstrated superiority when compared to auranofin on the effect on radiological erosion scores. According to one systematic review, auranofin appears to be efficacious in the short-term (6-month) treatment of patients with RA and has a small but clinically and statistically significant benefit on disease activity.

The use of gold is further limited by its side effect profile. Common side effects include dermatitis/stomatitis, pruritis, enterocolitis and metallic taste. Serious adverse reactions including persistent and significant proteinuria, hematologic toxicity, pulmonary toxicity, hepatitis, enterocolitis, and neuropathy can occur. Due to the potential for toxicity, baseline and monthly monitoring of complete blood count (CBC) with differential, platelet count, and urinalysis should be taken.

Gold therapy may be appropriate for patients with early and mild disease requiring less effective therapies. It may also be considered for use in the following circumstances: concerns regarding immunosuppression, coexisting chronic infection, contraindications to or failure of other therapies, lack of availability of other medications, and pregnancy planning in select women in whom treatment options may be limited. In summary, it is difficult to justify the use of auranofin due to its inferior efficacy, absence in clinical guidelines, and high cost compared to other agents for RA.

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Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Methotrexate	F	2.5 mg oral tablets	$5
Leflunomide (Arava®)	F	10 mg, 20 mg oral tablets	$9
adalimumab (Humira®)	F-QL	10 mg/0.1 mL, 20 mg/0.2 mL, 40 mg/0.4 mL, 40 mg/0.8 mL SQ single dose pen (other strengths and dose presentations are available)	$996 - $6,923
Enbrel® (etanercept)	F-PA	50 mg/mL SQ auto-injector, cartridge, pre-filled syringe; 25 mg/0.5 mL SQ pre-filled syringe, kit; 25 mg SQ vial	$8,158

^The manner in which the Drug Name is listed implies its availability. The generic name is listed first, with brand in parenthesis, if the product is available as a generic. The brand name is listed first, with the generic name in parenthesis, if the product is available as a brand only.

**Price per 28 days unless otherwise noted. Pricing for multi-source generic medications based on National Average Drug Acquisition Cost (NADAC). Pricing for single-source branded medications and generic drugs without NADAC data based on Wholesale Acquisition Cost (WAC). Price is based on maximum dosing for rheumatoid arthritis.*

¥2023 biosimilar entrants for Humira® have a WAC price of nearly 10% of brand Humira®; this pricing range reflects one of the current lowest WAC of the 11 biosimilar entrants up to current WAC of brand Humira ®. Additionally, price based on dosing when combined with methotrexate. Dosing (and price) can be doubled for patients not taking methotrexate.

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Drug Name: Sucraid (sacrosidase)

Manufacturer: QOL Medical

Approval Date: 4/9/1998

Marketing Date: 3/13/2009

Recommendation

- No changes
  - The current formulary status is NF
  - There was no utilization of this medication and no prior authorization requests from 1/1/2025 to 3/31/2025

Prescribing Information

Indication

Indicated for the treatment of sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID), in adult and pediatric patients 5 months of age and older

Mechanism of Action

Sacrosidase replaces deficient sucrase, which is produced naturally in the brush border of the small intestine, primarily the distal duodenum and jejunum, and hydrolyzes the disaccharide sucrose into its component monosaccharides (glucose and fructose). Isomaltase, which sacrosidase does not replace, breaks down disaccharides from starch into simple sugars.

Dosage and Administration

The recommended dosage is as follows:

- 1 mL (8,500 I.U.) per meal or snack for patients up to 15 kg in body weight.
- 2 mL (17,000 I.U.) per meal or snack for patients over 15 kg in body weight.

Sucraid is taken orally with each meal or snack diluted with 2 to 4 ounces of water, milk, or infant formula. The beverage or infant formula should be served cold or at room temperature and should not be warmed or heated before or after addition of Sucraid because heating is likely to decrease potency. Sucraid should not be reconstituted or consumed with fruit juice since its acidity may reduce the enzyme activity. It is recommended that approximately half of the dosage be taken at the beginning of the meal or snack and the remainder be taken during the meal or snack.

Black Box Warning

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None

Adverse Reactions

Most common: abdominal pain, constipation, diarrhea, nausea, vomiting, headache, nervousness, insomnia, and dehydration.

Serious: anaphylaxis (rare)

Use in Specific Populations, Pregnancy

Animal reproduction studies have not been conducted with Sucraid. Sucraid is not expected to cause fetal harm when administered to a pregnant woman or to affect reproductive capacity. Sucraid should be given to a pregnant woman only if clearly needed.

Drug Interactions

None known. Do not mix or consume Sucraid with fruit juice, since acidity may reduce the enzyme activity

How Supplied

Oral Solution: 8500 IU/1 mL

Price

$12,056

(Based on WAC and averaging 5 doses/day in a patient >15 kg.)

Clinical Studies

Completed

Title	Sacrosidase therapy for congenital sucrase-isomaltase deficiency NCT: N/A PMID: 9932843
Design	Randomized, multisite, double-blind, controlled trial.
Population	N=28 Age 4 months to 11.5 years diagnosed with CSID

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Arms	Two phases: 1) three sucrose breath H_2 tests with three single-dose treatments (placebo, sacrosidase, and sacrosidase plus milk), and 2) a dose-response phase consisting of four multidose treatments, each for 10 days of full-strength sacrosidase, 1:10 dilution, 1:100 dilution, and 1:1000 dilution. Patients consumed a normal diet during the dose-response phase.
Endpoint(s)	The number of stools and severity of symptoms were recorded daily for each concentration of sacrosidase administered and compared to a baseline period during which the patient took no sacrosidase and consumed a sucrose/starch-free diet.
Inclusion Criteria	History of chronic watery diarrhea with an acid pH, a small intestinal biopsy specimen with measurement of tissue disaccharidase levels showing sucrase activity of less than 10% of control specimens with normal lactase levels and normal or decreased maltase activity, normal villous architecture of the small intestine, and a normal result in a lactose breath hydrogen test.
Exclusion Criteria	Unavailable
Results	Breath H_2 excretion decreased significantly when patients received sacrosidase or sacrosidase plus milk compared to placebo during sucrose breath tests. During the dose-response phase significant treatment differences were observed between the two higher concentrations and the two lower concentrations of sacrosidase for both total stools ($p < 0.001$) and total symptom score ($p = 0.003$). Higher concentrations of sacrosidase were associated with fewer stools and a greater number of formed or hard stools compared to lower concentrations and compared to the baseline period. Higher concentrations were also associated with fewer symptoms of gas, abdominal cramps, or bloating, but no differences in vomiting. The only significant adverse event was wheezing in one child with a history of asthma.
Conclusion	Sacrosidase is a safe, effective, well-accepted treatment to prevent gastrointestinal symptoms in patients with CSID consuming a normal diet.
Interpretation	Study demonstrates efficacy of sacrosidase in reduction of symptoms of CSID. Most likely due to the relative rarity of the condition, only a very small number of subjects were enrolled in the trial.

Ongoing

Title	Evaluation of a 7-Day Therapeutic Trial Dose of Commercial Sucraid® (Sacrosidase) Oral Solution for Alleviating Congenital Sucrase-Isomaltase Deficiency (CSID) Symptoms in Pediatric Subjects with Low, Moderate, and Normal Sucrase Levels

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	NCT: 05480761
Design	A phase 4, single arm, open label trial using a 7-day therapeutic response dose (TRD) of commercial Sucraid to assess the response of treatment in 1100 symptomatic pediatric (6 months to 17 years old) subjects with low, moderate, and normal sucrase activity determined by a disaccharidase assay via EGD within 1 year of the Screening Visit. This study will also explore the relationship between known genetic CSID mutations and sucrase activities via (EGD) disaccharidase assay (low, moderate, and normal).
Completion Date	Estimated 12/25/2024; no results posted to date

Guidelines

No standard treatment guidelines were discovered. However, other treatment options are unavailable other than dietary sucrose and isomaltase restriction.

Clinical Opinions

Limited information in terms of clinical studies are available regarding Sucraid due to length of time the product has been available on the market. In terms of treatment for CSID, no other known treatment options are available besides strict dietary restriction. Many patients may require more than one bottle per month since it is administered prior to every meal/snack, and treatment is lifelong since it is merely replacing an enzyme which patients with CSID do not make. The indication appears to be relatively rare, so formulary management which includes confirmation of diagnosis seems appropriate based on the cost of the product. This may present challenges as the symptoms of the disease (chronic diarrhea, weight loss, and gas) can also be associated with a host of other gastrointestinal disorders. The diagnosis is rather difficult to make definitively without a genetic test, which can be costly and not available in some circumstances. Other historically used diagnostic methods include small bowel biopsy or a breath test but are not able to distinguish between CSID and acquired (secondary) sucrose deficiency. It is also important to note that while Sucraid treats the sucrase deficiency in these patients, it does not treat the isomaltase deficiency.

Alternatives

N/A

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Alameda MRGs for review Q2 2025 P&T Consent Agenda

Recommendation: No changes

Formulary, step therapy required *For drugs without specific criteria	
Therapeutic Classes (AHFS)	N/A
Medications	Formulary, step therapy required medications without specific criteria
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	None
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Initial criteria for approval:**
	• Appropriate diagnosis/indication for requested medication or meets off-label criteria below AND
	• *Off-label criteria:*
	  ○ No other formulary medication has a medically accepted use for the patient's specific diagnosis as referenced in the medical compendia AND
	  ○ Medication is being requested for an accepted off-label use and is listed in the standard clinical decision support resources (as noted in Covered uses section above) OR requested use can be supported by at least two published peer reviewed clinical studies
	• The quantity requested does not to exceed FDA approved or off-label dose (Requests for quantities above indicated Quantity Limits will be reviewed on a case by case basis) AND
	• Documentation provided that patient has had sufficient prior trial/failure or contraindication/inability to use required step therapy drug(s) OR
	• Provider has demonstrated knowledge of step therapy requirements AND
	• Medical justification why required step therapy drug(s) would be ineffective or have the potential to cause harm or deterioration of the member's condition OR
	• Medical justification why the requested drug would be superior to the required step therapy drug(s).
	
	Criteria for re-authorization:
	• Patient is stable and continuing the medication

Criteria Statement	Medications for drugs without specific criteria, where step therapy is required, are reserved for members who have tried and failed, or have an inability to use the current step therapy medications, or no other formulary medication with a medically accepted use for the patient's specific diagnosis is to be used, as referenced in the medical compendia, is available and medication is being requested and is listed in the standard clinical decision support resources or requested use can be supported by at least two published peer reviewed clinical studies.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Non-formulary and prior authorization required oral liquid formulations	
Therapeutic Classes (AHFS)	N/A
Medications	Non-formulary and prior authorization-required oral liquid formulations, where solid oral dosage forms exist
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age.
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Non-formulary and prior authorization-required oral liquid formulations, where solid oral dosage forms exist are approved when the following criteria are met:** • Documentation of difficulty swallowing, inability to swallow, or unable to use oral tablet/capsule formulation.
Criteria Statement	Non-formulary and prior authorization-required oral liquid formulations, where solid oral dosage forms exist are reserved for members who have difficulty swallowing or are unable to swallow tablets or capsules.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Medications for Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy	
Therapeutic Classes (AHFS)	Respiratory and CNS stimulants
Medications	**<u>Formulary, with age limits and selected quantity limits</u>** Atomoxetine (Strattera) 10 mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg Capsule Dexmethylphenidate (Focalin) 2.5mg, 5mg, 10mg tablet Dextroamphetamine (Dexedrine) 5mg, 10 mg Tablet Dextroamphetamine-amphetamine (Adderall) 5 mg, 7.5mg 10mg, 12.5mg, 15mg, 20mg, 30mg Tablet Dextroamphetamine-amphetamine ER (Adderall XR) 5mg, 10 mg, 15mg, 20mg, 25mg, 30mg 24Hr Capsule, Extended Release Guanfacine (Intuniv) ER 1mg, 2mg, 3mg, 4mg Tablet, Extended Release 24 Hr Methylphenidate (Ritalin) 5mg, 10mg, 20mg tablet Methylphenidate CD 10 mg, 20mg, 30mg, 40mg, 50mg, 60mg Biphasic 30-70 Capsule, Extended Release Methylphenidate ER 18mg, 27mg, 36mg, 54mg Tablet, Extended Release Methylphenidate LA 10 mg, 20mg, 30mg, 40mg, 60mg Capsule, Extended Release Biphasic 50-50 **<u>Formulary PA</u>** Lisdexamfetamine (Vyvanse) 10mg, 20mg, 30mg, 40mg, 50mg, 60mg, 70mg Capsule Lisdexamfetamine (Vyvanse) 10 mg, 20mg, 30mg, 40mg, 50mg, 60mg Chewable Tablet Daytrana (methylphenidate transdermal) 10 mg/9Hr, 15mg/9Hr, 20mg/9Hr, 30mg/9Hr, 30mg/9Hr Daily Patch Qelbree (viloxazine) ER 100mg, 150mg, 200mg capsule *Any new dosage form, strength, or newly marketed medication indicated for ADHD
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Initial authorization**: • Appropriate diagnosis/indication and dose used for the requested medication for use in narcolepsy OR • Appropriate diagnosis/indication for requested medication- For use in adults, clinic notes are needed with Attention Deficit Hyperactivity Disorder (ADHD) diagnosis. If the request is from psychiatry, clinic notes are not required. AND • Appropriate dose of medication based on age and indication AND • If request is for a non-formulary or formulary, prior authorization-required medication, documented trial and failure or intolerance with three preferred formulary medications (if available) used to treat the documented diagnosis. For medications where there is only one preferred formulary agent, only that agent must have been ineffective or not tolerated OR • No other formulary medication has a medically accepted use for the patient's specific diagnosis as referenced in the medical compendia. OR • All other formulary medications are contraindicated based on the patient's diagnosis, other medical conditions, or other medication therapy **Re-authorization:** • The patient is using the medication at an appropriate dose for an approved indication and is stable and obtaining clinical benefit
Criteria Statement	CNS stimulants are reserved for members who have a diagnosis of attention deficit hyperactivity disorder (ADHD) or narcolepsy are using the medication at an appropriate dose based on their age, other medical conditions, and other concurrent medications, and if the request is for a non-formulary or formulary, prior authorization-required medication, formulary agents must be tried and failed first.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Roflumilast (Daliresp)	
Therapeutic Classes (AHFS)	Phosphodiesterase type 4 inhibitors
Medications	Formulary, PA required: Roflumilast (Daliresp)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	18 years of age
Prescriber Restrictions	Prescribed by or in consultation with a pulmonologist
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**All of the following conditions must be met:** • Diagnosis of severe COPD associated with chronic bronchitis.as indicated by FEV ≤ 50% predicted with nonreversible obstructive lung disease. • Patient has history of COPD exacerbations within the previous 1 year. • Documented trial and failure or intolerance with a preferred inhaled long-acting beta2-agonist/ long-acting muscarinic antagonist (LABA/LAMA) combination, or long-acting beta2-agonist/ long-acting muscarinic antagonist/ inhaled corticosteroid (LABA/LAMA/ICS) combination for a minimum of 4 weeks of therapy in the previous 60 days • Documentation roflumilast (Daliresp) is being used as add-on treatment in conjunction with at least one: long-acting beta2-agonist (LABA) or long-acting muscarinic antagonist (LAMA)
Criteria Statement	Roflumilast (Daliresp) is reserved for members who have severe chronic obstructive pulmonary disease (COPD) and chronic bronchitis who have history of exacerbations within the last year and who have used (or cannot/should not use) a preferred inhaled long-acting beta2-agonist/ long-acting muscarinic antagonist (LABA/LAMA) combination, or long-acting beta2-agonist/ long-acting muscarinic antagonist/ inhaled corticosteroid (LABA/LAMA/ICS) combination for a minimum of 4 weeks of therapy in the previous 60 days and who are using roflumilast (Daliresp) in addition to a long-acting beta2-agonist (LABA) inhaler or long-acting muscarinic antagonist (LAMA).
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

febuxostat (Uloric)	
Therapeutic Classes (AHFS)	Antigout agents
Medications	Formulary, PA required: febuxostat (Uloric)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**All of the following conditions must be met:** • Patient has a diagnosis of gout AND • Documented contraindication/intolerance to allopurinol OR trial and failure of allopurinol 600 mg per day for at least 90 consecutive days in the last 365 days. AND • For patients with CKD, renal adjustment of allopurinol to the maximum tolerated dose is required for at least 90 consecutive days in the last 365 days.
Criteria Statement	Febuxostat (Uloric) is reserved for members who have gout and who have used (or cannot/should not use) allopurinol.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Levalbuterol (Xopenex/Xopenex HFA)	
Therapeutic Classes (AHFS)	Beta-adrenergic agonists
Medications	Formulary, step therapy required Levalbuterol HFA 45 mcg inhaler (Xopenex HFA) Levalbuterol 0.31mg/3 ml, 0.63 mg/3 ml, 1.25 mg/3 ml, 1.25mg/0.5 ml solution for (Xopenex)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Levalbuterol HFA or solution for nebulization is approved when the following criteria are met: • Documentation of a trial and failure of albuterol HFA or albuterol solution for nebulization
Criteria Statement	Levalbuterol HFA or levalbuterol solution for nebulization is reserved for members who have used (or cannot/should not use) albuterol HFA or albuterol solution for nebulization.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Lidocaine Patch	
Therapeutic Classes (AHFS)	ANTIPRURITICS AND LOCAL ANESTHETICS
Medications	Formulary-PA Lidocaine (Lidoderm) 5% transdermal patch Non-Formulary ZTlido (lidocaine) 1.8% patch Lidocaine 4% patch Lidaflex (lidocaine) 4% patch Any other newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months (for up to a maximum of #90 patches per 30 days) **Later Approvals** 12 months (for up to a maximum of #90 patches per 30 days) If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	**CRITERIA FOR AUTHORIZATION for lidocaine 5% patch** • Diagnosis of neuropathic pain AND • Documented trial and failure or intolerance to gabapentin at least 1800mg per day for 90 days in the last 365 days OR documented trial and failure or intolerance to pregabalin at least 300mg per day for 90 days in the last 365 days AND • Documented trial of a therapeutic dose and duration of one other formulary alternative (e.g., duloxetine, venlafaxine, amitriptyline) in the last 365 days OR • Member is using over 50 mg morphine equivalence/day for 3 months. **CRITERIA FOR AUTHORIZATION for non-formulary patches** • The member meets the criteria for lidocaine 5% patch, as outlined in the section above AND • Documented trial and failure or intolerance to lidocaine 5% patch
Criteria Statement	Lidocaine 5% patches are reserved for members with neuropathic pain who have used (or cannot/should not use) gabapentin 1800 mg (or more) OR pregabalin 300mg (or more) AND one other formulary alternative (e.g., duloxetine, venlafaxine, amitriptyline). Non-formulary patches are reserved for members with neuropathic pain who have used (or cannot/should not use) gabapentin 1800 mg (or more) OR pregabalin 300mg (or more) AND one other formulary alternative (e.g., duloxetine, venlafaxine, amitriptyline) AND who have used (or cannot/should not use) lidocaine 5% patches.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Fenofibrates	
Therapeutic Classes (AHFS)	Fibric acid derivatives
Medications	Formulary, with quantity limit (30/30) (pays at point-of-sale): fenofibrate nanocrystallized 48, 145 mg fenofibrate 54, 160 mg fenofibrate micronized 67, 134, 200 mg gemfibrozil 600mg Non-formulary (non-preferred, requires prior authorization): fenofibric acid [choline] (Trilipix) 45, 135 mg cap fenofibrate (Lipofen) 50, 150 mg cap fenofibrate (Fenoglide) 40, 120 mg tab fenofibrate micronized 43, 130 mg cap fenofibric acid (Fibricor) 35, 105 mg tab Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Non-preferred strengths and formulations of fenofibrate are approved when the following criteria are met: • Documentation of a trial and failure of at least 3 of the following: gemfibrozil 600mg, fenofibrate 54mg, 160mg, 48 mg, 145 mg, 67 mg, 134mg, or 200 mg tablets/capsules.
Criteria Statement	Non-formulary fenofibrates are reserved for members who have used (or cannot/should not use) 3 of the following drugs: gemfibrozil 600mg, fenofibrate 54mg, 160mg, 48 mg, 145 mg, 67 mg, 134mg, or 200 mg tablets/capsules
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Nutritional formulas, infant formulas	
Therapeutic Classes (AHFS)	Caloric agents
Medications	Nutritional formulas, infant formulas
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	N/A
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	N/A
PA Review Criteria	**CRITERIA FOR AUTHORIZATION** **These products/services are delegated to California Home Medical Equipment (CHME). Please call CHME by phone at 1-800-906-0626 or fax the prescription to CHME at 1-650-357-8551.**
Criteria Statement	N/A
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Lipotropics	
Therapeutic Classes (AHFS)	Antilipemic agents, miscellaneous
Medications	Formulary, quantity limit (120/30) omega-3-acid ethyl esters (Lovaza) Formulary, PA required icosapent ethyl (Vascepa) 0.5gm & 1gm capsule
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial/Re-Approval** If all conditions are met, the request will be approved for up to 12 months with a limit of 120 capsules per 30 days. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.

PA Review Criteria	**Initial Authorization**
	
	Cardiovascular risk reduction icosapent ethyl (Vascepa)
	• Member has a diagnosis of moderate hypertriglyceridemia (pre-treatment triglyceride ≥ 150 mg/dL) and ONE of the following is true:
	  ○ Member is ≥ 45 years of age and has established cardiovascular disease as evidenced by a history of at least ONE of the following:
	  ▪ Myocardial infarction or acute coronary syndrome
	  ▪ Stroke or transient ischemic attack
	  ▪ Coronary artery disease with stable angina
	  ▪ Coronary or other arterial revascularization
	  ▪ Peripheral vascular disease
	  ▪ Aortic aneurism
	  ○ Member is ≥ 50 years of age, has diabetes mellitus and at least TWO of the following:
	  ▪ Men ≥ 55 years or women ≥ 65 years
	  ▪ Cigarette smoker or stopped smoking within the past 3 months
	  ▪ Hypertension (pretreatment blood pressure ≥ 140 mmHg systolic or ≥ 90 mmHg diastolic)
	  ▪ HDL-C ≤ 40 mg/dL for men or ≤ 50 mg/dL for women
	  ▪ High-sensitivity C-reactive protein > 3.0 mg/L
	  ▪ Renal dysfunction (CrCl > 30 mL/min and < 60 mL/min)
	  ▪ Retinopathy
	  ▪ Micro- or macro-albuminuria
	  ▪ Ankle-brachial index (ABI) < 0.9 without symptoms of intermittent claudication
	• Member is taking and will continue on maximum tolerated statin dose while receiving icosapent ethyl (Vascepa), or documentation has been provided that the member is not able to tolerate a statin.
	• Documentation was provided indicating provider has counseled member on smoking cessation (if applicable) and following a "heart healthy diet."
	• The request is for an FDA approved dose.

	Triglyceride reduction • Member has a diagnosis of severe hypertriglyceridemia (pre-treatment triglyceride level ≥ 500 mg/dL). • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to an OTC fish oil or omega-3-ecid ethyl ester (generic Lovaza) • Documentation was provided indicating provider has counseled member on smoking cessation (if applicable) and following a "heart healthy diet." • The request is for an FDA approved dose. **Reauthorization** • Documentation was provided that the member has obtained clinical benefit from medication (e.g. triglyceride lowering from baseline by documentation of labs or provider attestation) • For cardiovascular risk reduction, the member will continue on maximum tolerated statin dose, or documentation has been provided that the member is not able to tolerate a statin. • The request is for an FDA approved dose.
Criteria Statement	For the diagnosis of hypertriglyceridemia, icosapent ethyl (Vascepa) is reserved for members who have used (or cannot/should not use) plain omega-3 fatty acid/fish oil capsules or omega-3-acid ethyl esters (Lovaza) but still have high triglycerides of 500 mg/dL or greater. For the indication of cardiovascular risk reduction, icosapent ethyl (Vascepa) is reserved for members who have used (or cannot/should not use) a statin, have documentation of cardiovascular disease OR are age ≥50 with diabetes with risk factors, but still have high triglycerides of 150 mg/dL or greater.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Long acting opioids		
Therapeutic Classes (AHFS)	Analgesics, narcotics	
Medications	**<u>Prior authorization required:</u>** Morphine sulfate ER (MS Contin) 15, 30, 60, 100, 200 mg tablet **-Preferred** Oxycodone HCl ER 10, 15, 20, 30, 40, 60, 80 mg Methadone 5, 10 mg tablet Methadone 10 mg/ml 5 mg/ml. 10 mg/5 ml solution Fentanyl (Duragesic) 12, 25, 50, 75, 100 mcg/h transdermal patch **<u>Non-Formulary</u>** Morphine ER (Kadian, Avinza) capsule Fentanyl (Duragesic) 37.5, 62.5, 87.5, mcg/h transdermal patch Oxymorphone ER tablet Hydromorphone ER tablet Hydrocodone ER (Zohydro ER) capsule Hydrocodone (Hysingla) ER tablet Nucynta ER tablet Tramadol ER capsule (Conzip) Tramadol ER (Ryzolt ER) Xtampza ER capsule Buprenorphine patch (Butrans) Any other non-formulary long-acting opioid medication	
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.	
Exclusion Criteria	Methadone for use in treatment of opioid use disorder is not a covered indication	
Required Clinical Information	See "**PA Review Criteria**" below	
Age Restrictions	N/A	
Prescriber Restrictions	N/A	
Coverage Duration	**Approval for initial and renewal when not otherwise specified**	If all of the conditions are met, the request will be approved for up to a 12 month duration.
	Initial approval for LTC or SNF requests	Approval duration limit is up to a 30-day supply with 1 refill (up to a total duration of 60 days)
	Partial Approval for chronic users	Partial approval duration limit for members with chronic use is up to a 3 month supply If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.

PA Review Criteria	**All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review**
	
	****Members who are on at least 90 MME with a continuous 6 months utilization, please use Partial Approval Authorization Criteria for Chronic Opioid Users.**
	
	If the member has a diagnosis of cancer, sickle cell disease, or is on hospice/palliative care please automatically authorize for up to 12 months (member must meet non-formulary criteria if request is for non-formulary medication)
	
	Criteria to start treatment for ALL drugs; administration location other than SNF/LTC*:
	***Please note for requests for members in SNF/LTC see separate criteria section below**
	• Documentation member has met all of the following:
	  ○ Clinic notes containing diagnosis and rationale for needing long-acting opioids for severe chronic pain requiring around-the-clock opioid treatment requiring more than 90 days of therapy.
	  ○ Previous use of an equianalgesic short-acting opioid and/or the total dose increase is not greater than 50% from the previous average daily dose
	  ○ Current and adherent to at least one non-opioid adjuvant (e.g., NSAIDs (documented by either attestation or claims data), tri-cyclic antidepressant, SNRI, gabapentin).
	  ○ Non-pharmacologic treatments (e.g., acupuncture, physical therapy, chiropractic adjustment, etc.) have been discussed with the member, if applicable
	  ○ The member is not opioid naïve (defined as no opioid claims in last 90 days)
	  ○ The member is not on another long-acting opioid OR documentation/attestation that member is switching from one long-acting opioid to another has been submitted.
	• For members with a high-risk condition stated in the CDC guidelines (ex. sleep apnea or other causes of sleep-disordered breathing, renal or hepatic insufficiency, older adults, pregnant women, depression or other mental health conditions, or alcohol or other substance use disorders) the prescriber attests to discussing the heightened risks of opioid use and has educated the member on naloxone use and has considered prescribing naloxone
	
	Criteria for the use of morphine sulfate ER tablets (MS Contin)
	• See “Criteria to start treatment for ALL drugs”
	
	Criteria for the use of fentanyl (Duragesic) 12, 25, 50, 75, 100 mcg/h transdermal patch, oxycodone ER (OxyContin) tablets, and methadone 5, 10, mg tablet, 10 mg/ml, 5mg/5 ml, 10 mg/5ml solution
	• See “Criteria to start treatment for ALL drugs”
	• Documentation of trial and failure, intolerance, contraindication to extended-release morphine sulfate [MS Contin])
	• For methadone, the prescriber attests naloxone has been prescribed for the member
	• For methadone liquid, documented reason (i.e. inability to swallow) or inability to use oral tablet formulation
	
	Criteria for non-formulary long-acting opioid medications

- See “Criteria to start treatment for ALL drugs”
- Documentation of trial and failure, intolerance, or contraindication to extended-release morphine sulfate [MS Contin]) AND at least one other formulary-prior authorization required medication
- If the request is for non-formulary fentanyl 37.5, 62.5, or 87.5 mcg/h patches, the member must have documentation of trial and failure, contraindication, or inability to use fentanyl 12, 25, 50, 75, 100 mcg/h transdermal patches
- If a non-formulary strength of fentanyl patch is requested, return with suggestion of separate patches (ex: 37.5mcg/hr, suggestion of 12mcg/hr + 25mcg/hr separate patches)

Criteria for requests for an opioid regimen above 500 morphine milligram equivalents (MME) per day, approve if:

- For members who are on 6 months of continuous utilization, refer to partial approval authorization criteria for chronic opioid users

Approve if:

- The criteria to start treatment for ALL drugs, above, and drug-specific criteria (i.e. criteria for the use of fentanyl patches) are met AND all of the additional following criteria are met:
  - The member has been referred to a pain management specialist
  - Documentation is provided that the prescribing provider has reviewed the CURES database for the member, and the member is not receiving opioids from any other prescriber outside the requesting provider’s practice
  - Documentation is provided that the prescriber reviewed the potential risks of ultra-high dose opioid use with the member
  - Documentation is provided that the prescriber has evaluated the member’s treatment history for evidence of benefit with opioid titration in terms of function as well as pain score goals
  - Documentation is provided that the member has received a prescription for naloxone and education for use
  - The provider attests that the member has no known opioid overdose episodes in the last year (i.e., hospitalizations or use of naloxone)
  - Documentation is provided that urine drug screens are being utilized to assess for illicit drug use and/or compliance.

Criteria for Skilled Nursing Facility (SNF) or Long-Term Care Facility (LTC) initial requests. Approval duration limit is up to a 30-day supply with 1 refill (up to a total duration of 60 days):

- Formulary and non-formulary opioids will be approved as a part of continued treatment from the hospital OR when started and administered in the SNF or LTC.
- Formulary and non-formulary opioids should not be denied unless more than a 60 day supply is requested, or the request is deemed unsafe by reviewer
- If the request is for a brand name opioid when a generic is available, it will be partialed for a generic unless they meet following:
  - The member must use the authorized generic (if available), if made by the maker of the brand-name product OR
  - The member must use the biosimilar product when available, prior to the approval of the brand OR
  - The member must use a generic formulation with the same inactive ingredients as the brand name product (if available)
  - AND, the member must try and have documented adverse reaction to

	three (3) different generic formulations. If there are fewer than 3 formulations available, the member must try all available generic formulations before the brand name product will be approved. • If the request is for a brand name opioid when a generic is NOT available, the request will be partialed for up to a 30-day supply with 1 refill (up to a total duration of a 60-day supply). • Subsequent requests will be reviewed using the initial criteria. **Partial Approval Authorization Criteria for Chronic Opioid Users:** • Members with a total opioid utilization of at least 90 MME AND 6 months of continuous utilization are eligible for 3 months approval until a treatment plan is provided. ○ Clinic notes and claims history will be used to confirm the above. ○ Members who are new to the plan must have a list of specific dates when they were on opioids. • Criteria above (e.g. Criteria to start treatment for ALL drugs, Criteria for fentanyl patches, Criteria for non-formulary medications, etc.) do NOT need to be met for a partial approval for chronic opioid users. • Subsequent requests will be reviewed using the same partial approval criteria for chronic opioid users. If the prescriber provides a treatment plan, the request will be approved up to the duration of the treatment plan with a maximum of a 1 year approval. **Reauthorization criteria for administration locations other than SNF/LTC** • Documentation (clinic notes or chart notes) showing why longer treatment is needed: should include treatment plan, non-pharmacological treatment (e.g., acupuncture, physical therapy, chiropractic adjustment, etc.), titration or tapering plan (if applicable).
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Serotonin Receptor Agonists (Triptans)	
Therapeutic Classes (AHFS)	Selective serotonin agonists
Medications	**FORMULARY STATUS** Formulary, Pays at Point-of-Sale (First Line), within quantity limits (QL) • Sumatriptan (Imitrex) tablets: QL 18/30 • Rizatriptan (Maxalt & Maxalt- MLT) tablets and ODT: QL 12/30 • Naratriptan (Amerge) tablets: QL 9/30 **FORMULARY STATUS** step-therapy required (Second Line, after trial and failure of sumatriptan tablets), within QL 6/30 • Zolmitriptan (Zomig) tablet • Zolmitriptan (Zomig-ZMT) ODT • Sumatriptan (Imitrex) nasal spray **FORMULARY STATUS** Non-preferred, prior authorization required (Third Line) • Sumatriptan (Imitrex) injection **FORMULARY STATUS** Non-formulary, prior authorization required (Last Line) • Almotriptan (Axert) • Frovatriptan (Frova) • Eletriptan (Relpax) • Sumatriptan/naproxen (Treximet) • Zembrace SymTouch (sumatriptan) • Onzetra Xsail (sumatriptan) • Migranow (Sumatriptan/menthol/camphor) 50 mg tablet/gel kit • Tosymra (sumatriptan) 10mg nasal spray • Zolmitriptan (Zomig) nasal spray **Any other newly marketed serotonin receptor agonists (triptans) treatment agents.**
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months, not to exceed 12 tablets per 30 days, 2 injections kits (4 injections) per 30 days, and 6 nasal spray units (1 box) per 30 days **Later Approvals** 12 months, not to exceed 12 tablets per 30 days, 2 injections kits (4 injections) per 30 days, and 6 nasal spray units (1 box) per 30 days If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Criteria for authorization:** **First line agents:** • An automatic approval for first line agents sumatriptan tablet, rizatriptan tablets or ODT, or naratriptan tablets at the point-of-sale will occur if the quantities prescribed do not exceed quantity limits. **Second line agents:** • Second line agents will pay automatically, at the point-of-sale if the quantities prescribed do not exceed quantity limits and the members has a history of paid claims for sumatriptan tablets

Serotonin Receptor Agonists (Triptans)	

	Third line agent:
	• **For sumatriptan (Imitrex) injection, approve if:**
	  ○ Documented trial and failure at therapeutic doses or intolerance, contraindication, or inability to use oral formulary alternatives sumatriptan tablets or naratriptan tablets AND rizatriptan ODT.
	  ○ Diagnosis of migraine headaches OR
	  ○ Diagnosis of cluster headaches
	
	Last line agents:
	• **For non-formulary triptans, approve if:**
	  ○ Documented trial and failure at therapeutic doses or intolerance, contraindication, or inability to use 1) sumatriptan tablets/nasal spray and 2) rizatriptan tablets/ODT and 3) naratriptan tablets and then 4) zolmitriptan tablets/ODT.
	  ○ Requests for sumatriptan/naproxen (Treximet) should be directed to using the two individual agents
	
	Criteria for Quantities Greater Than Allowed Per 30 Days:
	If the patient requires doses greater than the set limits after meeting approval the following conditions must be met:
	• Documentation provided that member is on prophylactic therapy.
	AND/OR
	• Documentation of medical necessity for increased quantity despite optimal prophylactic therapy.

Criteria Statement	Second line agents are reserved for members who have used (or cannot/should not use) sumatriptan tablets. Third line agent sumatriptan injection is reserved for members who have used (or cannot/should not use) sumatriptan tablets or naratriptan tablets AND rizatriptan ODT and have a diagnosis of migraine headaches or cluster headaches. Third line agents/non-formulary triptans are reserved for members who have used (or cannot/should not use) 1) sumatriptan tablets/nasal spray and 2) rizatriptan tablets/ODT and 3) naratriptan tablets and 4) zolmitriptan tablets/ODT.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Pregabalin (Lyrica and Lyrica CR)	
Therapeutic Classes (AHFS)	Anticonvulsants, miscellaneous
Medications	Formulary, quantity limit (90/30) Pregabalin (Lyrica) 25, 50, 75, 100, 150, 200, 225, 300 mg capsule Formulary, prior authorization required Pregabalin (Lyrica CR) 82.5, 165, 330 mg ER tablet Pregabalin (Lyrica) 20 mg/ml solution
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**FOR pregabalin (LYRICA) liquid OR ER tablet REQUESTS** • Documentation of trial and failure of, intolerance, or inability to use pregabalin IR oral capsules (i.e. difficulty swallowing for the liquid formulation) **For requests above the quantity limit** • The provider has submitted a medical reason why the plan's quantity limit will be inadequate based on the member's condition and treatment history. AND • The dose requested is supported by the Medical Compendia or current treatment guidelines
Criteria Statement	Pregabalin (Lyrica) oral solution and ER tablets are reserved for members who cannot use pregabalin IR oral capsules (for example, unable or difficulty swallowing).
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes, minor correction in the criteria statement.

Sedative Hypnotics	
Therapeutic Classes (AHFS)	Anxiolytics, sedatives, and hypnotics, misc
Medications	ramelteon (Rozerem) Edluar (zolpidem SL) zolpidem (Intermezzo) sublingual tablet Belsomra (suvorexant) doxepin (Silenor) tablet DayVigo (lemborexant) tablet Quviviq (daridorexant) tablet Any other newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial** — If all criteria are met, approve for up to a 6 month duration; if all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review. **Reauthorization** — If all criteria are met, approve for up to a 12 month duration; if all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.

PA Review Criteria	CRITERIA FOR AUTHORIZATION
	Ramelteon (Rozerem)
	• Diagnosis of insomnia.
	• Documented trial and failure, contraindication, or intolerance to one of the following: zolpidem (Ambien) IR or ER, eszopiclone (Lunesta) or zaleplon (Sonata) for at least 2 weeks (14 days) of therapy.
	  ○ For requests for members aged 65 or older OR for members with a history of substance abuse, only a diagnosis of insomnia is required
	
	Doxepin (Silenor) tablet
	• Diagnosis of insomnia.
	• Documented trial and failure, contraindication, or intolerance to one of the following: zolpidem (Ambien) IR or ER, eszopiclone (Lunesta), or zaleplon (Sonata) AND ramelteon (Rozerem) AND doxepin concentrate for at least 2 weeks (14 days) of therapy
	  ○ For members aged 65 or older, only diagnosis of insomnia AND documented trial and failure, contraindication, or intolerance to doxepin concentrate AND ramelteon (Rozerem) for at least 2 weeks (14 days) of therapy is required
	
	Edluar, zolpidem (Intermezzo)
	• Diagnosis of insomnia.
	• Documented trial and failure, contraindication, or intolerance to TWO of the following: zolpidem (Ambien) IR or ER, eszopiclone (Lunesta), or zaleplon (Sonata) for at least 2 weeks (14 days) of therapy

	• Documented trial and failure or intolerance to ramelteon (Rozerem) for at least 2 weeks (14 days) of therapy. **<u>DayVigo, Quviviq, or Belsomra</u>** • Diagnosis of insomnia. • Documented trial and failure, contraindication, or intolerance to TWO of the following: zolpidem (Ambien) IR or ER, eszopiclone (Lunesta), or zaleplon (Sonata) for at least 2 weeks (14 days) of therapy • Documented trial and failure or intolerance to ramelteon (Rozerem) for at least 2 weeks (14 days) of therapy. ○ For members aged 65 or older, only diagnosis of insomnia AND documented trial and failure, contraindication, or intolerance to doxepin concentrate AND ramelteon (Rozerem) for at least 2 weeks (14 days) of therapy is required • For Belsomra requests, the criteria above must be met AND documented trial and failure, contraindication, or intolerance to DayVigo is required • For Quviviq requests, the criteria above must be met AND documented trial and failure, contraindication, or intolerance to DayVigo AND Belsomra is required
Criteria Statement	Ramelteon is reserved for members with insomnia who are older than 65 years OR have history of substance abuse OR who have used (or cannot/should not use) one of the following: zolpidem IR or ER, eszopiclone, or zaleplon for at least 2 weeks. Edluar, zolpidem (Intermezzo) are reserved for members who have insomnia and who have used (or cannot/should not use) ramelteon and at least two of the following, zolpidem IR or ER, eszopiclone, or zaleplon AND ramelteon (Rozerem) for at least 2 weeks. DayVigo, Quviviq, or Belsomra are reserved for members who have insomnia and who have used (or cannot/should not use) two of the following: zolpidem IR or ER, eszopiclone, or zaleplon AND ramelteon for at least 2 weeks. If a member is 65 or older, DayVigo is reserved for members who have a diagnosis of insomnia and who have used (or cannot/should not use) doxepin concentrate and ramelteon for at least 2 weeks. If a member is 65 or older, Belsomra is reserved for members who have a diagnosis of insomnia and who have used (or cannot/should not use) doxepin concentrate and ramelteon and DayVigo. If a member is 65 or older, Quviviq is reserved for members who have a diagnosis of insomnia and who have used (or cannot/should not use) doxepin concentrate and ramelteon and DayVigo and Belsomra. Doxepin (Silenor) is reserved for members who have insomnia who have used (or cannot/should not use) one of the following: zolpidem IR or ER, eszopiclone, or zaleplon AND ramelteon AND doxepin concentrate. If a member is 65 or older, doxepin (Silenor) is reserved for members who have a diagnosis of insomnia and used (or cannot/should not use) doxepin concentrate and ramelteon.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Hepatitis C Medications: All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review

MAVYRET (glecaprevir/ pibrentasvir) - PREFERRED AGENT
SOFOSBUVIR /VELPATASVIR (GENERIC EPCLUSA)-PREFERRED AGENT
LEDIPASVIR /SOFOSBUVIR (GENERIC HARVONI)-PREFERRED AGENT

ZEPATIER (elbasvir/ grazoprevir)
VOSEVI (sofosbuvir/ velpatasvir/ voxilaprevir)
EPCLUSA (sofosbuvir/velpatasvir)
HARVONI (ledipasvir/ sofosbuvir)
SOVALDI (sofosbuvir)
PEG-INTRON (peginterferon alfa-2b) PEGASYS (peginterferon alfa-2a)
RIBAVIRIN
VIEKIRA PAK (ombitasvir, paritaprevir, ritonavir and dasabuvir)
ANY OTHER NEWLY MARKETED AGENT for treatment of Hepatitis C

NOTE: Where applicable and appropriate: MAVYRET (glecaprevir/pibrentasvir), SOFOSBUVIR/VELPATASVIR (GENERIC EPCLUSA), or LEDIPASVIR/SOFOSBUVIR (GENERIC HARVONI) are the PREFERRED AGENTS for Hepatitis C requests unless a documented medical reason has been provided (intolerance, hypersensitivity, contraindication, etc.) why the member is not able to use Mavyret, sofosbuvir/velpatasvir (generic Epclusa), or ledipasvir/sofosbuvir (generic Harvoni).

All initial requests MUST meet the following requirements:

1. Life expectancy ≥ 12 months.
2. Lab testing required before starting treatment (copy of results required) if required for treatment selection per AASLD guidelines
    - Genotype must be provided if:
        - Genotype testing required for all who are not going to receive Mavyret or generic Epclusa
        - Genotype testing required for generic Epclusa in treatment naive patients with compensated cirrhosis
        - Genotype testing required for patients who do not qualify for simplified treatment (treatment-experienced, have or had decompensated cirrhosis (Child-Pugh B and C), have ESRD, are HIV positive, have current HBV infection (positive for HbsAg), are pregnant, have known or suspected hepatocellular carcinoma, or have had a liver transplant)
2. Provider has addressed all potential drug interactions with Hepatitis C regimen (including discontinuation of the interacting drug, dose reduction, or counseling of the patient of the risks associated with the use of both medications), AND
3. **Dose and Duration of Therapy: (SEE TREATMENT SUMMARY THAT FOLLOWS)**: Approvals of requests will be consistent with package labeling or current guidelines, at FDA approved dosing. These regimens are subject to change as newly marketed agents become available. Pediatric patients will be limited to one tablet/packet per day. Medications must be dose consolidated to 1 tablet/packet daily, as appropriate.
   ALL regimens are for 28 day supply per fill.

Hepatitis C Treatment Summary
*****For all charts, sofosbuvir/velpatasvir (generic Epclusa) and ledipasvir/sofosbuvir (generic Harvoni) refer to their generic formulations*****

Treatment Naïve			
Genotype	**Treatment Option**	**Duration**	
		No Cirrhosis	**Compensated Cirrhosis (Child-Pugh A)**
All	**Mavyret**	**8 weeks**	**8 weeks**
All^	**sofosbuvir/velpatasvir (generic Epclusa)**	**12 weeks**	**12 weeks**

^Genotype testing required; for genotype 3 with compensated cirrhosis, only use sofosbuvir-velpatasvir (generic Epclusa) if no Y93H resistance

Treatment Experienced, with and without compensated cirrhosis		
Genotype	**Prior Treatment**	**Preferred Regimen**
All	**Sofosbuvir-based and Zepatier treatment failures, including:** Sovaldi + ribavirin ± interferon Harvoni Epclusa Zepatier	12 weeks Vosevi (± ribavirin)^
	Mavyret treatment failures Mavyret only	16 weeks Mavyret + Sovaldi + ribavirin 12 weeks Vosevi (± ribavirin)[a]
	Multiple DAA treatment failures, including: Vosevi Sovaldi + Mavyret	16 weeks Mavyret + Sovaldi + ribavirin* 24 weeks Vosevi + ribavirin

^Add ribavirin for 12 weeks in patients with genotype 3 and cirrhosis, if no contraindications

[a] Add ribavirin if the patient has compensated cirrhosis

*Extension of treatment to 24 weeks should be considered in extremely difficult cases (eg, genotype 3 with cirrhosis) or failure following Sovaldi + Mavyret.

Unique patient populations Refer to current AASLD guidelines @ http://www.hcvguidelines.org/ For all unique and key populations: NOTE: If Mavyret, sofosbuvir/velpatasvir (generic Epclusa), or ledipasvir/sofosbuvir (generic Harvoni) are recommended treatment options, they are preferred unless medical reason provided that member is unable to use Mavyret, sofosbuvir/velpatasvir (generic Epclusa), or ledipasvir/sofosbuvir (generic Harvoni).
HIV/HCV Coinfection
Decompensated Cirrhosis (Child-Pugh B or C)
Recurrent HCV Infection Post-Transplant
HCV-Uninfected Transplant Recipients Receiving Organs From HCV-Viremic Donors
Renal Impairment
Kidney Transplant
Pregnancy
Pediatrics *Medications should be dose consolidated to no more than one tablet/packet daily if possible.

Last Review/Revision Date: ~~6/2024~~6/2025

Recommendation: No changes

Phosphate Binders	
Therapeutic Classes (AHFS)	Phosphate-removing agents
Medications	**Formulary** Calcium acetate Sevelamer carbonate (Renvela) 800 mg tablet **Formulary, PA required** sevelamer hcl (Renagel) tablet **- PREFERRED** Lanthanum carbonate (Fosrenol) tablets **- PREFERRED** Sevelamer carbonate (Renvela) powder pack Fosrenol (lanthanum carbonate) powder pack Auryxia (ferric citrate) tablets Velphoro (sucroferric oxyhydroxide) chewable tablets
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Sevelamer HCL (Renagel) tablet and lanthanum carbonate (Fosrenol) tablet are approved when the following criteria are met: • Documentation of a trial and failure, contraindication, or intolerance sevelamer carbonate (Renvela) tablet Sevelamer carbonate (Renvela) powder packets, Fosrenol (lanthanum carbonate) powder packets, Auryxia tablets, and Velphoro tablets are approved when the following criteria are met: • Documentation of a trial and failure, contraindication, or intolerance to sevelamer carbonate (Renvela) tablet • Documentation of a trial and failure, contraindication, or intolerance to Sevelamer HCL (Renagel) tablet OR lanthanum carbonate (Fosrenol) tablet
Criteria Statement	Sevelamer hcl (Renagel) tablets and lanthanum carbonate (Fosrenol) tablets are reserved for members who have used (or cannot/should not use) sevelamer carbonate (Renvela) tablets. Sevelamer carbonate (Renvela) powder packets, Fosrenol (lanthanum carbonate) powder packets, Auryxia tablets, and Velphoro tablets are reserved for members who have used (or cannot/should not use) sevelamer carbonate (Renvela) tablet AND sevelamer hcl (Renagel) tablets or lanthanum carbonate (Fosrenol) tablets.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Xolair (omalizumab) for Asthma, Urticaria, and IgE-Mediated Food Allergy	
Therapeutic Classes (AHFS)	RESPIRATORY TRACT AGENTS, MISCELLANEOUS
Medications	Xolair (omalizumab)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	• Use of Xolair concomitantly with another pulmonary biologic (e.g, Cinqair, Fasenra, Dupixent, Tezspire, or Nucala) • Use of Xolair concomitantly with Palforzia • Use of Xolair for emergency treatment of allergic reactions, including anaphylaxis
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	N/A
Prescriber Restrictions	Prescribed by an allergist/immunologist, pulmonologist, or dermatologist, or in consultation with one of these specialists
Coverage Duration	**Initial Approval** Up to a 6 month duration **Later Approvals** Up to a 6 month duration If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	****For nasal polyposis, please refer to the "Biologic Agents for Nasal Polyposis" policy**** **<u>INITIAL AUTHORIZATION FOR ASTHMA:</u>** • The patient has at least a 6 month history of moderate-to-severe asthma. • The drug is indicated for the patient's age and is prescribed at an approved dose according to the patient's weight and IgE level • Patient is taking maximally tolerated ICS/LABA combination in addition to a LAMA (e.g. tiotropium) for at least 3 months or there is a documented medical reason why the patient is unable to take these medications • Patient's asthma is uncontrolled as defined by having one of the following: ○ Frequent severe exacerbations requiring two or more bursts of systemic glucocorticoids (more than three days each) in the previous year ○ History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year ○ Airflow limitation defined as a forced expiratory volume in 1 second (FEV1) less than 80% of predicted ○ Poor symptom control including at least THREE of the following: ▪ Asthma Control Questionnaire (ACQ) consistently > 1.5 or Asthma Control Test (ACT) < 20 ▪ Daytime asthma symptoms more than twice per week ▪ Use of an inhaled short acting B-2 agonist to relieve asthma symptoms more than twice per week (not including use prior to exercise) ▪ Limited physical activity due to asthma symptoms ▪ Nighttime awakening due to asthma symptoms • The patient has a positive documented immediate response on RAST test and/or skin prick test to at least 1 common allergen (e.g. dermatophagoides farinae, dermatophagoides pteronyssinus, dog, cat, or

	cockroach) and there is documented evidence that the positive skin tested allergen(s) is an asthma trigger (copy of results required). • Pre-treatment serum IgE levels must be greater than or equal to 30IU/mL **INITIAL AUTHROIZATION FOR CHRONIC IDIOPATHIC URTICARIA:** • The drug is indicated for the patient's age and is prescribed at an approved dose • The patient has a documented history of urticaria for at least 6 weeks • The patient requires oral steroids to control symptoms. • The patient remains symptomatic despite a minimum two week trial (or has medical reason for not utilizing) of two formulary second generation H1 antihistamines at the maximum tolerated dose **INITIAL AUTHORIZATION FOR IgE-MEDIATED FOOD ALLERGY:** • Diagnosis of IgE-mediated food allergy with documented allergy to one or more of the following foods: o Peanut, milk, egg, wheat, cashew, hazelnut, or walnut • Attestation Xolair will be used in conjunction with food allergen avoidance • The drug is being prescribed at an FDA approved dose according to the member's weight and IgE level **REAUTHORIZATION: AFTER 4 MONTHS OF THERAPY FOR ASTHMA OR CHRONIC IDIOPATHIC URTICARIA:** • Documentation submitted indicates that the member has benefited clinically from the medication (e.g. patient has marked improvement in pulmonary function tests such as FEV1 or peak expiratory flow rate, decrease in asthma exacerbations, decrease in skin manifestations or severe itching, and/or a decrease in inhaled or oral corticosteroid use since receiving Xolair therapy). • The prescribed dose is within approved FDA dosing guidelines.
Criteria Statement	N/A
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Short acting opioid containing products		
Therapeutic Classes (AHFS)	OPIATE AGONISTS	
Medications	Short-acting opioid containing products	
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.	
Exclusion Criteria	N/A	
Required Clinical Information	See "PA Review Criteria" below	
Age Restrictions	N/A	
Prescriber Restrictions	N/A	
Coverage Duration	**Approval for initial and renewal when not otherwise specified** **Initial approval for LTC or SNF requests** **Partial Approval for chronic users** **Later Approvals**	If the criteria are met, the request will be approved for up to six months duration; if the criteria are not met, the request will be referred to a clinical reviewer for medical necessity review Approval duration limit is up to a 30-day supply with 1 refill (up to a total duration of 60 days) Partial approval duration limit for members with chronic use is up to a 3 month supply If the criteria are met, the request will be approved for up to six month duration; if the criteria are not met, the request will be referred to a clinical reviewer for medical necessity review ****If a member does not meet the criteria but is actively tapering off of opioids and the prescriber has explained medical necessity, the request should be approved for 6 months****
PA Review Criteria	****All requests for narcotics must be reviewed by a clinical pharmacist**** ****Members who are on at least 90 MME with a continuous 6 months utilization, please use Partial Approval Authorization Criteria for Chronic Opioid Users.** **If the member has a diagnosis of cancer, sickle cell disease, or is on hospice/palliative care please automatically authorize for up to 12 months (member must meet non-formulary criteria if request is for non-formulary medication with the exception of ALL formulations of short acting oxycodone products which will be approved for 12 months)** Day supply limits apply to opioid naive patients. <u>Initial Authorization</u>: **treatment for administration location other than SNF/LTC*: *Please note for requests for members in SNF/LTC see separate criteria section below** • Documentation member has met all of the following: o Documented diagnosis of pain. o The member has tried and failed two non-opioid containing pain medications (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs [NSAIDs] (documented by either attestation or claims data); tri-cyclic antidepressant, SNRI, gabapentin).	

	○ Non-pharmacologic treatments (e.g., acupuncture, physical therapy, chiropractic adjustment, etc.) have been discussed with the member, if applicable ○ The prescriber has justified the medical necessity for dosing above the current quantity limit (for medications with quantity limits) or day supply limit (i.e. active tapering) ○ The member is not taking concurrent benzodiazepines. If the member is taking benzodiazepines, the prescriber has provided documentation as to why, and attests to discussing with the member the risks of using opioids and benzodiazepines concurrently, and has outlined a plan for tapering if appropriate. ○ The member is not taking concurrent muscle relaxants that are classified as controlled substances. If the member is taking muscle relaxants classified as controlled substances, the prescriber has provided documentation as to why, and attests to discussing with the member the risks of using opioids and muscle relaxants concurrently, and has outlined a plan for tapering if appropriate. ○ If the request is for a non-formulary short acting opioid, the member must meet the above criteria AND one of the following conditions: ▪ Documented trial and failure or intolerance with up to three formulary medications used to treat the documented diagnosis. For medications where there is only one preferred agent, only that agent must have been ineffective or not tolerated. ▪ No other formulary medication has a medically accepted use for the member's specific diagnosis as referenced in the medical compendia. ▪ All other formulary medications are contraindicated based on the member's diagnosis, other medical conditions, or other medication therapy. • If the request is for an opioid regimen above 500 morphine milligram equivalents (MME) per day, see below: ○ For members who are on 6 months of continuous utilization, refer to partial approval authorization criteria for chronic opioid users • Approve if: ○ The criteria for initial authorization, above, are met AND all of the additional following criteria are met: ▪ The member has been referred to a pain management specialist ▪ Documentation is provided that the prescribing provider has reviewed CURES database for the member, and the member is not receiving opioids from any other prescriber outside the requesting provider's practice ▪ Documentation is provided that the prescriber reviewed the potential risks of ultra-high dose opioid use with the member ▪ Documentation is provided that the prescriber has evaluated the member's treatment history for evidence of benefit with opioid titration in terms of function as well as pain score goals ▪ Documentation is provided that the member has received a prescription for naloxone and education for use ▪ The provider attests that the member has no known opioid overdose episodes in the last year (i.e., hospitalizations or use of naloxone) ▪ Documentation is provided that urine drug screens are being utilized to assess for illicit drug use and/or compliance.

Criteria for Skilled Nursing Facility (SNF) or Long-Term Care Facility (LTC) initial requests. Approval duration limit is up to a 30-day supply with 1 refill (up to a total duration of 60 days):

- Formulary and non-formulary opioids can be approved as a part of continued treatment from the hospital OR when started and administered in the SNF or LTC.
- Formulary and non-formulary opioids should not be denied unless more than 60 days supply is requested, or the request is deemed unsafe by reviewer
- If the request is for a brand name opioid when a generic is available, it will be partialed for generic unless they meet the following:
    - The member must use the authorized generic (if available), if made by the maker of the brand-name product OR
    - The member must use the biosimilar product when available, prior to the approval of the brand OR
    - The member must use generic formulation with the same inactive ingredients as the brand name product (if available)
    - AND, the member must try and have documented adverse reaction to three (3) different generic formulations. If there are fewer than 3 formulations available, the member must try all available generic formulations before the brand name product will be approved.
- If the request is for a brand name opioid when a generic is NOT available, the request will be partialed up to a 30-day supply with 1 refill (up to a total duration of 60 days supply)
- Subsequent requests will be reviewed using initial criteria

Partial Approval Authorization Criteria for Chronic Opioid Users

- Members with a total opioid utilization of at least 90 MME AND 6 months of continuous utilization are eligible for 3 months approval until a treatment plan is provided.
    - Clinic notes and claims history will be used to confirm the above
    - Members who are new to the plan must have a list of specific dates when they were on opioids
- Criteria above (e.g. initial authorization) do NOT need to be met for partial approval for chronic opioid users.
- Subsequent requests will be reviewed using partial approval criteria for chronic opioid users. If the provider provides a treatment plan, the request will be approved up to duration of treatment plan with a maximum of 1 year of approval.

Reauthorization Criteria for administration locations other than SNF/LTC

- The prescriber has explained the medical necessity for continued dosing above the current quantity limit (for medications with quantity limits) and if the dose is not being titrated, has provided medical justification explaining why the dose cannot be decreased
- The provider has submitted documentation of the member's response to the requested medication (ex. Improvement in severity level of pain, improvement in ADL's, etc.)
- The member is not taking concurrent benzodiazepines. If the member is taking benzodiazepines, the prescriber has provided documentation as to why, and attests to discussing with the member the risks of using opioids and benzodiazepines concurrently, and has outlined a plan for tapering if appropriate.
- Non-pharmacologic treatments (e.g., acupuncture, physical therapy, chiropractic adjustment, etc.) have been discussed with the member and/or

	the member has tried and failed appropriate non-pharmacological alternatives for pain • The member is not taking concurrent muscle relaxants that are classified as controlled substances. If the member is taking muscle relaxants classified as controlled substances, the prescriber has provided documentation as to why, and attests to discussing with the member the risks of using opioids and muscle relaxants concurrently and has outlined a plan for tapering if appropriate. • For members over 500 daily MME, the reauthorization criteria above, are met AND all of the additional following criteria are met: o The member has been referred to a pain management specialist o Documentation is provided that the prescribing provider has reviewed CURES database for the member, and the member is not receiving opioids from any other prescriber outside the requesting provider's practice o Documentation is provided that the prescriber reviewed the potential risks of ultra-high dose opioid use with the member o Documentation is provided that the prescriber has evaluated the member's treatment history for evidence of benefit with opioid titration in terms of function as well as pain score goals o Documentation is provided that the member has received a prescription for naloxone and education for use o The provider attests that the member has no known opioid overdose episodes in the last year (i.e., hospitalizations or use of naloxone) o Documentation is provided that urine drug screens are being utilized to assess for illicit drug use and/or compliance.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Alprazolam (Xanax)	
Therapeutic Classes (AHFS)	BENZODIAZEPINES (ANXIOLYTIC,SEDATIVE/HYPNOTIC)
Medications	Non-formulary Alprazolam oral tablets (0.25mg, 0.5mg, 1mg and 2mg) Alprazolam oral ER tablets (0.5mg, 1mg, 2mg and 3mg) Alprazolam oral disintegrating tablets (0.25mg, 0.5mg, 1mg and 2mg)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	N/A
Prescriber Restrictions	Psychiatry
Coverage Duration	**Initial Approval** 3 months **Later Approvals** 3 months If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	**CRITERIA FOR AUTHORIZATION** • Request is for alprazolam oral tablets: o Diagnosis of anxiety or panic disorders o Clinic notes to show trial and failure of at least 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each (for example – clonazepam, diazepam and lorazepam) • Request is for alprazolam oral disintegrating (ODT) tablets: o Diagnosis of anxiety or panic disorder o Clinic notes to show trial and failure of at least 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each AND o Inability to swallow or another medical reason why alprazolam oral tablets cannot be used • Request is for alprazolam oral ER tablets: o Diagnosis of panic disorder o Clinic notes to show trial and failure of at least 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each AND o Trial and failure of alprazolam oral tablets **RE-AUTHORIZATION** Documentation of clinical benefit and/or titration schedule for discontinuation (if applicable). Treatment plan should also be given for those on long term treatment (more than 3 months of therapy).
	Alprazolam oral tablets are reserved for members who have used (or cannot/should not use) 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each. Alprazolam oral disintegrating (ODT) tablets are reserved for members who have used (or cannot/should not use) 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each AND who cannot/should not use alprazolam oral tablets or cannot swallow. Alprazolam ER tablets are reserved for members who have used (or cannot/should not use) 3 formulary benzodiazepines for at least 2 weeks (14 days) of therapy each AND who cannot/should not use alprazolam oral tablets.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Diuretics	
Therapeutic Classes (AHFS)	Loop Diuretics, Thiazide-like Diuretics
Medications	Formulary, step therapy required Bumetanide tablet Metolazone tablet (quantity limit 30/30)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Reauthorization** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Bumetanide step therapy criteria: • Documentation of a trial and failure or intolerance to torsemide 100 mg or furosemide 80 mg required. Metolazone step therapy criteria: • Documentation of a trial and failure or intolerance to hydrochlorothiazide AND furosemide required.
	Bumetanide is reserved for members who have used (or cannot/should not use) torsemide 100 mg or furosemide 80 mg. Metolozone is reserved for members who have used (or cannot/should not use) hydrochlorothiazide AND furosemide.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Rectiv (nitroglycerin) ointment	
Therapeutic Classes (AHFS)	Skin and Mucous Membrane Agents, Misc.
Medications	Non-Formulary Rectiv (nitroglycerin) rectal ointment 0.4%
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Concomitant use of a phosphodiesterase type 5 (PDE5) inhibitors (e.g. sildenafil, vardenafil, tadalafil).
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial/Re-Approval** If all conditions are met, the request will be approved for a one-time coverage duration of up to 3 weeks. If conditions are not met, the request will be sent to a clinical reviewer for medical necessity review.

PA Review Criteria	The following criteria must be met for initial requests:
	• Dose is appropriate per label or supported by compendia/standard of care guidelines
	• Diagnosis of moderate to severe pain associated with chronic anal fissures for at least 6 weeks
	• Documentation (by either attestation or claims data) of trial and failure (within past 60 days), contraindication, or intolerance to at least two conservative treatments for the underlying cause of the anal fissure:
	  ○ High-fiber diet or fiber supplements
	  ○ Sitz baths
	  ○ Topical analgesia/ medicated creams (e.g. hydrocortisone rectal suppository or topical cream, zinc oxide)
	  ○ Laxative or stool softeners (e.g. psyllium, docusate)
	
	The following criteria must be met for re-authorization requests:
	• Dose continues to be appropriate per label or supported by compendia/standard of care guidelines
	• Documentation submitted indicates a clinical benefit was observed and rationale for continuation of treatment

Criteria Statement	Rectiv is reserved for members with moderate to severe pain associated with chronic anal fissures for at least 6 weeks. The member should have used (or cannot/should not use) other conservative treatments for the underlying cause of the anal fissure.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No change

Acute Migraine Treatments	
Therapeutic Classes (AHFS)	CALCITONIN GENE-RELATED PEPTIDE ANTAG., SELECTIVE SEROTONIN AGONISTS
Medications	Formulary, PA required Ubrelvy (ubrogepant) PREFERRED Zavzpret (zavegepant) PREFERRED Non-formulary, PA required Nurtec ODT (rimegepant) - if the request is for migraine prevention please refer to the Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention Reyvow (lasmiditan) Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Prescribed by or in consultation with a neurologist, migraine specialist, pain specialist, or other specialist in the treatment of headaches
Coverage Duration	**Initial Approval** 3 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Initial Authorization:** Medications will be approved when all of the following criteria are met: • Diagnosis of migraine headache • Requested dose is within FDA approved dosing guidelines • Documented trial and failure of (or medical justification for not using) two triptan products • Attestation the patient was counseled regarding not driving or operating machinery until at least 8 hours after taking each dose (Reyvow only) • If the request is for a non-preferred agent, the member must have a documented trial of Ubrelvy or Zavzpret, or have a documented medical reason (e.g. contraindication, intolerance, hypersensitivity, etc.) for not utilizing Ubrelvy or Zavzpret **Criteria for Re-Authorization:** • Documentation of improvement in migraine pain and symptom (s) (e.g., photophobia, nausea, phonophobia) **Nurtec ODT QL of 8 units per month.** **Reyvow QL of 8 units per month.** **Ubrelvy QL of 16 units per month** **Zavzpret QL of 8 units per month** **Criteria for exceeding the quantity limit (note all of the above criteria must also be met)** • Documented trial and failure (or a medical justification for not using e.g. hypersensitivity, baseline bradycardia or hypotension, adverse events

Acute Migraine Treatments	
	experienced from previous trial, etc.) with at least one drug from two categories below for at least 4 weeks EACH, at minimum effective doses: o Beta-adrenergic blockers o Topiramate or divalproex ER or DR o Amitriptyline or venlafaxine o Frovatriptan, zolmitriptan or naratriptan (for menstrual migraine prophylaxis)
Criteria Statement	Ubrelvy and Zavzpret are reserved for members with a diagnosis of migraine headaches who have used (or cannot/should not use) two triptan medications, and are within the quantity limits. Reyvow and Nurtec are reserved for members with a diagnosis of migraine headaches who have used (or cannot/should not use) two triptan medications AND Ubrelvy or Zavzpret and are within the quantity limits. Quantities exceeding the quantity limits are reserved for members who have used (or cannot/should not use) a member from two prophylactic migraine medication classes.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors	
Therapeutic Classes (AHFS)	Antilipemic Agents, Miscellaneous
Medications	Formulary, PA required Nexletol (bempedoic acid) Nexlizet (bempedoic acid/ezetimibe) Any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	None
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	18 years or older
Prescriber Restrictions	Prescriber must be a cardiologist or specialist in the treatment of lipid disorders
Coverage Duration	**Initial Approval** 3 months **Later Approval** 12 months If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization:** **All Requests:** • Member must have documentation of baseline low density lipoprotein cholesterol (LDL-C) • Member has tried and failed a high-intensity statin (i.e. atorvastatin 40-80 mg, rosuvastatin 20-40 mg) at maximum tolerated dose for 3 months via claim history or chart notes OR documentation has been provided that the member is not able to tolerate a statin • Documentation was provided indicating provider has counseled member on smoking cessation and following a "heart healthy diet" • Dose is appropriate per label or supported by compendia/standard of care guidelines **For Hyperlipidemia**: • One of the following: o Member has a diagnosis of heterozygous familial hypercholesterolemia (FH) o Member has a diagnosis of primary hyperlipidemia • Member has tried and failed ezetimibe at a maximum tolerated dose or documentation has been provided that the member is not able to tolerate ezetimibe **For Cardiovascular Risk Reduction**: • Member has established cardiovascular disease (documented history of coronary artery disease, symptomatic peripheral arterial disease, and or cerebrovascular atherosclerotic disease) • Member does not have established cardiovascular disease but is considered high risk (one of the following): o Diabetes mellitus (type 1 or type 2) in females over 65 years of age or males over 60 years of age o A Reynolds Risk score > 30% or a SCORE Risk score > 7.5% over 10 years o A coronary artery calcium score >400 Agatston units at any time in the past.

	• Member must have a fasting LDL-C ≥ 70 mg/dL. **Reauthorization:** • Documentation was provided that the member has obtained clinical benefit from medication (e.g. LDL-C lowering from baseline) • Dose continues to be appropriate per label or supported by compendia/standard of care guidelines
Criteria Statement	Nexletol and Nexlizet are reserved for members who have a diagnosis of heterozygous familial hypercholesterolemia (FH) OR a diagnosis of primary hyperlipidemia who have used (or cannot/should not use) a high-intensity statin and ezetimibe, and who have received counseling on smoking cessation and are following a “heart healthy diet”. In addition, drugs are reserved for members who have high risk or established atherosclerotic cardiovascular disease (ASCVD) and have used (or cannot/should not use) a high-intensity statin and received counseling on smoking cessation and following a “heart healthy diet”.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Gonadotropin Releasing Hormone Antagonists	
Therapeutic Classes (AHFS)	ANTIGONADTROPINS
Medications	Formulary, PA required Oriahnn (elagolix, estradiol, and norethindrone acetate) capsule Orilissa (elagolix) Non-Formulary Myfembree (relugolix, estradiol, and norethindrone acetate)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	• Pregnancy • History of osteoporosis • History of hepatic impairment (Myfembree, Oriahnn), or severe hepatic impairment (Orilissa)
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	18 years or older
Prescriber Restrictions	Prescriber is an obstetrician/gynecologist
Coverage Duration	**Initial/Re-Approval** If the criteria are met, the request will be approved for (a maximum treatment duration of): • Initial Authorization: 6 months • Subsequent Authorizations: 6 months • Eligible maximum treatment duration: 24 months If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization for all requests:** • Medication is prescribed at an FDA approved dose • If patient is of childbearing potential, prescriber attests the patient is not currently pregnant • Prescriber attests the patient does not have a history of osteoporosis • Prescriber attests they have reviewed the patient's liver function **For a diagnosis of endometriosis associated with moderate to severe pain:** • Request is for Orilissa or Myfembree only • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to an analgesic pain reliever (e.g., NSAIDs, COX-2 inhibitors) taken in combination with combined estrogen progestin oral contraceptive pills (OCPs): ○ If one of the following drugs has been tried previously, a trial of OCPs is not required: progestins, gonadotropin releasing hormone (GnRH) agonists, danazol, or aromatase inhibitors (e.g., anastrozole, letrozole) **For a diagnosis of diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids):** • Request is for Oriahnn or Myfembree only • Documented trial and failure or medical reason for not using estrogen-progestin contraceptive therapy • If one of the following drugs has been tried previously, a trial of estrogen-progestin contraceptive therapy is not required: ○ GnRH agonists, ○ progestin-releasing intrauterine device

	○ tranexamic acid • If the request is for Myfembree, there is a documented trial and failure of Oriahnn, or medical reason why Oriahnn cannot be used **<u>Reauthorization:</u>** • Documentation or provider attestation of positive clinical response (i.e., reduction in pain, reduced menstrual bleeding) • Maximum lifetime treatment duration based on previous dosing and/or hepatic functioning has not been exceeded • Medication is prescribed at an FDA approved dose
Criteria Statement	Orilissa and Myfembree are reserved for members who have a diagnosis of endometriosis associated with moderate to severe pain who have used (or cannot/should not use) an analgesic pain reliever (e.g., NSAIDs, COX-2 inhibitors) taken in combination with combined estrogen progestin oral contraceptive pills (OCPs), however if one of the following drugs has been tried previously, a trial of OCPs is not required: progestins, GnRH agonists, danazol, or aromatase inhibitors (e.g., anastrozole, letrozole). Oriahnn and Myfembree are reserved for members who have a diagnosis of heavy menstrual bleeding associated with uterine fibroids who have used (or cannot/should not use) estrogen-progestin contraceptive therapy OR one of the following: GnRH agonists, progestin-releasing intrauterine devices, or tranexamic acid. Myfembree is reserved for members who have used (or cannot/should not use) Oriahnn.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

<table>
<tr><th colspan="2">Hereditary Angioedema (HAE)</th></tr>
<tr><td>Therapeutic Classes (AHFS)</td><td>COMPLEMENT INHIBITORS</td></tr>
<tr><td>Medications</td><td><u>Preferred:</u>
Orladeyo (berotralstat) oral capsule
Takhzyro (lanadelumab-flyo) SC injection
icatibant (Firazyr) SC injection
Haegarda (C1 esterase inhibitor, human) SC syringe
Cinryze (C1 esterase inhibitor, human) IV vial
Berinert (C1 esterase inhibitor, human) IV vial
Ruconest (C1 esterase inhibitor, recombinant) IV vial

<u>Non-Preferred:</u>
Kalbitor (ecallantide) SC syringe</td></tr>
<tr><td>Covered Uses</td><td>Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.</td></tr>
<tr><td>Exclusion Criteria</td><td>N/A</td></tr>
<tr><td>Required Clinical Information</td><td>See “PA Review Criteria” below</td></tr>
<tr><td>Age Restrictions</td><td>Check AAH active CCS cases for members < 21 years of age</td></tr>
<tr><td>Prescriber Restrictions</td><td>Prescriber must be an immunologist, allergist, rheumatologist, or hematologist</td></tr>
<tr><td>Coverage Duration</td><td>Initial Approval
If criteria are met, the request will be approved as follows:
• Acute treatment: initial fill + 5 refills
• Pre-procedural prophylaxis: 1 treatment
• Long-term prophylaxis: Initial approval: 6 months

Reauthorization
Long-term prophylaxis: Reauthorization:12 months

If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.</td></tr>
<tr><td>PA Review Criteria</td><td>All requests must meet the following criteria:
• Documentation submitted indicates the medication is being prescribed at FDA approved dose.
• The patient is not taking ACE inhibitors or estrogen containing oral contraceptives or hormone replacement therapy
• Documented diagnosis of one of the following:
▪ HAE with deficient or dysfunctional C1INH (e.g. type I, type II or acquired C1INH deficiency):
<table><tr><td>Deficiency Type</td><td>C4</td><td>C1INH antigenic level</td><td>C1INH functional level</td></tr><tr><td>Type I (deficiency of C1INH)</td><td>Low</td><td>Low</td><td>Low</td></tr><tr><td>Type II (dysfunction of C1INH)</td><td>Low</td><td>Normal or elevated</td><td>Low</td></tr><tr><td>Acquired C1INH deficiency</td><td>Low</td><td>Low or normal</td><td>Low</td></tr></table>▪ HAE with normal C1INH:
▪ If known origin, documentation of results of confirmatory genetic test (e.g. mutations in gene for factor XII, angiopoietin-1, plasminogen, kininogen-1, myoferlin, heparan sulfate-glucosamine 3-O-sulfotransferase 6)</td></tr>
</table>

	▪ If unknown origin (U-HAE), documentation of a prolonged trial of high-dose non-sedating antihistamines **For acute treatment (Ruconest, Berinert, Kalbitor, icatibant):** ▪ The patient is receiving only one agent for the treatment of acute attacks ▪ If the request is for a non-preferred agent, the member has documented trial and failure of or intolerance to a preferred agent or medical reason why the member cannot use a preferred agent. **For prophylaxis (Haegarda, Takhzyro, Cinryze, Orladeyo):** ▪ Pre-procedural o Documentation that patient will be undergoing a medical, surgical, or dental procedure associated with mechanical impact to the upper aerodigestive tract and anticipated date of the procedure ▪ Long-term o Documentation of at least one HAE attack per month o The patient is receiving one prophylactic HAE medication only o If the request is for Cinryze, the patient has a documented trial and failure of, or intolerance to, Haegarda o If the request is for Takhzyro and the patient has been well controlled (e.g. attack free) for 6 months or more while receiving Takhzyro the patient will be receiving 300 mg every four weeks, or a medical reason has been provided why continued therapy with 300 mg every two weeks is necessary **Renewal Criteria:** **For acute treatment:** • Documentation was submitted that the patient has clinically benefited from medication • The medication is being prescribed at FDA approved dose. • The patient is receiving no other medications for acute treatment **For prophylaxis:** • Documentation was submitted that the patient has clinically benefited from prophylactic therapy as demonstrated by a reduced number of attacks • The medication is being prescribed at an FDA approved dose • The patient is receiving no other medications for prophylaxis • If the request is for Takhzyro and the patient has been well controlled (e.g. attack free) for 6 months or more while receiving Takhzyro the patient will be receiving 300 mg every four weeks, or a medical reason has been provided why continued therapy with 300 mg every two weeks is necessary
	Treatments for hereditary angioedema are reserved for members with a diagnosis of hereditary angioedema (HAE) who are not using ACE inhibitors or estrogen containing oral contraceptives or hormone replacement therapy. If a non-preferred agent is requested for acute treatment, the patient is receiving only one medication for the treatment of acute attacks, and has used (or cannot/should not use) a preferred agent. If a non-preferred agent is requested for long-term prophylaxis, the patient is receiving only one medication for prophylaxis treatment, the member has a history of at least one attack and has used (or cannot/should not use) a preferred agent.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Lupkynis	
Therapeutic Classes (AHFS)	Immunosuppressive Agents
Medications	Formulary, PA required Lupkynis (voclosporin)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Patients must be 18 years age or older Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be rheumatologist, nephrologist or other specialist in the treatment of autoimmune disorders
Coverage Duration	**Initial Approval** If the criteria are met, the initial request may be approved for up to a 6-month duration. **Reauthorization** Reauthorization requests may be approved for 12 months. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization** • Member must have a diagnosis of lupus nephritis (LN) Class III, IV, or V • Documentation that the member has a baseline eGFR > 45 mL/min/1.73m^2 • Documentation of the member's urine protein/creatinine ratio (UPCR) is provided • Member is concurrently being treated with background immunosuppressive therapy, or has a medical reason for not using background immunosuppressive therapy • Member is NOT concurrently being treated with cyclophosphamide • Medication is prescribed at an FDA approved dose **Reauthorization** • Documentation of improvement in renal function (i.e. reduction in UPCR or no confirmed decrease from baseline eGFR ≥ 20%) • Medication is prescribed at an FDA approved dose
	Lupkynis is reserved for members with a diagnosis of lupus nephritis (LN) Class III, IV, or V and a baseline eGFR > 45 mL/min/1.73m^2, who have used (or cannot/should not use) background immunosuppressive therapy (and will continue using it), and is NOT currently using cyclophosphamide.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Radicava ORS (edaravone)	
Therapeutic Classes (AHFS)	Anticonvulsants, miscellaneous
Medications	Radicava ORS (edaravone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Initial:** • Member must have a diagnosis of ALS • Member must have a documented baseline evaluation of functionality using the revised ALS functional rating scale (ALSFRS-R) score ≥ 2 • Member's disease duration is 2 years or less • Member has a baseline forced vital capacity (FVC) of ≥ 80% • Member has been on riluzole (Rilutek), is beginning therapy as an adjunct to treatment with Radicava, or provider has provided a medical reason why patient is unable to use riluzole • Dose is within FDA approved limits **Reauthorization:** • Member is not ventilator-dependent • Provider documents clinical stabilization in symptoms (e.g. stabilization of ALSFRS-R score) • Dose is within FDA approved limits
Criteria Statement	Radicava ORS are reserved for members with a diagnosis of ALS, with a disease duration of 2 years or less, with a documented baseline evaluation of functionality using the revised ALS functional rating scale (ALSFRS-R) score ≥ 2 and a baseline forced vital capacity (FVC) of ≥ 80%, who is taking riluzole (Rilutek) or has used (or cannot/ should not use) riluzole (Rilutek).
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Daybue (trofinetide)	
Therapeutic Classes (AHFS)	CENTRAL NERVOUS SYSTEM AGENTS, MISC.
Medications	Daybue (trofinetide)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	According to package insert
Prescriber Restrictions	Prescribed by a neurologist
Coverage Duration	**Initial Approval** 3 months **Later Approvals** 6 months If criteria are not met, request will be sent to a clinical reviewer for medical necessity review.

PA Review Criteria	**Initial Authorization:**
	• Medication is prescribed at an FDA approved dose
	• Diagnosis of classic or typical Rett syndrome (RTT)
	• Documentation or attestation of mutation of the MECP2 gene
	• Documentation of patient weight
	• Documentation or provider attestation of all the following:
	  ○ RTT Clinical Severity Scale rating of 10–36
	  ○ Clinical Global Impression–Severity (CGI-S) score of ≥4
	  ○ Baseline Rett Syndrome Behavior Questionnaire (RSBQ) score
	
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response (i.e., decrease from baseline in RSBQ score, decrease in Clinical Global Impression–Improvement (CGI-I, etc.)
	• Medication is prescribed at an FDA approved dose

Criteria Statement	Daybue is reserved for members with a diagnosis of classic or typical Rett syndrome (RTT), with a mutation of the MECP2 gene, with documentation or provider attestation of all the following: RTT Clinical Severity Scale rating of 10–36, Clinical Global Impression–Severity (CGI-S) score of ≥4, and Baseline Rett Syndrome Behavior Questionnaire (RSBQ) score, with a documented patient weight.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Filspari	
Therapeutic Classes (AHFS)	OTHER MISCELLANEOUS THERAPEUTIC AGENTS
Medications	Filspari (sparsentan)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	• Pregnancy • Coadministration with renin-angiotensin-aldosterone system (RAAS) inhibitors, endothelin receptor antagonists, or aliskiren
Required Clinical Information	See "other criteria"
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be a nephrologist
Coverage Duration	**Initial Approval** 9 months **Later Approvals** 12 months If criteria are not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization:** • Medication is prescribed at an FDA approved dose • Diagnosis of primary immunoglobulin A nephropathy (IgAN) verified by biopsy • Total urine protein ≥1.0 g/day • eGFR ≥30 mL/min/1.73 m2 • Trial and failure with a maximized stable dose of ACE inhibitor or ARB **Re-Authorization:** • Documentation of positive clinical response as evidenced by a decrease in urine protein-to-creatinine ratio (UPCR) • Medication is prescribed at an FDA approved dose
Criteria Statement	Filspari is reserved for members with a diagnosis of primary immunoglobulin A nephropathy (IgAN) verified by biopsy, with a total urine protein ≥1.0 g/day and eGFR ≥30 mL/min/1.73 m2, who have used (or cannot/should not use) a maximized stable dose of angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) medication.
Last P&T Review Date	~~6/2024~~6/2024

Recommendation: No changes

Joenja	
Therapeutic Classes (AHFS)	IMMUNOMODULATORY AGENTS
Medications	Joenja (leniolisib)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Per prescribing information.
Prescriber Restrictions	Prescriber must be an immunologist, hematologist, medical geneticist, or other prescriber who specializes in the treatment of genetic or immunologic disorders.
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If criteria are not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization:** • Documentation of APDS/PASLI-associated PIK3CD/PIK3R1 mutation, confirmed by genetic testing. • Documentation of nodal and/or extranodal lymphoproliferation, history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver) • Prescriber attests that the member is not currently taking immunosuppressive medication • Prescriber attests that female patients have been advised of the potential risk to a fetus, will use effective contraception and have had a negative pregnancy test prior to initiation of treatment • Medication is being prescribed at an FDA approved dose **Reauthorization:** • Documentation has been submitted indicating member has experienced a clinical benefit from treatment (e.g., decreased lymph node size, increase in percentage of naïve B cells) • Prescriber attests that female patients will use effective contraception and have had a negative pregnancy test • Medication is being prescribed at an FDA approved dose
Criteria Statement	Joenja is reserved for members with a diagnosis activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS/PASLI-associated PIK3CD/PIK3R1 mutation) confirmed by genetic testing, with documentation of nodal and/or extranodal lymphoproliferation, history of repeated oto-sino-pulmonary infections and/or organ dysfunction (e.g., lung, liver), who is not currently taking immunosuppressive medication, and female patients have been advised of the potential risk to a fetus, will use effective contraception and have had a negative pregnancy test prior to initiation of treatment.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Skyclarys (omaveloxolone)	
Therapeutic Classes (AHFS)	OTHER MISCELLANEOUS THERAPEUTIC AGENTS
Medications	Skyclarys (omaveloxolone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See “other criteria”
Age Restrictions	Per prescribing information
Prescriber Restrictions	Prescriber must be a neurologist or specialist with expertise in treating patients with Friedreich’s Ataxia.
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization:** • Diagnosis of Friedreich’s Ataxia, confirmed via genetic testing (must submit documentation) • Modified Friedreich’s Ataxia Rating Scale (mFARS) score ≥20 and ≤80 • Medication is prescribed at an FDA approved dose **Re-Authorization:** • Documentation or provider attestation of positive clinical response to Skyclarys therapy (i.e. improvement in symptoms, slowing of disease progression, etc.) • Medication is prescribed at an FDA approved dose
Criteria Statement	Skyclarys is reserved for members with a diagnosis of Friedreich’s Ataxia, confirmed via genetic testing, and a modified Friedreich’s Ataxia Rating Scale (mFARS) score ≥20 and ≤80.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Vyjuvek	
Therapeutic Classes (AHFS)	GENE THERAPY
Medications	Vyjuvek (beremagene geperpavec-svdt)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	• Other forms of epidermolysis bullosa, such as epidermolysis bullosa simplex, junctional epidermolysis bullosa, kindler epidermolysis bullosa • Concurrent use of Vyjuvek and Filsuvez
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a dermatologist, geneticist, or specialist experienced in the treatment of dystrophic epidermolysis bullosa.
Coverage Duration	If the criteria are met, the initial request will be approved for up to a 3 month duration; reauthorization requests will be approved for up to 6 months.
PA Review Criteria	**Initial Authorization:** • Patient has a diagnosis of dystrophic epidermolysis bullosa, with confirmed mutation(s) in the COL7A1 gene via genetic testing. • Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected • Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated • Medication is prescribed at an FDA approved dose, and maximum weekly dispensable amount is not exceeded o Requests exceeding more than one vial per week will not be approved **Re-Authorization:** • Documentation or provider attestation of positive clinical response (i.e. improvement in wound appearance, wound closure, healing, etc.) • Documentation indicating need for continued treatment is needed (either to partially healed wounds or to other wound sites) • Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected • Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated • Medication is prescribed at an FDA approved dose, and maximum weekly dispensing amount is not exceeded. o Requests exceeding more than one vial per week will not be approved
Criteria Statement	Vyjuvek is reserved for members who have a diagnosis of dystrophic epidermolysis bullosa (DEB), with confirmed mutation(s) in the COL7A1 gene, with wound(s) that are clean with adequate granulation tissue, excellent vascularization, and do not appear infected, and with no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes, minor addition that the tube is for single use for clarity

Filsuvez	
Therapeutic Classes (AHFS)	Skin and Mucous Membrane Agents, Misc
Medications	Filsuvez (birch triterpenes)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	• Other forms of epidermolysis bullosa, such as epidermolysis bullosa simplex, kindler epidermolysis bullosa • Concurrent use of Filsuvez and Vyjuvek
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age Per prescribing information
Prescriber Restrictions	Prescriber must be a dermatologist, geneticist, or specialist experienced in the treatment of epidermolysis bullosa
Coverage Duration	**Initial Approval** 3 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer

PA Review Criteria	**Initial Authorization:**
	• Patient has a diagnosis of dystrophic or junctional epidermolysis bullosa, with genetic mutation(s) confirmed via genetic testing
	• Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected
	• Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated
	• Medication is prescribed at an FDA approved dose, and maximum dispensable amount is not exceeded
	  ○ Documentation of size of treatment area(s) and frequency of dressing changes is required. One single use tube of Filsuvez covers up to 250 cm^2 surface area. Requests exceeding use more than once daily will not be approved.
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response (i.e. improvement in wound appearance, wound closure, healing, etc.)
	• Documentation indicating need for continued treatment is needed (either to partially healed wounds or to other wound sites)
	• Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected
	• Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated
	• Medication is prescribed at an FDA approved dose, and maximum dispensable amount is not exceeded.
	  ○ Documentation of size of treatment area(s) and frequency of dressing changes is required. One single use tube of Filsuvez covers up to 250 cm^2 surface area. Requests exceeding use more than once daily will not be approved.

Criteria Statement	Filsuvez is reserved for members who have a diagnosis of dystrophic or junctional epidermolysis bullosa with wound(s) that do not appear infected, clean with adequate

	granulation tissue, excellent vascularization and no evidence of squamous cell carcinoma.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Wegovy	
Therapeutic Classes (AHFS)	Incretin Mimetics
Medications	Wegovy (semaglutide) injection ****Please Note: If the request is for Wegovy to reduce excess body weight and maintain weight reduction long term, refer to criteria for Anti-Obesity Medications*****
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	• Requests for Wegovy for a diagnosis of weight reduction and maintenance for overweight or obesity • Concurrent use of any glucagon-like-peptide-1 receptor agonist • Personal history of Type 1 or Type 2 diabetes • Personal or family history of medullary thyroid carcinoma • Multiple Endocrine Neoplasia syndrome type 2
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	Member must be ≥ 45 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review

PA Review Criteria	**Initial Authorization:**
	• Medication is prescribed for reducing the risk of adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with **established cardiovascular** disease. Documentation demonstrates patient has history of one or more of the following:
	  ○ Prior myocardial infarction
	  ○ Prior stroke
	  ○ Symptomatic peripheral arterial disease, as evidenced by ≥1 of the following:
	  ▪ Intermittent claudication with ankle brachial index <0.85 (at rest)
	  ▪ Peripheral arterial revascularization procedure
	  ▪ Amputation due to atherosclerotic disease
	• Documentation is provided that patient is overweight or obese, defined as a body mass index (BMI) ≥ 27 kg/m2
	• Patient is receiving standard of care treatment of CVD, as appropriate/indicated, including an antiplatelet agent (ex. aspirin or P2Y12 inhibitor), lipid-lowering drug (ex. statin, otherwise ezetimibe, fibrate, and/or PCSK-9 inhibitor), antihypertensive (ex. beta blocker, ACE-I, ARB)
	• Documentation is provided patient's Hb A1c ≤ 6.5%
	Re-Authorization:
	• Patient is receiving standard of care treatment of CVD, as appropriate/indicated, including an antiplatelet agent (ex. aspirin or P2Y12 inhibitor), lipid-lowering drug (ex. statin, otherwise ezetimibe, fibrate, and/or PCSK-9 inhibitor), antihypertensive (ex. beta blocker, ACE-I, ARB)
	• Patient continues to not have Type 1 or Type 2 diabetes

Criteria Statement	Wegovy is reserved for members who are overweight or obese, have an established cardiovascular disease, receive standard of care treatment for CVD, have Hb A1c ≤ 6.5% and do not have diabetes.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Rezdiffra	
Therapeutic Classes (AHFS)	Hepatotropics
Medications	Rezdiffra (resmetirom)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.

Exclusion Criteria	• Patients with decompensated cirrhosis
	• Patient with thyroid disease including:
	  ○ active hyperthyroidism
	  ○ untreated hypothyroidism (TSH >7 IU/L with symptoms of HT or >10 IU/L without symptoms

Required Clinical Information	See "PA Review Criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age According to package insert
Prescriber Restrictions	Prescriber must be a hepatologist, gastroenterologist, or a specialist in the treatment of liver disease
Coverage Duration	**Initial Approval** Up to a 12 month duration **Later Approvals** Up to a 12 month duration If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review
PA Review Criteria	**Initial Authorization:** • Diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis • Documentation of stage F2 to F3 fibrosis confirmed by biopsy or a noninvasive test (NIT) • Prescriber attestation to providing lifestyle counseling on nutrition and exercise • Prescriber attestation that member avoids excess alcohol intake • The drug is being prescribed at an FDA approved dose according to the member's weight **Re-Authorization:** • The member has clinically benefited from the medication (e.g. the resolution of steatohepatitis and no worsening of liver fibrosis, or at least one stage improvement in liver fibrosis and no worsening of steatohepatitis) • The member continues to have a fibrosis stage of ≤ 3 • The drug is being prescribed at an FDA approved dose according to the member's weight
Criteria Statement	Rezdiffra is reserved for members who have a diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis stage F2 to F3, who were provided lifestyle counseling on nutrition and exercise, and avoid excess alcohol intake.
Last P&T Review Date	~~6/2024~~6/2025

Alameda PADs for review Q2 2025 P&T Consent Agenda

Recommendation: No changes

SMN2 Splicing Modifiers for the Treatment of Spinal Muscular Atrophy (SMA)	
Medications	Spinraza (nusinersen) Evrysdi (risdiplam)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	Concomitant use of Evrysdi and Spinraza
Required Clinical Information	For Evrysdi: Patient's body weight
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	Neurologist
Coverage Duration	For Evrysdi: If all of the conditions are met, the request will be approved for 6 months for initial approval, followed by 12 months for reauthorization requests. For Spinraza: If all of the conditions are met, the request will be approved for 6 months for 5 doses (4 loading doses and 1st maintenance dose) for initial approval, and 12 months for 3 additional maintenance doses for reauthorization requests.
Maximum Billable Units	Variable
Other Criteria	**For Initial Approval:** • Member has confirmed diagnosis of spinal muscular atrophy (SMA) types I, II or III and the molecular genetic test with mutation analysis was submitted • For Spinraza: Documentation of genetic testing confirming either two or three copies of the SMN2 gene OR four copies of the SMN2 gene with symptomology of SMA • For Evrysdi: Documentation of genetic testing confirming two or three or four copies of the SMN2 gene • Baseline motor function or motor milestone achievement was submitted with request [e.g. CHOP Infant Test of Neuromuscular Disorders (CHOP-INTEND), or Hammersmith Functional Motor Scale Expanded Scores (HFMSE), or Hammersmith Infant Neurological Examination (HINE), or 6 minute walk test in subjects able to walk, or Upper Limb Module (ULM) score] • The request is for an FDA approved dose **Reauthorization:** • Documentation of a positive clinical response was submitted with request (e.g. improvement, maintenance, or reduction in decline of motor function/motor milestone achievement scores using CHOP-INTEND, HFMSE, 6 minute walk test, ULM score, or HINE) • The request is for an FDA approved dose If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~6/2024~~6/2025

Recommendation: No changes

Naglazyme	
Medications	Naglazyme (galsulfase)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	N/A
Coverage Duration	If the criteria are met, the initial request will be approved for up to a 6 month duration; reauthorization requests will be approved for up to 12 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of Mucopolysaccharidosis VI as confirmed by one of the following:
	  ○ Enzyme assay demonstrating a deficiency in N-acetygalactosamine 4-sulfatase (arylsulfatase B) enzyme activity
	  ○ DNA testing
	• Patient's weight
	• Dosing is consistent with FDA-approved labeling or is supported by compendia or standard of care guidelines
	
	Reauthorization
	• Documentation of clinical response was submitted with request (i.e., stabilization or improvement in 12-minute walk test [12-MWT], 3-minute stair climb test, urinary glycosaminoglycan (GAG) levels)
	• Patient's weight
	• Dosing is consistent with FDA-approved labeling or is supported by compendia or standard of care guidelines
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~6/2024~~6/2025

Recommendation: No changes

Leqembi	
Medications	Leqembi (lecanemab-irmb)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	Patients with moderate to severe Alzheimer's Disease (AD) Patients with neurodegenerative disease caused by a condition other than AD
Required Clinical Information	See "other criteria"
Age Restrictions	age 50-90 years
Prescriber Restrictions	Prescriber must be a neurologist
Coverage Duration	For initial authorization: the request will be approved for 6 months For reauthorization: if all of the conditions are met, the request will be approved for 6 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of mild cognitive impairment (MCI) caused by AD or mild AD consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ Clinical Dementia Rating Global (CDR-G) score of 0.5-1.0 and a Memory Box score of 0.5 or greater
	  ○ Mini-Mental State Examination (MMSE) score ≥ 22 and ≤ 30
	  ○ Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) score at least 1 standard deviation below age-adjusted mean
	• The request is for an FDA approved dose
	• Documentation of BOTH of the following:
	  ○ Recent, within past year, positive results for the presence of beta-amyloid plaques on a positron emission tomography (PET) scan or cerebrospinal fluid testing
	  ○ Recent, within past year, baseline Magnetic Resonance Imaging (MRI) scan
	• Physician has assessed baseline disease severity utilizing an objective measure/tool (i.e., Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog-14], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version [ADCS-ADL-MCI], Clinical Dementia Rating Sum of Boxes [CDR-SB], etc.)
	• No recent (past 1 year) history of stroke, seizures or transient ischemic attack (TIA), or findings on neuroimaging that indicate an increased risk for intracerebral hemorrhage.
	
	Reauthorization
	• The request is for an FDA approved dose
	• Patient continues to have a diagnosis of mild cognitive impairment (MCI) caused by AD or mild AD consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ CDR-G score of 0.5-1.0 and a Memory Box score of 0.5 or greater
	  ○ MMSE score of 22-30

	○ Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) score at least 1 standard deviation below age-adjusted mean • Provider attestation of safety monitoring and management of amyloid related imaging abnormalities (ARIA) and intracerebral hemorrhage, as recommended per the manufacturer's prescribing information. • Documentation that member has experienced clinical benefit from the medication (such as: stabilization or decreased rate of decline in symptoms from baseline on CDR-SB, ADAS-Cog14, or ADCS MCI-ADL scales) • No recent (past 1 year) history of stroke, seizures or TIA If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~6/2024~~6/2025

Recommendation: No changes

Radicava (edaravone)	
Medications	Radicava (edaravone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "Other Criteria" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist
Coverage Duration	If the criteria are met, requests will be approved for up to 6 month duration;
Maximum Billable Units	Variable
Other Criteria	**Initial:** • Member must have a diagnosis of ALS • Member must have a documented baseline evaluation of functionality using the revised ALS functional rating scale (ALSFRS-R) score ≥ 2 • Member's disease duration is 2 years or less • Member has a baseline forced vital capacity (FVC) of ≥ 80% • Member has been on riluzole (Rilutek), is beginning therapy as an adjunct to treatment with Radicava, or provider has provided a medical reason why patient is unable to use riluzole • Dose is within FDA approved limits **Reauthorization:** • Member is not ventilator-dependent • Provider documents clinical stabilization in symptoms (e.g. stabilization of ALSFRS-R score) • Dose is within FDA approved limits If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~6/2024~~6/2025

Recommendation: No changes

Vyjuvek	
Medications	Vyjuvek (beremagene geperpavec-svdt)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	• Other forms of epidermolysis bullosa, such as epidermolysis bullosa simplex, junctional epidermolysis bullosa, kindler epidermolysis bullosa • Concurrent use of Vyjuvek and Filsuvez
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a dermatologist, geneticist, or specialist experienced in the treatment of dystrophic epidermolysis bullosa.
Coverage Duration	If the criteria are met, the initial request will be approved for up to a 3 month duration; reauthorization requests will be approved for up to 6 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Patient has a diagnosis of dystrophic epidermolysis bullosa, with confirmed mutation(s) in the COL7A1 gene via genetic testing.
	• Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected
	• Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated
	• Medication is prescribed at an FDA approved dose, and maximum weekly dispensable amount is not exceeded
	  ○ Requests exceeding more than one vial per week will not be approved
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response (i.e. improvement in wound appearance, wound closure, healing, etc.)
	• Documentation indicating need for continued treatment is needed (either to partially healed wounds or to other wound sites)
	• Documentation is provided that wound(s) to be treated are clean with adequate granulation tissue, excellent vascularization, and do not appear infected
	• Documentation is provided that there is no evidence of, or history of squamous cell carcinoma in the wound(s) to be treated
	• Medication is prescribed at an FDA approved dose, and maximum weekly dispensing amount is not exceeded
	  ○ Requests exceeding more than one vial per week will not be approved
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~6/2024~~6/2025

Recommendation: No changes

Generalized Pustular Psoriasis (GPP) Agents	
Medications	Spevigo (spesolimab-abzo)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a dermatologist or geneticist
Coverage Duration	Acute Flares (IV vial): If all of the criteria are met, the request will be approved for up to 2 doses. Maintenance Treatment (SQ syringe): If all criteria are met, the initial request will be approved for 12 months. Reauthorization requests will be approved for 12 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of generalized pustular psoriasis (GPP)
	• If request is for an acute GPP flare (IV vial), member must be experiencing an acute flare of GPP of moderate to severe intensity as defined by having all of the following:
	  ○ Generalized Pustular Psoriasis Physician Global Assessment (GPPPGA) total score of 3 or greater
	  ○ Presence of fresh pustules (new appearance or worsening of pustules)
	  ○ GPPPGA pustulation sub score of 2 or greater
	  ○ At least 5% of body surface area covered with erythema and the presence of pustules
	• If request is for maintenance treatment of GPP (SQ syringe), member must have all of the following:
	  ○ History of at least two GPP flares in the past year of moderate to severe intensity
	  ○ GPPPGA score of 0 or 1
	  ○ Documented trial and failure, intolerance, or contraindication to TWO of the following: oral retinoids, methotrexate, and cyclosporine
	• Medication is prescribed at an FDA approved dose
	
	Reauthorization
	• If request is for an acute GPP flare (IV vial), member must have achieved a clinical response, defined as achieving a GPPPGA score of 0 or 1, to previous treatment and is now experiencing a new flare
	• If request is for maintenance treatment of GPP (SQ syringe), member must have documentation of positive clinical response to therapy (i.e., reduction in GPP flares)
	• Medication is prescribed at an FDA approved dose
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Amtagvi	
Medications	Amtagvi (lifileucel)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	• Uncontrolled brain metastases • Melanoma of uveal or ocular origin • Systemic steroid therapy for any reason
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be an oncologist
Coverage Duration	If all of the criteria are met, the initial request will be approved for a one-time treatment
Other Criteria	**Initial Authorization:** • Diagnosis of unresectable or metastatic melanoma (Stage IIIc or Stage IV) • Member must have progressed through at least one prior systemic therapy including a PD-1/PD-L1 blocking antibody and, if BRAF V600 mutation–positive, a BRAF inhibitor or BRAF inhibitor in combination with a MEK inhibitor • Member must have at least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection • Eastern Cooperative Oncology Group (ECOG) score of 0 or 1 • Medication is prescribed at an FDA approved dose **The safety and effectiveness of repeat administration of Amtagvi has not been evaluated and will not be approved** If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: No changes

Lenmeldy	
Medications	Lenmeldy (atidarsagene autotemcel)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines
Exclusion Criteria	N/A
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age According to package insert
Prescriber Restrictions	Prescribed by a neurologist or geneticist
Coverage Duration	If all of the criteria are met, the initial request will be approved for a one-time treatment

Other Criteria	**Initial Authorization:**
	• Member has diagnosis of one of the following metachromatic leukodystrophies (MLD):
	  ○ Pre-symptomatic late infantile (PSLI) MLD
	  ○ Pre-symptomatic early juvenile (PSEJ) MLD
	  ○ Early symptomatic early juvenile (ESEJ) MLD
	• Documentation patient has both of the following:
	  ○ Arylsulfatase A (ARSA) activity below the normal range (normal range 31-198 nmol/mg/h)
	  ○ Identification of two disease-causing ARSA alleles
	• Medication is prescribed at an FDA approved dose
	
	The safety and effectiveness of repeat administration of Lenmeldy has not been evaluated and will not be approved
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last P&T Review Date	~~6/2024~~6/2025

Alameda Alliance for Health (IHSS)

Q2 2025 INTERIM FORMULARY UPDATES

These changes have been made to the Alliance's formulary recently. The changes were necessary to enhance the formulary.

Medication	Formulary Change
Topiramate Oral Capsule Sprinkle 50 MG	NF to F-PA
Simlandi (2 Syringe) Subcutaneous Prefilled Syringe Kit 20 MG/0.2ML	NF to F-QL (maintenance: 4 syringes per 28 days; loading dose: should use 40mg strength for loading
Simlandi (1 Syringe) Subcutaneous Prefilled Syringe Kit 80 MG/0.8ML	NF to F-QL (maintenance: 2 syringes per 28 days; loading dose: 4 syringes)
Liraglutide Subcutaneous Solution Pen-injector 18 MG/3ML	NF to F-PA
Victoza Subcutaneous Solution Pen-injector 18 MG/3ML	F-PA to NF
Rybelsus Oral Tablet 4 MG	NF to F-ST-QL (ST: requires trial and failure of a metformin containing product; QL:30 tablets/30 days)
Rybelsus Oral Tablet 9 MG	NF to F-ST-QL (ST: requires trial and failure of a metformin containing product; QL:30 tablets/30 days)
Rybelsus Oral Tablet 1.5 MG	NF to F-ST-QL (ST: requires trial and failure of a metformin containing product; QL:30 tablets/30 days)
Simlandi (1 Pen) Subcutaneous Auto-injector Kit 80 MG/0.8ML	NF to F-QL (maintenance: 2 pens per 28 days; loading dose: 4 pens)
Purified Cortrophin Gel Subcutaneous Prefilled Syringe 80 UNIT/ML	NF to F-PA
Purified Cortrophin Gel Subcutaneous Prefilled Syringe 40 UNIT/0.5ML	NF to F-PA
Ferric Citrate Oral Tablet 1 GM 210 MG(Fe)	NF to F-PA
Auryxia Oral Tablet 1 GM 210 MG(Fe)	F-PA to NF
Sunlenca Oral Tablet 300 MG	NF to F
Paxlovid Oral Tablet Therapy Pack 6 x 150 MG & 5 x 100MG	NF to F-QL-AL (QL: 11 tabs/180 days, AL: 12 years and older)
Ticagrelor Oral Tablet 90 MG	NF to F-PA
Brilinta Oral Tablet 90 MG	F-PA to NF
Amnesteem Oral Capsule 30 MG	NF to F-PA
Adalimumab-aaty CD/UC/HS Start Subcutaneous auto-injector kit 80 mg/0.8ml	NF to F-QL (loading dose: 4 pens)

Alameda Alliance for Health Q2 2025 PAD Updates

These changes have been made to the Alliance Physician Administered Drug (PAD) recently.
This list includes summary of changes and is not comprehensive.

HCPCS Code	HCPCS Description	Action
J0139	ADALIMUMAB	Add PA Requirement
J0177	AFLIBERCEPT HD	Add PA Requirement
J0725	CHORIONIC GONADOTROPIN	Add PA Requirement
J1299	ECULIZUMAB	Add PA Requirement
J1326	ZOLBETUXIMAB-CLZB (VYLOY)	Add PA Requirement
J2351	OCRELIZUMAB, 1 MG AND HYALURONIDASE-OCSQ	Add PA Requirement
J3391	ATIDARSAGENE AUTOTEMCEL (LENMELDY)	Add PA Requirement
J7172	MARSTACIMAB-HNCQ (HYMPAVZI)	Add PA Requirement
J9024	ATEZOLIZUMAB, 5 MG AND HYALURONIDASE-TQJS (TECENTRIQ HYBREZA)	Add PA Requirement
J9037	BELANTAMAB MAFODOTIN-BLMF (BLENREP)	Add PA Requirement
J9038	NIKTIMVO (AXATILIMAB-CSFR)	Add PA Requirement
J9054	BORTEZOMIB (BORUZU)	Add PA Requirement
J9161	DENILEUKIN DIFTITOX-CXDL	Add PA Requirement
J9174	DOCETAXEL (BEIZRAY)	Add PA Requirement
J9275	COSIBELIMAB-IPDL (UNLOXCYT)	Add PA Requirement
J9276	ZANIDATAMAB-HRII (ZIIHERA)	Add PA Requirement
J9289	NIVOLUMAB, 2 MG AND HYALURONIDASENVHY (OPDIVO QVANTIG)	Add PA Requirement
J9341	THIOTEPA (TEPYLUTE)	Add PA Requirement
J9342	THIOTEPA, NOT OTHERWISE SPECIFIED	Add PA Requirement
J9382	ZENOCUTUZUMAB-ZBCO	Add PA Requirement
Q2058	OBECABTAGENE AUTOLEUCEL (AUCATZYL)	Add PA Requirement
Q5098	USTEKINUMAB-SRLF (IMULDOSA)	Add PA Requirement
Q5099	USTEKINUMAB-STBA (STEQEYMA)	Add PA Requirement
Q5100	USTEKINUMAB-KFCE (YESINTEK)	Add PA Requirement
Q5139	ECULIZUMAB-AEEB (BKEMV)	Add PA Requirement
Q5140	ADALIMUMAB-FKJP (HULIO)	Add PA Requirement
Q5141	ADALIMUMAB-AATY (YUFLYMA)	Add PA Requirement
Q5142	ADALIMUMAB-RYVK (SIMLANDI)	Add PA Requirement
Q5143	ADALIMUMAB-ADBM (CYLTEZO)	Add PA Requirement
Q5144	ADALIMUMAB-AACF (IDACIO)	Add PA Requirement
Q5145	ADALIMUMAB-AFZB (ABRILADA)	Add PA Requirement
Q5146	TRASTUZUMAB-STRF (HERCESSI)	Add PA Requirement
Q5147	AFLIBERCEPT-AYYH (PAVBLU)	Add PA Requirement
Q5148	FILGRASTIM-TXID (NYPOZI)	Add PA Requirement
Q5149	AFLIBERCEPT-ABZV (ENZEEVU)	Add PA Requirement

Q5150	AFLIBERCEPT-MRBB (AHZANTIVE)	Add PA Requirement
Q5151	ECULIZUMAB-AAGH (EPYSQLI)	Add PA Requirement
Q5152	ECULIZUMAB-AEEB (BKEMV)	Add PA Requirement
Q5153	AFLIBERCEPT-YSZY (OPUVIZ)	Add PA Requirement
Q9996	USTEKINUMAB-TTWE (PYZCHIVA), SUBCUTANEOUS,	Add PA Requirement
Q9997	USTEKINUMAB-TTWE (PYZCHIVA), INTRAVENOUS	Add PA Requirement
Q9998	USTEKINUMAB-AEKN (SELARSDI)	Add PA Requirement
Q9999	USTEKINUMAB-AAUZ (OTULFI)	Add PA Requirement
S0122	MENOTROPINS	Add PA Requirement
S0126	FOLLITROPIN ALFA	Add PA Requirement
S0128	FOLLITROPIN BETA	Add PA Requirement
S0132	GANIRELIX ACETATE	Add PA Requirement
J1300	ECULIZUMAB (SOLIRIS)	Remove from PA

ALAMEDA Alliance FOR HEALTH
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POLICY AND PROCEDURE

Policy Number	RX-001
Policy Name	Pharmaceutical Operating Processes Summary
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	IHSS
Effective Date	04/01/2021
Subcommittee Approval Date	6/17/2025
Administrative Oversight Committee Approval Date	TBD~~5/21/2025~~

POLICY STATEMENT

The purpose of this document is to outline the procedure for the structure, operation, functions, and scope of the Alameda Alliance for Health (the "Alliance") Pharmacy Department Operations.

PROCEDURE

To help assure continuing patient access to a quality-driven, cost-effective, rational, drug benefit through the Alliance Drug Formulary, the Alliance Pharmacy Department will complete the following activities and adhere to the following operating procedures. The elements of the pharmacy program (as specified below) will be reviewed and approved annually by the Pharmacy and Therapeutics (P&T) committee meeting.

I. Pharmacy and Therapeutics (P&T) Committee

A committee shall exist within the Alliance that will function as the policy-making body for all matters related to the therapeutic use of drugs and certain medical supplies. The P&T Committee is a subcommittee of the Alliance Board of Governors.

Details of P&T Committee operations and scope can be found in *RX 005 P&T Committee Roles and Scope.*

II. Formulary Management

The Alliance has an established process for maintaining, reviewing, and updating its drug formulary. The Alliance is committed to ensuring that all eligible Alliance members have access to high quality and cost-effective pharmaceutical care. The Alliance's formulary management process complies with the standards set by the Health & Safety Code, Sections

1367.20, 1367.21, 1367.24, 1367.25, and 1367.215.

Formulary management decisions are made by the P&T Committee and are based upon documented medical evidence. The formulary is updated and reviewed at least quarterly. Details of formulary management operations can be found in *RX-004 Formulary Management.*

III. Prior Authorization Process

The Alliance is committed to ensuring that all eligible Alliance members have timely access to covered pharmaceutical services that require authorization. The Alliance has an established process for reviewing and determining medical necessity of Prior Authorization (PA) requests. The Alliance's pharmaceutical authorization process complies with the standards set by the Health & Safety Code, Sections 1367.01, and CCR, Title 28, Section 1300.67.241, and the Welfare & Institutions Code, Section 14185. Prior authorization is not required for the provision of an emergency three (3) day supply of drugs. The Alliance considers the Prior Authorization process described in *RX-002 Prior Authorization Review Process* to be inclusive of all elements of the request process as defined by the National Committee for Quality Assurance (NCQA).

A request for a drug is only considered to be a PA request when there is an existing PA guideline (also known as criteria) for review. If a guideline does not exist, then it is treated as an exception request (see section IV below).

Providers are informed of the Alliance's prior authorization process for pharmaceutical services via the Alliance's Provider Manual, which can be found on the Alliance's website. Members are informed of the Alliance's prior authorization process for pharmaceutical services via the Alliance's Evidence of Coverage documents. The Alliance supplies all providers with the Medication Prior Authorization (PA) form and instructions for its use on the Alliance's website.

IV. Exception Process

The Alliance has an established process for reviewing and processing exception requests for pharmaceutical services that are not covered on the formulary and for which there exists no review guidelines, step therapy, or quantity limits. The Alliance is committed to ensuring that all eligible Alliance members have timely access to covered pharmaceutical services that require an exceptions review. The Alliance's pharmaceutical authorization process complies with the standards set by the Health & Safety Code, Sections 1367.01, and CCR, Title 28, Section 1300.67.241, and the Welfare & Institutions Code, Section 14185. Exceptions review is not required for the provision of an emergency three (3) day supply of drugs. The Alliance considers the Exception process described in *RX-003 Exception Review Process* to be inclusive of all elements of the NCQA-defined exceptions request process.

V. Generic Substitution

The Alliance requires that the generic version of a drug must be dispensed unless a medical reason prohibits the use of the generic version. If no generic drug exists, or if the

prescribing provider has provided medical documentation that no substitution should be made, a brand name drug may be dispensed**.** If a member needs a brand medication when the generic is available, the provider must submit a PA on the member's behalf for review. The PA must specify why the member would medically benefit from the branded version and cannot tolerate the generic version.

VI. Therapeutic Interchange

The Alliance promotes the use of the most cost-effective drug among all therapeutically comparable drugs within a particular therapeutic class. For covered drug classes, the most cost-effective drug(s) within that drug class is often selected as the drug of choice (upon approval from the P&T committee). When applicable, the PA guidelines may also steer the reviewer to recommend the most cost-effective drug within the requested drug class. Occasionally, the Alliance performs targeted provider outreach to switch patients from a less cost-effective drug to a more cost-effective one within the same class. If a member cannot use the most cost-effective drug within a class, the provider can submit a PA on the member's behalf for review. The PA must specify why the member would medically benefit from the less cost-effective drug and cannot use the most cost-effective drug.

VII. Step Therapy

The Alliance utilizes a step therapy program for certain medical conditions in which the most cost-effective and/or safest drug therapy has to be used first before other costly or risky drugs can be approved. The claims adjudication system of the contracted pharmacy benefit manager (PBM) scans for paid claims for the preferred drug before allowing the more costly or risky drug to pay at the time of claim submission. The history of paid claims would indicate that the member has a therapeutic failure to the preferred drug. In instances where there is no claims history for the claims adjudication system to review, the provider can submit an Exceptions Request on the member's behalf for review. The Exceptions Request must specify why the member would medically benefit from the more costly or risky therapy or why they cannot use the preferred therapy. These types of exceptions will be made following the procedures outlined in the policy and procedure document *RX-003 Exception Review Process* and found in the online Provider Manual Section 16 *Formulary and Pharmacy Services.*

VIII. Limits and Quotas

Certain drugs may be recommended to be limited to a determined number of doses (e.g., quantity limit) based on criteria including but not limited to: safety, potential overdose hazard, abuse potential, or approximation of usual doses per month. The P&T Committee will review all decisions regarding limits and quotas. If a member needs a medication beyond the specified quantity limit or quota, the provider can submit an Exceptions Request on the member's behalf for review. The Exceptions Request must specify why the member would medically benefit from a higher dose or treatment duration. These types of exceptions will be made following the procedures outlined in the policy and procedure document *RX-003 Exception Review Process* and found in the online Provider Manual Section 16 *Formulary and Pharmacy Services*. Prescription drug exclusions are also listed in RX-004 and in the Group Care Evidence of Coverage (EOC).

Practitioners and members are educated and notified about limits and quotas and the exception request process through the practitioner and member notification mechanisms described in Sections IX and X below.

IX. Practitioner Notification of Pharmaceutical Management Procedures

Practitioners are notified of pharmaceutical management procedures and changes to lists and procedures through a number of mechanisms including the provider newsletter, fax bulletins, and the provider manual, which is provided to each practitioner both in writing and on the website. The information includes how to request authorizations or exceptions. The above information will be provided annually, at minimum, and after each modification.

X. Member Notification of Pharmaceutical Management Procedures

Members are notified at least once quarterly through member bulletins of the formulary rules and any formulary changes. In addition, the member bulletin will provide a link to the member section of the Alliance web site for detailed information on the formulary changes.

Information on practitioner and member notification is outlined in *RX-004 Formulary Management.*

XI. Override at the point of service

1. Contracted pharmacy staff can call the PBM's Provider Call Center to request an override for refill-too-soon rejections in certain situations.
   a. Pharmacy will call the PBM's provider call center for these overrides.
   b. PBM call center staff is allowed to enter the override according to the timeline set below:
      ~~**i. Lost:** One (1) incident allowed per rolling 12 months (30-day supply only).~~
      ~~**ii. Spilled:** One (1) incident allowed per rolling 12 months (30-day supply only).~~
      ~~**iii. Stolen:** One (1) incident allowed per rolling 12 months (30-day supply only).~~
      ~~**iv.**~~**i. Vacation:** One (1) incident allowed per rolling 12 months (up to 90-day supply only).
   c. Additional requests require a PA and the plan review (Outlined in *RX-003 Exception Review Process*)

XII. Member Eligibility

1. If a prescription claim is rejected at point-of-sale (POS) for "MEMBER WAS NOT ELIGIBLE ON DATE FILLED", the Alliance Member Services Department will verify member eligibility with the following steps before calling the Pharmacy Services department:
   a. Darwin: Point-of-sale system used to verify claims history
   b. HealthSuite: Customer relation module where member demographics are stored, claims are processed, and calls are documented.
      i. If current eligibility is found, the Member Services Department will contact Pharmacy Services to update eligibility in RXNova. If Pharmacy Services is not available, please contact the Alliance IT Enrollment department to update eligibility.
      ii. If current eligibility is NOT found, the Alliance pharmacy personnel will forward case to Business Operation for eligibility update.

XIII. Regulatory Reporting

The Alliance will send required reports to regulatory agencies, including but not limited to the Department of Managed Health Care (DMHC) and the Centers for Medicare and Medicaid Services (CMS).

DEFINITIONS / ACRONYMS

Pharmacy and Therapeutics Committee (P&T) - The policy-making body for all matters related to the therapeutic use of drugs and certain medical supplies.

Department of Managed Health Care (DMHC) – State regulatory body governing health care plans.

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Department
Pharmacy Benefit Manager (Currently – *PerformRx*)
Member Services
Business Operation

RELATED POLICIES AND PROCEDURES

P&T Charter

RX-002 Prior Authorization Review Process
RX-003 Exception Review Process
RX-004 Formulary Management
RX-005 P&T Committee Roles and Scope

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

4/1/2018, 3/25/2018, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 3/28/2023, 4/10/2024, 5/21/2025, 6/17/2025

REFERENCES

- NCQA UM 12, Element B
- Alliance Provider Manual
- Health & Safety Code, Sections 1367.01
- CCR, Title 28, Section 1300.67.241
- Welfare & Institutions Code, Section 14185
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-Cal Rx
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx

MONITORING

This policy will be reviewed annually to ensure effectiveness.

POLICY AND PROCEDURE

Policy Number	RX-003
Policy Name	Exception Review Process
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	IHSS
Effective Date	6/16/2020
Subcommittee Approval Date	6/17/2025
Administrative Oversight Committee Approval Date	TBD~~5/21/2025~~

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance") has an established process for reviewing and processing medical necessity-based authorization requests for pharmaceutical services that are not on the formulary. The Alliance is committed to ensuring that all eligible Alliance members have timely and efficient access to covered pharmaceutical services that require authorization. The Alliance's pharmaceutical authorization process complies with the standards set by the California Health & Safety Code, Sections 1367.01; the California Code of Regulations (CCR) Title 28, Section 1300.67.241; and the California Welfare & Institutions Code, Section 14185. Prior authorization is not required for the provision of an emergency three (3) day supply of drugs (see RX-009, Pharmaceutical Emergency Supply Provision).

This policy and the associated procedures also pertain to the review process for exceptions to pharmaceutical management procedures, such as Step Therapy, Quantity Limits and Age Limits.

PROCEDURE

I. Exception Process Guidelines

A. Members and their providers are expected to follow pharmaceutical management procedures set forth by the Alliance. However, in some cases a member or provider may opt to seek an exception based on medical necessity. Examples of exception requests include (but are not limited to):

1. A request for coverage of a non-formulary item with no existing Medication

Review Guidelines (MRG)

2. A request to bypass an implemented formulary management program, such as step therapy
3. A request to authorize a greater supply than standard quantity limits
4. Any request outside the existing pharmaceutical management procedure and authorization process

B. The Alliance's exception process instructions are available to practitioners and providers through the Alliance's Provider Manual, provider newsletters and on the Alliance's website. Likewise, it is available to members through the Alliance's Evidence of Coverage documents, member newsletters, and on the Alliance's web site. The Alliance mails newsletters to members and providers annually, at minimum. Provider manuals are sent to providers when they join the Alliance and upon request thereafter. Evidence of Coverage documents are sent to members when they join the Alliance, and upon request thereafter. Any change to the exception process will be communicated to providers through mail, e-mail, or fax.

C. The review is based on medical necessity. Specific attention is given to the medical necessity for the situation and whether there is sufficient reason to create an exception to the established procedures.

II. Exception Review Requirements and Process

A. An exception request may originate from a member or a provider. When requested by the member, an Alliance member services representative will contact the provider to initiate the request. Also, the Alliance pharmacy staff may advise a provider to redirect a Prior Authorization request to an exception request if the request falls outside the standard Prior Authorization rules.

B. Providers are responsible for submitting all required information for medical necessity review. A Pharmacy Technician reviews the requests to determine whether all required information has been provided. The Pharmacy Technician pends the request to obtain missing information from the requestor (via phone or fax). The following information may be requested from the pharmacy, provider, member, or family member can include but are not limited to:

1. Reason for the exception request
2. Other medications tried and/or failed
3. Other pertinent history
4. Office and hospital records
5. Drug allergies, resistance, or reactions
6. Ability to reliably self-administer the medication
7. Other medications the member is taking
8. A history of present illness, with treatment plans and progress notes
9. A clinical exam
10. Diagnostic testing results
11. Patient psychosocial history
12. Evaluations from other health care providers and providers
13. Photographs
14. Operative and pathological reports
15. Information regarding benefits for services or procedures
16. Information regarding the local delivery system
17. Patient characteristics and information

C. Types of Exception Requests – All Exception requests must be reviewed by an appropriate healthcare professional and decisions shall be made based on the available clinical evidence in the medical literature as well as any patient-specific factors. Types of Exceptions include (but are not limited to):

1. Quantity Limit (QL) Override

a) Quantity limits are established through the P&T Committee and are a part of the Medication Request Guidelines for that drug/class.

b) Providers must provide documentation for why the quantity limit is insufficient for the member and why formulary alternatives or alternate doses cannot be used. Potential QL override requests may involve:

i. Split dosing for tolerability

ii. One-time dose titration

iii. Requirement of a higher dose for efficacy (must be supported by clinical evidence)

2. Step Therapy (ST) Override

a) Step Therapy protocols are established through the P&T Committee and are a part of the Medication Request Guidelines for that drug/class.

b) Providers must submit necessary justification and supporting clinical documentation(through clinic notes documenting previous medication trials including dose/duration/time frame and/or pharmacy fill history) supporting the provider's determination that the required prescription drug is inconsistent with good professional practice for provision of medically necessary covered services to the member, taking into consideration the member's needs and medical history, along with the professional judgment of the member's provider. The basis of the provider's determination may include, but is not limited to, any of the following criteria:

i. The required prescription drug is contraindicated or is likely, or expected, to cause an adverse reaction or physical or mental harm to the member in comparison to the requested prescription drug, based on the known clinical characteristics of the member and the known characteristics and history of the member's prescription drug regimen.

ii. The required prescription drug is expected to be ineffective based on the known clinical characteristics of the member and the known characteristics and history of the member's prescription drug regimen.

iii. The member has tried the required prescription drug while covered by their current or previous health coverage or Medicaid, and that prescription drug was discontinued due to lack of efficacy or effectiveness, diminished effect, or an adverse reaction. The health care service plan may require the submission of documentation demonstrating that the member tried the required prescription drug before it was discontinued.

iv. The required prescription drug is not clinically appropriate for the member because the required drug is expected to do any of the following, as determined by the member's prescribing provider:

(1) Worsen a comorbid condition.

(2) Decrease the capacity to maintain a reasonable

functional ability in performing daily activities.

(3) Pose a significant barrier to adherence to, or compliance with, the member's drug regimen or plan of care.

v. The member is stable on a prescription drug selected by the member's prescribing provider for the medical condition under consideration while covered by their current or previous health coverage or Medicaid.

(1) For non-transitioning members who are already established with Alliance, the Alliance does not consider use of medication samples provided through a physician office as a valid reason for approval/continuation of that medication, or as an acceptable step therapy to another medication.

(2) For non-transitioning members who are already established with Alliance, the Alliance shall allow provider attestation for OTC products that the member has been taking.

(3) For transitioning members until the Beneficiary can be seen by a Plan provider to establish a care plan, as required by Welfare & Institutions (W&I) Code, Section 14185(b), the Alliance will allow for continuation of single-source medications, including medication samples, if provided clinic notes showing all the following:

(a) Patient name

(b) Medication name, dose, and route of administration

(c) Quantity distributed

(d) Date medication was started and date last given/filled

c) The Alliance provides coverage for prescription drugs may require step therapy if there is more than one drug that is clinically appropriate for the treatment of a medical condition.

3. Age Limit (AL) Override

a) Age Limits are established through the P&T Committee and are a part of the Medication Request Guidelines for that drug/class.

b) For override of Age Limits, the provider must submit clinic notes, any relevant labs, and supporting clinical evidence (e.g., national guidelines, primary literature) that the drug being requested is safe and effective for the patient and why formulary alternatives cannot or should not be used.

4. Fill Limit (FL) Override

a) Fill limits (a maximum number of fills over a certain period of time) are established through the P&T Committee and are a part of the Medication Request Guidelines for that drug/class.

b) For override of Fill Limits, the provider must submit documentation for why the member requires additional medication beyond the limit in place, why formulary alternatives cannot or should not be used in the patient, and any relevant labs results and/or other clinical references, national guidelines, or primary literature to support continued use of the

drug requested.

5. **Maximum Dose Exceeded Override**
   a) Maximum doses are set by the prescribing information/package insert for the medication upon FDA approval or by national guidelines for the condition being treated.
   b) For use of doses beyond the maximum labeled dose, the provider must submit any relevant labs results, clinical references, national guidelines, and/or primary literature to support the use of a dose beyond the standard dose and justification for why a formulary alternative cannot be used in place of a higher dose of the requested medication.
6. **Dose Consolidation Override**
   a) Quantity limits are established through the P&T Committee and are a part of the Medication Request Guidelines for that drug/class.
   b) For approval of a doubling (or higher) of the number of tablets/capsules per prescription for a medication that has a higher strength tablet/capsule available, justification must be submitted for why that higher dose tablet/capsule cannot be used.
7. Partial Fill
   a) The Alliance has availability of prescription partial fills of approved medically necessary medications.

~~8. **Lost/Stolen Medication Override**~~
   ~~a) Requests for non-controlled medications can be approved by Alliance pharmacy technicians upon request by the member, pharmacy, or provider.~~
   ~~b) For Lost/Stolen controlled medications, the member or provider must submit a police report to the plan that documents which medications were taken and the date the event occurred.~~
   ~~c) For more than one loss of controlled medications per 365 days, future approvals will be authorized only in consultation with the prescriber and your pharmacy.~~

~~9.~~8. **Refill-Too-Soon Override**
   a) Refill-Too-Soon overrides will be handled on a case-by-case basis and by the medical necessity of the situation.
   b) Lost/Stolen medication and vacation overrides will be handled by the corresponding exception policies.

~~10.~~9. **Vacation Override**
   a) Vacation Overrides for up to 3 months (90 days) for travel outside California can be approved by the PBM or by the Alliance pharmacy technicians upon request by the member, pharmacy, or provider when documentation of the departure date, destination, and return date are provided for the following:
      i. Non-specialty medications
      ii. Non-single-source medications, and/or
      iii. Non-controlled medications
   b) One vacation override per drug per 365 days can be approved by the PBM and by the Alliance Pharmacy Technicians for medications described in section (C) 10a.
   c) For ANY of the following scenarios, providers must submit a standard

PA request for review by an Alliance clinical pharmacist with all required information described in section (C) 10a and medical necessity.

i. Vacation overrides over 90 days outside California or over 30 days within California
ii. More than one vacation override per drug per 365 days
iii. Request for specialty, single-source, and/or controlled medications

~~11.~~10. Member Reimbursements

a) The Alliance will allow member reimbursement of pharmaceutical drugs when required documents are received and appropriate criteria exclusions do not apply. G&A will submit the following required documents to distgrpPharmacy@alamedaalliance.org email:
   i. Member ID Number
   ii. Case Number
   iii. AAH member reimbursement form
   iv. Pharmacy receipt or Pharmacy report print out (must include price paid out of pocket, date, and Rx number)
   v. Pharmacy Leaflet (this includes medication details and member details as well as Rx number).

b) Reimbursements are not valid and will not be approved when the following criteria exclusions apply:
   i. If the request is made before the 180 days accepted time frame per EOC requirement.
   ii. If the drug was not covered and required a Prior Authorization and Perform PA does not show any active approval for the date paid out of pocket.
   iii. If the required documents are not submitted (Note: re-review can be considered once all documents are received).
   iv. If the request is made for pharmaceutical services received outside of the United States.

c) The Alliance Pharmacy Services Technician(s) will review each request to ensure that the required documents are available and criteria exclusions do not apply.

d) Approved requests will be sent to Perform Rx for final review and appropriate reimbursement determination (e.g., check reimbursement mail-out dates, member eligibility and formulary product availability) that will take 7 – 10 business days.

~~12.~~11. Continuation of Therapy Override

a) The Alliance shall allow continuation of therapy for members using medically necessary drugs when it can be shown through clinic notes/provider attestation for OTC products or prescription fill history that the member has been taking the medication prior to enrollment.

b) For non-transitioning members who are already established with Alliance, the Alliance does not consider use of medication samples provided through a physician office as a valid reason for approval/continuation of that medication, or as an acceptable step therapy to another medication.
c) For non-transitioning members who are already established with Alliance, the Alliance shall allow provider attestation for OTC products that the member has been taking.
d) For transitioning members until the Beneficiary can be seen by a Plan provider to establish a care plan, as required by Welfare & Institutions (W&I) Code, Section 14185(b), the Alliance will allow for continuation of medically necessary medications, including medication samples, if provided clinic notes showing all the following:
   i. Patient name
   ii. Medication name, dose, and route of administration
   iii. Quantity distributed
   iv. Date medication was started and date last given/filled
e) For override of the formulary based on continuation of therapy the provider must submit clinical documentation showing the member has previously tried without success or cannot/should not take formulary alternatives, including any relevant labs.

~~13.~~12. **Discharge Medication Override**

a) Members being discharged on a medication will be approved given a one-time override for up to a 30-day supply. Future approvals will be based on the MRGs and the member's previous use of therapeutic alternatives.

~~14.~~13. **Therapeutic Duplication Override**

a) If the member is currently taking a medication that is therapeutically equivalent to the medication requested, the reviewing health care provider may deny the request.
b) For approval of a request of a medication that is therapeutically equivalent to a medication the member is already taking requires documentation from the provider that that the member is no longer taking the first medication, or the provider must submit any relevant labs results, clinical references, national guidelines, and/or primary literature to support the use of both medications together.

~~15.~~14. **Day Supply Limit**

a) The Alliance will cover up to 30 days' worth of medication per prescription, with the exception of the following:
   i. Certain maintenance medications: Up to 90 days per fill
   ii. Certain Specialty medications: Up to 14 days per fill
   iii. Contraceptives: Up to 365 days per fill

D. Exception Requests Based on Medical Necessity:

1. Since exception requests, by definition, do not have a MRG in place, the Pharmacy Technician will not be able to approve the request.
2. The reviewer documents the reason why the request qualifies as an Exception request and refers the case to a pharmacist for review.

3. The pharmacist reviews the case and background materials. The pharmacist can approve Exception Requests when ALL the following criteria are met:
    a) History of failure, contraindication, or intolerance to all formulary alternatives, or no formulary alternatives exist (if applicable)
    b) The treatment plan is:
        i. Safe, effective, and within national standards of practice.
        ii. Not experimental or part of a current clinical trial or study.
        iii. Specific and treats the identified condition.
        iv. Expected to improve health or prevent or delay progression of the condition from getting worse.
        v. Not primarily for convenience.
        vi. Not being used to avoid legal consequences.
        vii. Not contraindicated or have other reasons why use of the drug should not be used.
    c) One of the following:
        i. Requested drug is FDA-approved for the condition being treated.
        ii. If requested for an off-label indication, the use is supported in compendia.
        iii. If the off-label use is supported by nationally recognized treatment guidelines or by two (2) peer reviewed articles.
3. The pharmacist will defer cases that cannot be denied based on the above listed denial reasons. These requests and any other highly complicated cases will be sent to an Alliance board-certified Medical Director for review.
    a) The Alliance Medical Director reviews the background of the case and, if needed, contacts the requesting provider for any additional information needed for the review.
    b) The Medical Director may render one of 3 decisions: approve, deny, or modify.
    c) The Medical Director finalizes the review and returns the case to the reviewing pharmacist with documentation of their decision and the rationale.
4. The reviewer documents the criteria and rationale for the decision in the pharmacy authorization system.
5. A pharmacist or a medical director can use nationally recognized treatment guidelines and other clinical information in support of making the decision.
6. Members receive a notice of action (NOA) letter with the outcome of the request and their rights and the process to appeal the decision. The provider also receives an identical copy of the NOA via fax or regular mail. All NOA letters sent to members and providers include their rights and the process to appeal the decision.

E. The qualifications and role of each reviewer in the medication exception review process is consistent with the reviewer roles documented in the *RX- 002 Prior Authorization Review Process*.

E. **External Review**

A request for an external review when the Alliance denies a prior authorization (PA) can be made for a drug that is not covered by the plan or for an investigational drug or therapy. A request for an external review will not prevent the filing of a grievance or

Independent Medical Review (IMR) with the California Department of Managed Health Care (DMHC). Requests for external review will be made and completed in the Alliance Grievance and Appeals (G&A) Department. Pharmacy Services will assist in forwarded requests (from the Alliance G&A) for external review. ~~and then forwarded to Pharmacy Services to proceed with external review.~~

III. Pain Medication Requests for the Terminally Ill

A. Alameda Alliance shall define a Terminal Illness as an incurable or irreversible condition that has a high probability of causing death within one year or less (Health & Safety Code Section 1373.96 (c)(4)).
B. All prior authorization and exception requests submitted to Alameda Alliance shall be reviewed by clinical pharmacy staff to determine if the patient meets terminally ill status.
C. Terminally ill members shall identify as:
    1. Any member who is currently being treated by a hospice provider
    2. Members with terminal cancer
    3. Any physician directed end-of-life treatment plan that requires the use of the following medications:
        1) morphine 5mg/mL concentrated solution
        2) oxycodone 5mg/mL concentrated solution
        3) sublingual fentanyl formulations
D. Requests from providers for authorization of coverage for a member who has been determined to be terminally ill are approved or denied within 24 hours of the Alliance's receipt of the information requested to make the decision.
E. The requested treatment for a terminally ill member is deemed authorized if the applicable turn-around time has expired.
F. Any medications for pain for members deemed to be terminally ill shall be approved based on medical necessity.
G. The pharmacy department shall keep a log of any requests for pain medication that are deemed to be for a terminally ill member.
    1. The log shall be reviewed on a weekly basis for any denials.
    2. Pain medication requests for terminally ill members shall be tracked monthly and any trends shall be reported on to the Health Care Quality Committee (HCQC) on a quarterly basis.

A. All other medication requests for the terminally ill members

1. Requests from providers for authorization of coverage for a member who has been determined to be terminally ill are approved, modified, or denied **within 24 hours of the Alliance's receipt of the information requested to make the decision.** Only licensed physicians or health care professionals, competent to evaluate the clinical issues, make decisions to deny pain management for terminally ill patients.
2. The requested treatment for a terminally ill member is deemed authorized if the applicable time frame has expired when all the necessary medical information has been provided.
3. For terminally ill members, if a request is denied or more information is required, the Alliance contacts the requesting provider within 24 hours of the determination and provides an explanation of the determination and the

reason for the denial or need for more information.

IV. Provision of Drugs during Emergency Circumstances

In emergency circumstances, prior authorization is not required for an emergency three (3) day supply of drugs that would otherwise require authorization. See *RX-009 Pharmaceutical Emergency Supply Provision*

A. Alliance providers are informed of this policy via the Alliance's Provider Manual.
B. Alliance members are informed of this policy via member's Explanation of Coverage.
C. Alliance providers are responsible for following the prior authorization process for the remainder of the prescription.
D. The Alliance allows for payment of the three (3) day supply of the drugs even if the prior authorization request is subsequently denied.
E. Continuity of care requirements do not require the Alliance to continue coverage of drugs dispensed under this provision if they are not found to be medically necessary.

VI. **Non-Specialty Mental Health Services (NSMHS) has various services that will be provided when medically necessary, and is provided by PCPs or by licensed mental health Network Providers within their scope of practice (this includes, but is not limited to):**

A. Outpatient services for the purpose of monitoring drug therapy

VII. **Monitoring Process**

F. The Alliance provides oversight of its PBM through an annual audit of the PA review process.
G. The Senior Director of Pharmacy Services or designee reviews a monthly authorization report, which provides statistics on all approvals, denials, and modifications to ensure that providers and members have been notified in accordance within the mandated turnaround times.
H. Inter-rater Reliability Review (IRR)
    1. The **Senior Director of** Pharmacy Services **or designee** will conduct IRR annually for clinical pharmacists who review and make determinations for the exceptions requests.
    2. 8 cases will be pulled and reviewed. If 100% clinical pharmacist agreement is not found in all 8 cases then another 22 will be pulled and reviewed for a total of 30 cases.
    3. When a total of 30 cases are reviewed, at least 90% agreement between the clinical pharmacists will be attained. Otherwise, additional sessions will be held until the 90% agreement threshold is reached in a total of 30 cases.
    4. The Alliance will immediately supply remediation if the passing threshold is not met.
    5. New staff require testing prior to conducting utilization review without supervision.
    6. Results of the IRR will be reported to UM Committee.

DEFINITIONS / ACRONYMS

Pharmaceutical Management Procedures: Formulary drugs that have additional requirements or limits on coverage, such as Step Therapy (ST), Quantity Limits (QL) and Age Limits (AL).

Emergency Circumstances: When the enrollee's condition is such that the enrollee faces an imminent and serious threat to his or her health, including, but not limited to, the potential loss of life, limb, or other major bodily function, it is considered an emergency (Health and Safety Code § 1367.01 (h)(2)).

HCQC: Health Care Quality and Compliance Committee

NCQA: National Committee on Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently PerformRx)

RELATED POLICIES AND PROCEDURES

RX-002 Prior Authorization Review Process
RX-006 Pharmacy Services Staff Description
RX-008 PBM Delegated Audit Oversight
RX-009 Pharmaceutical Emergency Supply Provision

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

Table 1 – Decision & Notification Time Frames
Attachment 1 – Exception Review Process Flow Chart

REVISION APPROVAL HISTORY

9/12/2012, 5/19/2016, 8/30/2018, 12/11/2018, 12/17/2019, 6/16/2020, 3/16/2021, 12/21/2021, 6/21/2022, 3/28/2023, 6/20/2023, 9/26/2023, 12/19/2023, 3/19/2024, 5/21/2025, 6/17/2025

REFERENCES

- California Code of Regulations (CCR), Health & Safety Code, §§1367.01, 1367.21, 1367.22, 1367.24, 1367.206 and 1373.96
- CCR, Welfare & Institutions Code, §14185
- CCR, Title 22, §§51003, 51014.1, 51014.2, 53854 and 53894
- CCR Title 28 §1300.67.24
- MMCD Policy Letter 08-013
- NCQA, 2016 HP Standards & Guidelines, UM 13 (Procedures for Pharmaceutical Management), Element E (Considering Exceptions)
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-Cal Rx
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx
- DMHC APL 18-001 (OPL): Newly Enacted Statutes Impacting Health Plan License Filings
- DHCS Contract #23-30212, Exhibit A – Scope of Work

MONITORING

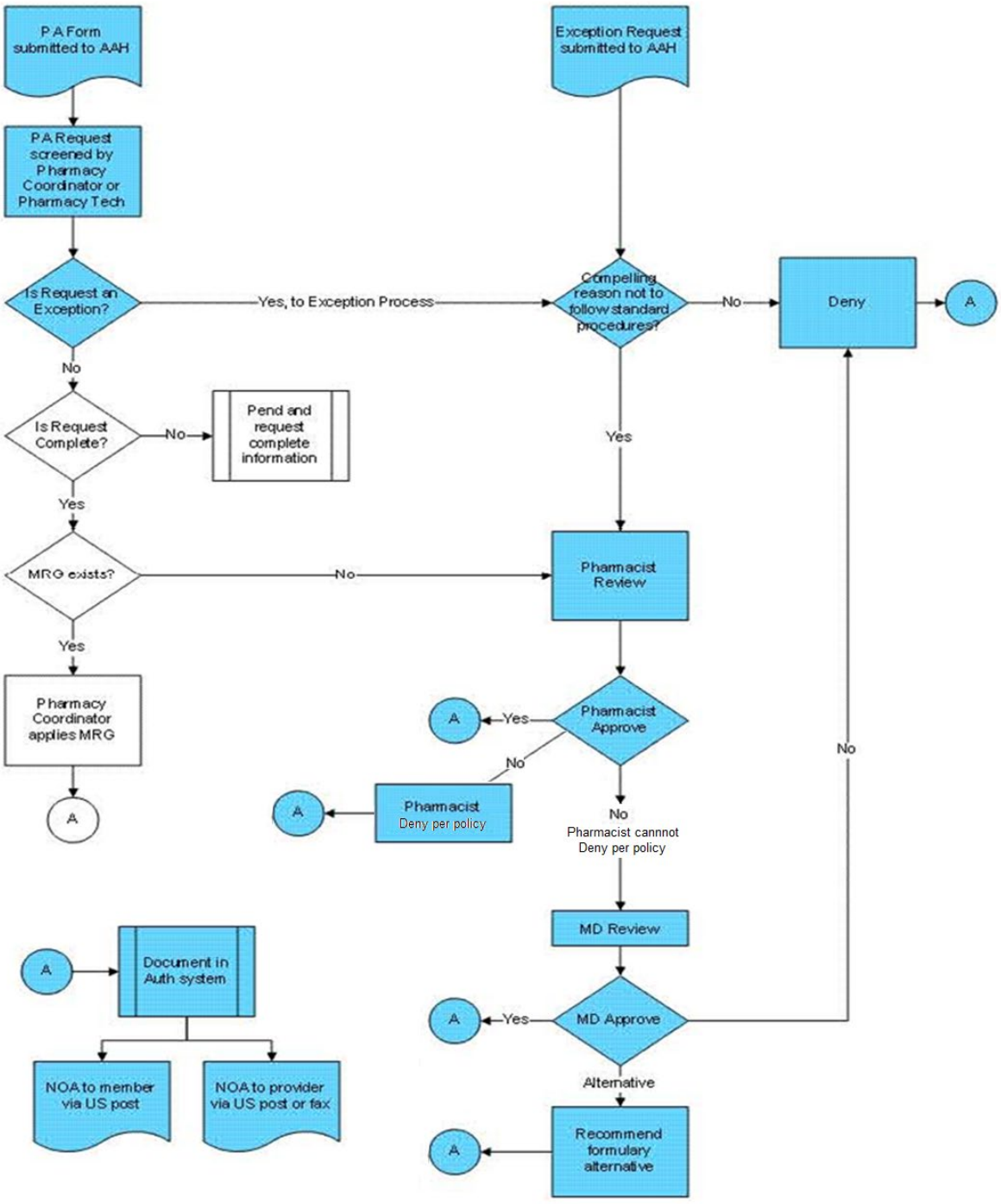
This P&P is reviewed annually to ensure effectiveness.

APPENDIX

Table 1: Decision & Notification Time Frames

Type of Request	Decision	Initial Notification	Written Notification
Prospective, Urgent	Approval	A fax is sent to the requesting provider within 24 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision
	Denial		
Prospective, Non-Urgent	Approval	A fax is sent to the requesting provider within 72 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision
	Denial		
Post-service	Approval	A fax is sent to the requesting provider within 72 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision

Pharmaceutical Management Procedures
(Prior Authorization and Exception Process)



POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-004
Policy Name	Formulary Management
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	IHSS
Effective Date	10/01/2007
Subcommittee Approval Date	6/17/2025
Administrative Oversight Committee Approval Date	TBD~~5/21/2025~~

POLICY STATEMENT

The Alameda Alliance for Health ("Alliance") has an established mechanism for maintaining, reviewing, and updating its drug formulary. The Alliance is committed to ensuring that all eligible Alliance members have access to high quality and cost-effective pharmaceutical care. The Alliance's formulary management process complies with the standards set by the Health and Safety Code, CCR, Section 1367.20, 1367.205, 1367.21, 1367.24, 1367.25, 1367.215.

PROCEDURE

A. Formulary

1. The Alliance's formulary is managed by the Pharmacy and Therapeutics (P&T) Committee.
2. The P&T Committee objectively appraises, evaluates, and selects pharmaceutical products for formulary inclusion or exclusion. Products are evaluated based on efficacy, safety, ease of use, and cost. This is an ongoing process to ensure the optimal use of therapeutic agents.
3. The Alliance's formulary is updated on a continuing basis after each meeting of the P&T Committee as well as between P&T Committee meetings when interim changes are implemented by Alliance pharmacy services. Alliance Providers are notified of all formulary changes in a timely manner, using provider bulletins on the Alliance's website.

4. Drugs newly approved by the Food and Drug Administration (FDA) are reviewed by the P&T Committee within six (6) months of FDA approval. The P&T Committee determines whether the newly approved drugs will require prior authorization from the Alliance or be included on the Alliance's formulary.
5. In accordance with Health & Safety Code, CCR, Section 1367.21, the Alliance allows for the coverage of any drug that is prescribed for use that is different from the FDA-approved use(s), provided that **all of the following conditions** are met:
   a. The drug is prescribed by a participating licensed health care professional for the treatment of:
      i. A life-threatening condition; or
      ii. A chronic and seriously debilitating condition, and the drug is medically necessary to treat that condition, and the drug is on the Alliance's formulary. If the drug is not on the Alliance's formulary, the prescriber's request is reviewed in accordance with Health & Safety Code, CCR, Section 1367.24 (see Policy #RX-0002a and RX-0002b, Prior Authorization and Exception Process).
   c. The drug has been recognized for the treatment of that condition by any of the following:
      i. The American Medical Association Drug Evaluations
      ii. The American Hospital Formulary Service Drug Information
      iii. The United States Pharmacopoeia Dispensing Information, Volume I, "Drug Information for Health Care Professionals"
      iv. Two articles from major peer reviewed medical journals that present data supporting the proposed off-label use(s) as generally safe and effective unless there is clear and convincing contradictory evidence presented in a major peer reviewed medical journal.
      v. It is the prescriber's responsibility to submit the supporting documentation.

6. The Alliance does not cover drugs within the following categories (unless treating gender dysphoria or alleviating mental health or substance use):
   a. Drugs for the treatment of cosmetic conditions
   b. Investigational or experimental drugs that are under clinical trial
   c. Over the Counter (OTC) drugs, with the following exceptions:
      (i) Certain OTCs are on the formulary based on plan review
7. The Alliance provides coverage for FDA-approved prescription contraceptive methods in accordance with Health & Safety Code, CCR, Section 1367.25.
8. The Alliance's formulary is located on the Alliance's website and is available to Alliance Providers, Pharmacies, and Members upon request.
9. The Alliance provides coverage of standard infertility ~~preservation~~ services ~~when a covered treatment may directly or indirectly cause iatrogenic infertility, and are not within the scope of coverage for treatment infertility.~~
10. The Alliance provides copayments that will not be higher than the in-network pharmacy's retail price for a prescription drug.
11. The Alliance provides formulary prescription coverage for antiretroviral medications including PrEP without prior authorization/step therapy requirement.
12. ~~12.~~ The Alliance provides coverage for at least one medication approved by the FDA in each of the following categories without prior authorization, step therapy, or utilization review:
    a.

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~~(1)~~ Medication for the reversal of opioid overdose, including a naloxone product or another opioid antagonist.

b. ~~(2)~~ Medication for the detoxification or maintenance treatment of a substance use disorder, including a daily oral buprenorphine product.

c. ~~(3)~~ A long-acting buprenorphine product.

d. ~~(4)~~ A long-acting injectable naltrexone product.

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B. Pharmacy and Therapeutics (P&T) Committee:

1. The P&T Committee's voting membership is as described in RX-005 P&T Committee Roles and Scope.
2. Per the P&T Charter, the P&T Committee is responsible for the following:
   a. Develop and implement effective drug utilization review treatment outcome systems to optimize the quality of the pharmacy services
   b. Review the formulary on a quarterly basis
   c. Ensuring that the formulary review considers all drugs approved by the Federal Drug Administration (FDA)
   d. Ensuring that deletions from the formulary are documented and justified.
3. The following are considered by the P&T Committee when reviewing the formulary:
   a. Alliance Provider recommendations for additions or deletion of drugs to the formulary
   b. Bioavailability data
   c. Cost comparisons against other drugs available to treat the same medical condition(s)
   d. Current therapeutic guidelines
   e. Dosage ranges by route and age
   f. Findings from the following agencies: governmental agencies, medical and pharmaceutical associations, the National Institute of Health, and regulatory body publications
   g. Medical literature and clinical trials
   h. Off-label uses
   i. Patient risk factors relative to contraindications, warnings, and precautions
   j. Patient utilization and experience
   k. Pharmacokinetic data
   l. Pharmacologic considerations (e.g. drug class, similarity to existing drugs, side effect profile, mechanism of action, therapeutic indication, drug-to-drug interaction potential, and clinical advantages over other products in the specific drug class)
   m. Risks versus benefits regarding clinical efficacy and safety of a particular drug relative to other drugs with the same indication
   n. Special monitoring or medication administration requirements

C. Notification of Formulary Changes to Providers and Members

1. The Alliance notifies its Providers about formulary additions, deletions, and modifications to policies and procedures - and after each quarterly P&T Committee meeting, or more frequently as needed. Providers are notified through the provider bulletin updates. Information will include, at a minimum:

a. Copayment and coinsurance requirements and the pharmaceuticals or pharmaceutical classes to which they apply
b. List of preferred pharmaceuticals or formularies
c. Prior authorization criteria
d. Procedures for generic substitution, therapeutic interchange, step therapy, or other management methods to which the practitioner's prescribing decisions are subject
e. Any other requirements, restrictions, limitations, or incentives that apply to the use of certain pharmaceuticals

2. The Alliance notifies its members about formulary additions, deletions, and modifications to policies and procedures after each quarterly P&T Committee meeting, or more frequently as needed. In addition, bulletins will provide a link to the Alliance web site for detailed information on the formulary changes. Information will include, at a minimum:
   a. Copayment and coinsurance requirements and the pharmaceuticals or pharmaceutical classes to which they apply
   b. List of preferred pharmaceuticals or formularies
   c. Prior authorization criteria
   d. Procedures for generic substitution, therapeutic interchange, step therapy, or other management methods to which the practitioner's prescribing decisions are subject
   e. Any other requirements, restrictions, limitations, or incentives that apply to the use of certain pharmaceuticals

3. Member Services Department is also notified of formulary changes. A copy of the Summary of Formulary Updates will be emailed to the Director of Member Services once available. The Director of Member Services will disseminate the information to Member Services Representatives as of the effective date of the change. In addition, any interim formulary or benefit changes will be communicated to the Director on an as-needed basis.

4. Providers may submit requests for formulary changes by using the Request for Formulary Review Form. (Attachment 1)
   a. The Request for Formulary Review Form is available on the Alliance's website and can be provided upon request.
   b. The P&T Committee reviews requests for change to the formulary on a quarterly basis.

D. Content Management of Formulary Changes

1. The Alliance regularly updates material available online to Providers and Members. The Alliance synchronizes the dates that different information resources are updated to ensure consistency. Upon completion, the following content is updated:

a. Alliance Provider website:
   i. Document of Summary of Formulary Updates document uploaded
   ii. Online Drug Formulary Search Tools: Current PBM updates the On-line Search tool to reflect the changes.

b. Printed version: PBM will prepare the printed version of the formulary after the changes have been implemented. This document will be posted on the website within 45 days of the P&T decisions. Alliance Member website:
   i. Online Drug Formulary Search Tools: Current PBM updates the On-line Search tool to reflect the changes.

Printed version: PBM will prepare the printed version of the formulary after the changes have been implemented. This document will be posted on the website within 45 days of the P&T decisions.

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E. ~~Non-Covered Drug Classes (unless treating gender dysphoria or alleviating mental health or substance use)~~Prescription Drug Exclusions:

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Note: These exclusions do not apply to Medically Necessary Treatment of Mental Health or Substance Use Disorder furnished or delivered by, or under the direction of, a Health Care Provider acting within the scope of practice of the provider's license or certification under applicable state law.

~~**E.**~~

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- When prescribed for cosmetic services. For purposes of this exclusion, cosmetic means drugs solely prescribed for the purpose of altering or affecting normal structure of the body to improve appearance rather than function.
- When prescribed solely for the treatment of hair loss, sexual dysfunction, athletic performance, cosmetic purposes, anti-aging for cosmetic purposes, and mental performance. The exclusion does not apply to drugs for mental performance when they are Medically Necessary to treat diagnosed mental illness or medical conditions affecting memory, including, but not limited to, treatment of the conditions or symptoms of dementia or Alzheimer's disease.
- When prescribed solely for the purpose of losing weight, except when Medically Necessary for the treatment of [Class III or severe] obesity.
- When prescribed solely for the purpose of shortening the duration of the common cold.
- Replacement of lost or stolen drugs.
- Drugs when prescribed by non-contracting providers for non-covered procedures and which are not authorized by a plan or a plan provider, except when coverage is otherwise required in the context of Emergency Services and Care.

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- ~~Drugs used to treat hair loss or hair growth~~
- ~~Drugs solely used for cosmetic purposes~~
- ~~Over-the-counter medications (unless approved by the Alliance)~~
- ~~Non-FDA approved medications (e.g. Medical Foods, herbal remedies, certain supplements, special foods or diet items)~~
- ~~Nutrition products or household items used for convenience~~
- ~~Investigational drugs (drugs being studied in clinical trials)~~

- ~~Comfort or convenience items~~
- ~~Items used for hygiene (unless criteria have been met. The Alliance will cover incontinence creams and washes when there is a medical need)~~
- ~~Items used to test blood or other fluids (except blood glucose monitors)~~
- ~~Drugs used to treat worker's compensation related injury~~

DEFINITIONS / ACRONYMS

- Formulary: list of drugs covered by the Alliance
- NCQA: National Committee on Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

Utilization Management
Pharmacy Services
Member Services
Provider Relations

Communications and Outreach

RELATED POLICIES AND PROCEDURES

RX-002 Prior Authorization Review Process
RX-005 P&T Committee Roles and Scope

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

Attachment 1: Request for Formulary Review
P&T Charter

REVISION APPROVAL HISTORY

10/1/2007, 3/25/2016, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 9/20/2022, 12/27/2022, 3/28/2023, 4/10/2024, 12/17/2024, 5/21/2025, 6/17/2025

REFERENCES

- NCQA UM 12, Element A**,** B, D

- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-Cal Rx
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx
- DMHC APL 20-001 (OPL): Newly Enacted Statutes Impacting Health Plans
- DMHC APL 19-002 (OPL): Newly Enacted Statutes Impacting Health Plans
- DMHC APL 21-018 Guidance Regarding Preventative Health Services Coverage for HIV Preexposure Prophylaxis (PrEP)

This policy will be reviewed annually to ensure effectiveness.

ALAMEDA Alliance FOR HEALTH

Health care you can count on.
Service you can trust.

POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-012
Policy Name	Medicare Part D Fraud, Waste and Abuse (FWA)
Department Name	Pharmacy Services
Department Officer	Chief Medical Director
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	DSNP
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

This policy addresses the Center of Medicare and Medicaid Services (CMS) requirement for Alameda Alliance for Health (Alliance) to implement an effective compliance program as well as measures to prevent, detect, and correct fraud, waste, and abuse. Fraud, Waste and Abuse (FWA) is a risk both internally and externally to the plan sponsor and Medicare benefit.

PROCEDURE

1. Alliance has a process to receive, record and respond to instances of potential compliance or FWA issues that are identified by beneficiaries, associates, and subcontractors. Confidentiality is maintained, allowing anonymity if desired and without retaliation.

2. Alliance utilizes Compliance Hotline posters, Alliance website, the Compliance Plan, Alliance Compliance Training, email TIP's, confidential contact to the CO as resources for education and reporting. Reporting via the dedicated Compliance Hotline and to the Compliance Officer is available 24 hours a day.

2.1 Alliance will work with the Compliance Officer to generate an annual workplan to determine which Pharmacy Operations First Tier, Downstream and Related Entities (FDRs) will be audited each year. Alliance will use the

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following data when determining which FDRs will be audited:

2.1.1 Member complaints

2.1.2 Payment Reports to identify over and under payments, duplicate payments, timely payments, correct pricing and pricing inconsistencies

2.1.3 Drug Utilization Reports (DURs) to identify the volume of prescriptions filled by a particular member, and especially for controlled substance medications to identify possible therapeutic abuse or illegal activity.

2.1.4 Provider Utilization Reports (PURs) that detail number and types of visits and services submitted for payment to identify increases or inconsistencies such as services not normally performed by the provider's specialty.

2.1.5 Prescribing and referral patterns by Physician Reports to identify the number of prescriptions and referral written by a particular provider which focus on type of drug (e.g. controlled substances) or DME (e.g. scooters).

2.1.6 Geographic Zip Code Reports that identify potential doctor shopping schemes and "prescription mills" by comparing zip code of member, zip code of prescription writer and zip code of dispensing pharmacy. Alliance will determine if more than "normal distance" exists between member, doctor and pharmacy based on residence of member (i.e. rural versus urban).

2.2 Alliance will review and respond timely to all CMS fraud alerts. Alliance will review all past paid claims from entities identified in the CMS alert. Alliance may deny or reverse claims based on internal research to CMS alerts and potential for FWA.

2.3 Alliance will maintain the following files for a period of 10 years to identify history of provider complaints:

2.3.1 In-network and out-of-network providers who have been the subject of complaints, investigations, violations, and prosecutions.

2.3.2 Member provider complaints

2.3.3 National Benefit Integrity Medicare Drug Integrity Contractor (NBI MEDIC) investigations

2.3.4 Office of Internal General (OIG) and/or Department of Justice (DOJ) investigations

2.3.5 US Attorney prosecution, and any other civil, criminal, or administrative action for violations of Federal health care

Confidential

program requirements

2.3.6 Documented warnings (i.e., fraud alerts) and educational contacts

2.3.7 The results of previous investigations, and copies of complaints resulting in investigations.

2.4 Alliance has a Special Investigation Unit (SIU) for conducting surveillance, interviews and other methods of investigation to determine FWA. Alliance will forward all potential FWA cases to the SIU. SIU responsibilities include:

2.4.1 Forwarding all potential FWA issues to the Compliance Officer

2.4.2 Reducing or eliminating Medicare Parts C and D benefit costs due to FWA

2.4.3 Reducing or eliminating fraudulent or abusive claims paid for with federal dollars

2.4.4 Preventing illegal activities

2.4.5 Identifying enrollees with overutilization issues

2.4.6 Identifying and recommending providers for exclusion to the NBI MEDIC and/or law enforcement

2.4.7 Referring suspected, detected or reported cases of illegal drug activity, including drug diversion, to the NBI MEDIC and/or law enforcement and supporting them in Assisting law enforcement by providing information needed to develop successful prosecutions

2.5 Alliance does not have an SIU, and all responsibilities usually delegated to an SIU is performed by the Compliance Department. Alliance will forward all potential FWA cases to the Compliance Department. The Compliance Department will forward all potential FWA issues to the Compliance Officer and the NBI MEDIC or law enforcement. Compliance Department responsibilities include:

2.5.1 Forwarding all potential FWA issues to the Compliance Officer

2.5.2 Reducing or eliminating Medicare Parts C and D benefit costs due to FWA

2.5.3 Reducing or eliminating fraudulent or abusive claims paid for with federal dollars

2.5.4 Preventing illegal activities

2.5.5 Identifying enrollees with overutilization issues

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2.5.6 Identifying and recommending providers for exclusion to the NBI MEDIC and/or law enforcement

2.5.7 Referring suspected, detected or reported cases of illegal drug activity, including drug diversion, to the NBI MEDIC and/or law enforcement and supporting them in subsequent case development

2.5.8 Assisting law enforcement by providing information needed to develop successful prosecutions

2.6 Alliance has contracted with their PBM to perform pharmacy on-site and desk audits.

2.6.1 On-site Audits

2.6.1.1 The PBM or Alliance Client owned/contracted pharmacy networks managed by the PBM, are subject to audit to verify claim accuracy, promote consumer safety, and assess compliance with the PBM agreements, contract terms, Provider Manual, and Federal Pharmacy Practice Act and related legislation.

2.6.1.2 Onsite Audits are scheduled based on client requests, member complaints, desk audit findings, regulatory requirements, contractual agreements, monitoring of pharmacies in regions known to have a history of potentially fraudulent activity, and/or as recommended by the PBM's Pharmacy Compliance, FWA Team, the PBM's Pharmacy Adjudication Committee (PAC), and/or the PBM's designee.

2.6.1.3 The PBM will audit a minimum of 100 claims per Pharmacy audited and claims selection is based on:

2.6.1.3.1 Number of prescriptions dispensed

2.6.1.3.2 Compound percentage

2.6.1.3.3 Total dollars paid

2.6.1.3.4 Average price per refill

2.6.1.3.5 Number of prescriptions per Member

2.6.1.3.6 DAW 1 percentage

2.6.1.3.7 HIV drugs highly diverted drugs

2.6.1.3.8 Dollars paid per member

2.6.1.3.9 Controlled substance percentage

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2.6.1.3.10 Reversal percentage

2.6.1.3.11 Reject percentage

2.6.1.4 The PBM will conduct audits using internal audit processes that include audit preparation, entrance interview, observations, items to request and review (credentialing, copies of FWA and Compliance Training, evidence of OIG & General Services Administration (GSA) sanction checks, LEIE, State Board of Pharmacy sanctions), review and scanning of prescription records, verification of delivery, outcome report and exit interview and audit close out.

2.6.1.5 Alliance will receive a monthly Onsite Audit Report listing all onsite pharmacy audits in the previous month.

2.6.1.6 Alliance will receive an Explanation of Audit Report that shows claims with discrepancies that have been adjusted or reversed.

2.6.1.6.1 Part D TrOOP recalculations, adjustments and reversals are also reported on the Explanation of Audit Report after recalculation and processing of claim adjustments/reversals.

2.6.1.7 If discrepancies are found, the PBM may place the Pharmacy on the FWA Watch List, recommend a CAP and subsequent Desk Audit, suspend, or terminate the Pharmacy from the network.

2.6.1.8 In situations of potential fraud, waste and/or abuse, the appropriate parties are notified at the conclusion of the Onsite Audit. The PBM will provide detailed information of investigations to law enforcement, state insurance or State Boards of Pharmacy, MEDICs, etc.

2.6.2 Desk Audits

2.6.2.1 The PBM or Alliance Client owned/contracted pharmacy networks managed by the PBM, are subject to audit to verify claim accuracy, promote consumer safety, and assess compliance with the PBM agreements, contract terms, Provider Manual, and Federal Pharmacy Practice Act and related legislation.

2.6.2.2 Desk Audits are conducted on pharmacies monthly,

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as dictated by regulatory requirements or contractual agreements and/or as recommended by the PBM Pharmacy Compliance team, FWA Auditing staff based upon results of Alliance requests, Member complaints, onsite audit findings, and monitoring of pharmacies in regions known to have a history of potentially fraudulent activity. Special Desk Audits may also be conducted to monitor pharmacies and/or regions known to have a history of potentially fraudulent activity.

2.6.2.3 Adjudicated claims are run through the PBM's proprietary algorithms and flag claims with suspicious and/or inappropriate attributes or elements. PBM auditors will review claims with flags.

2.6.2.4 Flags may include, but are not limited to, the following:

2.6.2.4.1 High dollar

2.6.2.4.2 Compounds

2.6.2.4.3 Incorrect Day Supply

2.6.2.4.4 Maximum dose

2.6.2.4.5 DAW

2.6.2.4.6 Diabetic Supply Overuse

2.6.2.4.7 High Quantity

2.6.2.4.8 Controlled Substances

2.6.2.4.9 Standard Deviation

2.6.2.4.10 Maximum Quantity by Therapeutic Indication

2.6.2.4.11 Members using multiple Pharmacies/Prescribers

2.6.2.4.12 Package Size/Unit of Measure

2.6.2.4.13 Expired Prescriptions

2.6.2.4.14 Out of State Prescribers

2.6.2.4.15 Dosage Form

2.6.2.5 The PBM auditor will send a letter requesting supporting documentation for claims with potential discrepancies to the dispensing pharmacy. The letter

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will request, but is not limited to, copies of the identified prescription numbers, signature logs/proof of delivery, proof of member cost share payment, and any additional supporting documentation (e.g., for compounds include: Compounding Worksheets/Records per State and/or USP Guidelines, etc.)

2.6.2.6 Alliance will receive an Explanation of Audit Report that shows claims with discrepancies that have been adjusted or reversed during a desk audit.

2.6.2.6.1 Part D TrOOP recalculations, adjustments and reversals are also reported on the Explanation of Audit Report after recalculation and processing of claim adjustments/reversals.

2.6.2.7 If discrepancies are found, the PBM may place the pharmacy on the FWA Watch List, recommend a CAP and subsequent Desk Audit, suspend, or terminate the Pharmacy from the network.

2.6.2.8 In situations of potential fraud, waste and/or abuse, the appropriate parties are notified at the conclusion of the Onsite Audit. The PBM will provide detailed information of investigations to law enforcement, state insurance or State Boards of Pharmacy, MEDICs, etc.

2.6.2.9 Alliance can request the termination of a PBM network pharmacy based on internal investigation and auditing, whether or not the PBM investigation results in the same conclusion.

DEFINITIONS / ACRONYMS

CAP – Corrective Action Plan
CMS – Centers for Medicare and Medicaid Services
FDR - First Tier, Downstream, and Related Entities
FWA – Fraud, waste and abuse
GSA – General Services Administration – The Federal Administration that helps manage and support the
basic functioning of federal agencies
HHS – Department of Health and Human Services – The Federal department under which CMS resides
LEIE – List of Excluded Individuals and Entities – The list of people and entities that are barred from participating in Government programs
MEDIC - Medicare Drug Integrity Contractor - organizations that CMS contracts with to perform specific program integrity functions for Parts C and D under the Medicare Integrity

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Program. MEDIC's primary role is to identify potential fraud and abuse in Medicare Part C and Part D.
NBI MEDIC - National Benefit Integrity Medicare Drug Integrity Contractor
OIG – Office of the Inspector General – The agency which protects the integrity of HHS programs and the health and welfare of the programs' beneficiaries
SIU – Special Investigation Unit
CO – Complaince Officer

AFFECTED DEPARTMENTS/PARTIES

[List the departments impacted by this policy, or required to comply with this policy]

RELATED POLICIES AND PROCEDURES

[List related Policies]

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

[List related documents]

REVISION HISTORY

[List revision dates starting with original effective date – this is the date that revisions were approved at AOC, and is a running list of approval dates from AOC]

REFERENCES

42 CFR §422.503(b)(4)(vi)
42 CFR §423.504(b)(4)(vi)
Medicare Prescription Drug Benefit Manual Chapter 9 - Compliance Program guidelines and Medicare Managed Care Manual Chapter 21 - Compliance Program Gudelines

MONITORING

Alliance understands that follow-through of potential FWA is as important as the discovery. Alliance will:

- Monitor the Annual Compliance Workplan to ensure that all tasks are completed and in a timely manner.
- Review, track, and respond to all CMS fraud alerts in a timely manner.
- Maintain files of potential FWA complaints for 10 years and review and identify for history of provider potential FWA. Any potential FWA will be reported to the Compliance Officer
- Track and ensure all FWA cases sent to the SIU are being researched and acted upon.

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- Track and ensure all FWA cases sent to the Compliance Department are being researched and acted upon.

- Review, track, and monitor all monthly Onsite Audit Reports and Explanation of Audit Reports as well as Explanation of Audit Reports resulting from desk audits.

    - A sample of adjusted claims will be reviewed to ensure that all adjustments are accounted for in the member's claims history and that the adjustments are correct.

- Regularly review the PBM FWA watch list will be reviewed regularly and any Pharmacy Corrective Action Plans will be reviewed regularly. Alliance will work with the PBM as needed to close any CAPs.

RECORD RETENTION

- Alliance will maintain all books, documents, papers and/or records relating to Medicare members for up to ten (10) years from the final date of the contract period or ten (10) years from the date of any audit if later. Alliance agrees to permit CMS, the U.S. Department of Health and Human Services (HHS), and the Comptroller General, or their designees the right to inspect any pertinent information related to the contract during the contract term, for up to ten (10) years from the final date of the contract period, and in certain instances described in the Medicare Advantage regulation(s), periods in excess of ten (10) years, as appropriate, (ten (10) years from the date of any audit, if later.)

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POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-013
Policy Name	Explanation of Benefits (EOB) Oversight and Monitoring
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	D-SNP
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

Alameda Alliance for Health (Alliance) contracts with a Pharmacy Benefit Manager to provide prescription adjudication to its beneficiaries and monthly creation of Medicare Part D Explanation of Benefits (EOB). When a beneficiary utilizes their prescription drug benefit, an EOB is created to document use and report accumulated True out-of-pocket (TrOOP) expense. The EOB is provided to the beneficiary by the last day of the following month of utilization.

PROCEDURE

1.The Centers for Medicare and Medicaid Services (CMS) releases an updated EOB template with instructions every year.

2. Your EOB must include all model language exactly as written, except:

- Minor grammar or punctuation changes and font type or color changes.
- References to a specific plan name in brackets may be replaced with generic language such as “our plan.”
- References to Member Services may be changed to the name your plan uses.

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- References to the plan's Supplemental Drug Coverage may be changed to the name your plan uses. (This is coverage for non-Part D drugs.)
- References to "cost-sharing tiers" may be expanded to include additional description, including the standardized names of the tiers used by your plan.
- References to "brand-name/tier-level" deductible may be changed to the appropriate name your plan uses.
- Date formatting (such as "mm/dd/yy"), unless specific date formatting instructions are given.
- References to "calendar year" may be changed to "plan year".

3. Formatting Guidelines:
- Standard window envelopes can be used, the Plans may use either portrait or landscape orientation for all pages of the document.
- The document can be printed double-sided to save space.
- Plans are permitted to eliminate empty spaces between sections and/or widen text boxes and columns to save space.
- The document must include page numbers.
- Plans must include the following information as a footer on every page excluding the cover page (where the information is already included): the plan name, plan phone number, including the TTY number and a statement that calls to the plan are free, and plan URL. Plans may choose to add a header or footer that includes some or all of this information: member identifiers; month and year; additional contact information; page number.
- Charts that continue from one page to the next must be marked with "continue" at the bottom on the page that continues. In an actual EOB, rows of a chart must not break across the page.
- Costs included may be displayed with or without decimals and cents (e.g., $0.00).
- CMS provides examples each year to help visualize what the document will look like when substitution text is used in various situations.

4. Beneficiary information in the EOB must include per CMS guidance:
- Summary of adjudicated claims during the prior month, to include drug names, strength, fill date, Pharmacy National Council for Prescription Drug Programs number (NCPDP) and National Provider Identifier (NPI)

- A summary of payments made by the beneficiary (out-of-pocket), the plan, and (as applicable), other programs or organizations

- Information about the beneficiaries' current drug payment stage (deductible, initial coverage, or catastrophic coverage stage)

- A record of their total out-of-pocket costs and total drug costs transferred from their previous plan(s) (if a beneficiary changed plans during the calendar year)

- Any adjustments for that plan year (e.g. a reversed claim or wraparound payment) or corrections (e.g. a clerical error) to beneficiaries' total out-of-pocket costs and total drug costs that are not shown in a previous EOB (if applicable).

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- As applicable: 1. Totals for month 2. Year-to-date totals 3. Member out-of-pocket spending totals (TrOOP)
- Any updates to the drug plan's formulary that will affect medications a beneficiary is currently utilizing (if applicable)
- Contact information for Member Services
- Language instructing members about reporting fraud
- Language informing members about what to do if they disagree with the plan's coverage decision or if they think the EOB is not accurate and contains errors

DEFINITIONS / ACRONYMS

CMS – Centers for Medicare and Medicaid Services
EOB – Explanation of Benefits
NCPDP – National Council for Prescription Drug Programs
NPI – National Provider Identifier
PBM – Pharmacy Benefit Manager
TrOOP – True out-of-pocket

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently – PerformRx)

RELATED POLICIES AND PROCEDURES

RX-D-013 Explanation of Benefits (EOB) Oversight and Monitoring

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

New Policy

REFERENCES

42 CFR 423.128(e)
Medicare Prescription Drug Manual Chapters 5 and 6.
Medicare Marketing Materials- Part D EOB Instructions and Exhibits

MONITORING

To ensure compliance with CMS requirements, Alliance Pharmacy Department reviews a sample of Part D EOB letters, provided by the PBM, for accuracy prior to approval for

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member distribution.

The following procedure provides guidance for the Part D EOB review for Alliance beneficiaries:

1. Select 5-10 sample EOBs for in-depth review

2. Ensure the most recent CMS approved EOB template is being used.

3. Verify member services toll-free and TTY phone numbers are listed correctly on the coverage page.

4. Verify claims data accuracy by comparing to claims in the adjudication system

5. Verify beneficiaries' placement in coverage stage by ensuring that monthly TrOOP accumulators are accurate

6. Verify beneficiaries year-to-date out-of-pocket totals (year-to-date TrOOP)

7. Verify EOB includes appeal rights

8. Verify timeliness of previous month's PBM mailings (health plan should be on mailing distribution list to validate mailing timeframes)

9. Provide PBM email correspondence with outcome of review (positive or negative)

10. Document monthly review results and provide to Compliance Department

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POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-019
Policy Name	Medicare Prescription Payment Plan (M3P) Process, Monitoring and Oversight
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	DSNP
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

This policy addresses the Center of Medicare and Medicaid Services (CMS) and Inflation Reduction Act 1860D–2(b)(2)(E)(iv) (IRA) of 2022 requirement for Alameda Alliance for Health (Alliance) to implement an effective Medicare Prescription Payment Plan with appropriate notifications, confirmation, True-out-of-Pocket (TrOOP) and billing. As well as track measures for MARx submission and Part D Reporting for the Medicare Prescription Payment Plan.

PROCEDURE

The purpose of this document is to provide the plan with guidance which was established by section 11202 of the Inflation Reduction Act of 2022 (IRA) (P.L. 117-169) and signed into law on August 16, 2022. The IRA makes health care more accessible, equitable, and affordable. Section 1860D 2(b)(2)(E) of the Social Security Act (the Act), as added by section 11202 of the IRA, requires all Medicare prescription drug plans to offer their Part D enrollees the option to pay their out-of-pocket (OOP) Part D drug costs through monthly payments over the course of the plan year instead of as upfront payments at the pharmacy point of sale (POS) beginning January 1, 2025.

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Alameda Alliance for Health (Alliance) must, among other requirements:
(1) provide all Part D enrollees prior to and during the plan year with the option to opt into the Medicare Prescription Payment Plan, to pay their OOP cost sharing in monthly amounts that are spread throughout the plan year according to a statutory formula;
(2) determine a maximum monthly cap for each month's amount.
(3) bill the program participant for an amount that must not exceed the monthly cap applicable for a month; and
(4) have in place a mechanism to notify a pharmacy during the plan year when a Part D enrollee incurs OOP costs with respect to covered Part D drugs that make it likely the Part D enrollee may benefit from the program.

PROCESS

1.0 Part D Enrollee Outreach and Communication Requirements

1.1 Alliance is required by guidance to provide enrollees with promotional and education materials on the Medicare Prescription Payment Plan prior to and during the plan year. Mechanisms to fulfill this requirement:

- Include with membership ID card hard copy mailing or in a separate mailing (within the same required 10 calendar days of enrollment confirmation) include a Medicare Prescription Payment Plan election request form, and information on the Medicare Prescription Payment Plan.
- CMS encourages plans to provide the CMS fact sheet Part One and Part Two (issued February 29, 2024, and July 16, 2024).
- Alliance can create alternative materials using final guidance and MCMG and submit to HPMS if documents are required to be reviewed and approved.
- Alliance will distribute the annual EOC and ANOC as applicable to current enrollees or within required guidance to new enrollees with the new added information to define the Medicare Prescription Payment Plan.
- Distribute the enrollees Explanation of Benefits as applicable, that contains the CMS template approved information about the Medicare Prescription Payment Plan.

1.2 Alliance will post on their Medicare Advantage Prescription Drug Plan (MAPD) website information on the Medicare Prescription Payment Plan per guidelines in Final Part One Section 70.3.1 and include election request mechanism for the plans enrollees, it they to choose to participate in the Medicare Prescription Payment Plan.

- Alliance will provide a confirmation number when opted in.
- Will provide an overview of the program that all Part D plans will present and information regarding this voluntary program.
- Alliance will demonstrate examples of how the plan works with cost sharing scenarios.
- Alliance will describe to enrollees that are likely to benefit.
- Alliance will demonstrate the financial implications of participation in the Medicare Prescription Payment Plan. Alliance will not charge the participant fees or interest charges to participate or for processing their

payments. Alliance will explain that participation does not reduce participants cost share for their prescriptions but allows them to spread the expense over the months of the benefit year (initial month of opting in and remaining months of the year).

- Alliance will provide information on the TrOOP for the benefit year and OOP cap for the plan year.
- Alliance will provide information on paying monthly bills including the voluntary/involuntary disenrollment, urgent election or reinstatement for good cause process.
- Alliance will provide participant with information on how to file complaints/grievances related to the Medicare Prescription Payment Plan.
- Alliance will provide general information about the Low-Income Subsidy (LIS) program, including information on the recent LIS expansion of eligibility, and how to apply and enroll in the LIS program (as an additional or alternative avenue for addressing prescription drug costs), noting that LIS enrollment, for those who qualify, is likely to be more advantageous than participation in the Medicare Prescription Payment Plan.

2.0 Part D Enrollee Election Requirements

Elections are guided by the requirements in the Eligibility, Enrollment, and Disenrollment chapter of the Medicare Prescription Drug Benefit Manual, as applicable. Specifically, the Part D enrollee or their legal representative must complete an election request to opt into the Medicare Prescription Payment Plan.

2.1 Alliance must have the following mechanisms available to Part D enrollees who wish to opt into the Medicare Prescription Payment Plan:

- An election request form as part of the Part D (or MA-PD) member ID card issuance when an individual enrolls.
- A paper option that can be mailed; Refer to Medicare Prescription Drug Benefit Manual; Chapter 3 - Eligibility, Enrollment and Disenrollment.
- A toll-free telephone number, that must provide the individual with evidence the election request was received (e.g., a confirmation number); and
- A website application that must provide the individual with evidence the election request was received (e.g., a confirmation number).

2.2 Election validations:

- Each telephonic election request must be recorded and include statements of the Part D enrollee's agreement and a verbal attestation of the intent to opt into the Medicare Prescription Payment Plan. Authorized representatives must record their authority and included attestation and be able to provide proof upon request. Recordings must be reproducible and maintained with CMS record retention guidance.
- Paper election requests can either be filled out electronically and printed or filled out by hand by a Part D enrollee or their representative. Signatures can be by pen and ink or electronically. A telephone request is complete

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with a verbal attestation of intent to opt in and electronic request requires the participant to activate a "Opt In Now" or " I Agree" button or tool.

- If an election request is submitted without a signature, Alliance must verify the election through the mail, phone call or electronic contact (unless enrollee has opted out of phone and electronic contact) with in 10 calendar days.
- Electronic option must include a time and date stamp when the electronic signature is applied to the election request.
- Alliance must acknowledge receipt of the request electronically (if applicable) or within 10 calendar days of receipt and provide:
    - Approval of the request to participate and the effective start date of participation in the Medicare Prescription Payment Plan.
    - A request for additional information (if required, for any missing information within 10 calendar day) or
    - A denial of the request through a written notice of denial if additional information is not received within 21 calendar days of request for additional information. (any denial reason must me explained in the written notice of denial).
        - Denial must include the grievance process that is available to the enrollee or their representative within 10 calendar days of the denial or the expiration of the timeframe for submission of additional information.

4.0 Participants Billing Rights

4.1 Under the Act, the annual TrOOP cost threshold for 2025 is $2,000. "Incurred costs" means any costs incurred or treated as incurred under section 1860D2(b)(4)(C) of the Act. When an individual opts into the Medicare Prescription Payment Plan prior to or during the plan year, the individual's incurred costs used to calculate the first month maximum cap are equal to the individual's accumulated TrOOP before opting into the program. The number of months remaining in the plan year includes the month when an individual opts into the program.

4.2 Participants billing statement must include:

4.2.1 Identify bill is for the Medicare Prescription Payment Plan and a description of the program.
4.2.2 Effective date
4.2.3 Last payment received, date, amount of last payment and means of payment
4.2.4 Any carry-over balance or missed payment
4.2.5 Itemized OOP costs for prescription for the month being billed
4.2.6 The amount due for the month being billed
4.2.7 The remaining total OOP cost sharing balance
4.2.8 Next steps if payment is not paid by the due date
4.2.9 Information on how to voluntarily opt out of the program and balance dur if participation is terminated
4.2.10 Information on the dispute process available if participant disputes their bill
4.2.11 General information about applying for the LIS program m and how to enroll (as an additional or alternative avenue for addressing prescription

drug costs), noting that LIS enrollment, for those who qualify, is likely to be more advantageous than participation in the Medicare Prescription Payment Plan; and

4.2.12 Part D plan contact information for question about the billing statement

4.3 Alliance as a Part D provider cannot bill participant more than the maximum monthly cap amount, late fees, interest payments or or other fees, such as different payment mechanisms.

5.0 Part D Enrollee Terminations, Reinstatement and Preclusion

5.1 Voluntary Terminations – Participants may opt-out at any time during the plan year. Sponsors must continue to bill amounts owed under the program in monthly amounts not to exceed the maximum monthly cap amount. Participants may continue to pay monthly or have the option to pay the full outstanding amount. If voluntarily terminated the member will pay the plan copy amount at the POS at the pharmacy. Voluntary termination is also triggered when participant switches plans during a coverage year.

5.1.1 Volunteer termination letter (including the Multi-Language Insert (MLI)) must be sent to the participant upon completion of the termination of participation within 10 calendar days. CMS has issued a "*The Notice of Voluntary Removal"* model. The notice must include:

- Pertinent dates, including the date on which the individual's participation in the program ends;
- An explanation that the individual is receiving the notice either because they requested a voluntary termination or because they changed Part D plans;
- A statement clarifying that the notice only applies to participation in the Medicare Prescription Payment Plan, and that the individual's Part D drug coverage will not be impacted;
- A statement clarifying that the individual will continue to be billed monthly or can choose to pay the amount owed all at once, and that the individual will not pay interest or fees on the amount owed;
- A statement clarifying that the individual can join the Medicare Prescription Payment Plan again and instructions for how to do so, which may differ depending on whether the voluntary termination was requested by the individual or if it was because the individual changed Part D plans; and
- An overview of other Medicare programs that can help lower costs, including Extra Help, the Medicare Savings Program, the State Pharmaceutical Assistance Program, and the Manufacturer's Pharmaceutical Assistance Program, and how to learn more about these programs.

5.2 Involuntary Terminations – Alliance is required to terminate participants from the Medicare Prescription Payment Plan for their failure to pay their monthly billed amount. Alliance will send a notification within 15 calendar days of payment due

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date. CMS has issued a "*Notice for Failure to Make Payments"* model. The notice of failure to pay must include:

- Pertinent dates and key pieces of information, including the date the missed monthly payment was due, the amount the individual must pay to remain in the program, and the date by when payment must be received, which is the date of the end of the grace period;
- A statement clarifying that the notice only applies to participation in the Medicare Prescription Payment Plan, and that the individual's Part D drug coverage will not be impacted;
- Instructions for how to submit payment;
- Information about procedures for involuntary termination due to failure to pay, including the date on which the participant would be removed if payment is not received, and how to submit an inquiry or file a grievance;
- A statement on how individuals should pay their Part D plan premium first if they cannot afford both their premium and their program balance; and
- An overview of other Medicare programs that can help lower costs, including Extra Help, the Medicare Savings Program, the State Pharmaceutical Assistance Program, and the Manufacturer's Pharmaceutical Assistance Program, and how to learn more about these programs.

5.2.1 After the 2-month grace period of none payment, Alliance is required to send the "*The Notice of Voluntary Removal"* model to notify participant of involuntary termination within . The notice of termination must include:

- Pertinent dates, including the date the individual was originally notified of the missed monthly payment and the due date for that payment, as well as the date on which the individual's participation in the program ends, which should be the same date as the notice;
- A statement clarifying that the notice only applies to participation in the Medicare Prescription Payment Plan, and that the individual's Part D drug coverage will not be impacted;
- Instructions for how to submit payment and the amount owed;
- How to submit an inquiry or file a grievance;
- A statement clarifying that the individual can join the Medicare Prescription Payment Plan again if they pay the amount owed; and
- An overview of other Medicare programs that can help lower costs, including Extra Help, the Medicare Savings Program, the State Pharmaceutical Assistance Program, and the Manufacturer's Pharmaceutical Assistance Program, and how to learn more about these programs.

5.3 Reinstatement- Part D sponsor must reinstate an individual who has been terminated from the Medicare Prescription Payment Plan if the individual demonstrates good cause for failure to pay the program billed amount within the grace period and pays all overdue amounts billed. Part D sponsors are expected to reinstate individuals into the program within a reasonable timeframe 78 after the

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individual has repaid their past due program balance in full. To demonstrate good cause, the individual must establish by a credible statement that failure to pay the monthly amount billed within the grace period was due to circumstances for which the individual had no control, or which the individual could not reasonably have been expected to foresee.

5.3.1- Based on the "good cause" criteria discussed in section 60.2.4 of Chapter 3 of the Medicare Prescription Drug Benefit Manual,20 CMS is stating in this final part one guidance that, in general, the following circumstances constitute good cause:

• A serious illness, institutionalization and/or hospitalization of the program participant or their authorized representative (i.e., the individual responsible for the participant's financial affairs), that lasted for a significant portion of the grace period for Medicare Prescription Payment Plan payment;

• Prolonged illness that is not chronic in nature, a serious (unexpected) complication to a chronic condition or rapid deterioration of the health of the participant, a spouse, another person living in the same household, a person providing caregiver services to the participant, or the participant's authorized representative (i.e., the individual responsible for the participant's financial affairs) that occurs during the grace period for the Medicare Prescription Payment Plan payment;

• Recent death of a spouse, immediate family member, person living in the same household, or person providing caregiver services to the participant, or the participant's authorized representative (i.e., the individual responsible for the participant's financial affairs);

• Home was severely damaged by a fire, natural disaster or other unexpected event, such that the participant or the participant's authorized representative was prevented from making arrangement for payment during the grace period for the Medicare Prescription Payment Plan;

• An extreme weather-related, public safety or other unforeseen event declared as a Federal or state level of emergency prevented premium payment at any point during the Medicare Prescription Payment Plan grace period. For example, the participant's bank or U.S. Post Office closes for a significant portion of the grace period; or

• For Part D plan disenrollments effectuated by CMS for failure to pay Part D IncomeRelated Monthly Adjustment Amount (IRMAA), Federal government error (i.e., CMS, SSA or RRB) caused the Medicare Prescription Payment Plan payment to be incorrect or late, and the participant was unaware of the error or unable to take action prior to the disenrollment effective date. There may be situations in addition to those listed above that result in favorable good cause determinations. If an individual presents a circumstance which is not captured in the listed examples, it must meet the regulatory standards of being outside of the participant's control or unexpected such that the participant could not have reasonably foreseen its occurrence, and this circumstance must be the cause for the non-payment of past due program balances.

Part D sponsors may also reinstate, at the sponsor's discretion and within a reasonable timeframe, an individual who has been terminated from the

Medicare Prescription Payment Plan if the individual pays all overdue amounts billed, even if the individual does not demonstrate good cause.

DEFINITIONS / ACRONYMS

CMS – Centers for Medicare and Medicaid
IRA – Inflation Reduction Act
LIS – Low-Income Subsidy
MCMG – Medicare Communication and Marketing Guidelines
OOP – Out-of-Pocket
TrOOP – Total Out-of-Pocket

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services

RELATED POLICIES AND PROCEDURES

None

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

New

REFERENCES

Medicare Prescription Payment Plan: Final Part One Guidance on Select Topics, Implementation of Section 1860D-2 of the Social Security Act for 2025, and Response to Relevant Comments
Medicare Prescription Payment Plan: Final Part Two Guidance on Select Topics, Implementation of Section 1860D-2 of the Social Security Act for 2025, and Response to Relevant Comments
Medicare Communication and Marketing Guidelines

MONITORING

Alliance Pharmacy Department Staff will include results of ongoing monitoring in monthly Delegated Function Oversight/Monitoring statistics.

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POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-020
Policy Name	Part D Delegation Oversight Auditing (PBM)
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Medicare Advantage
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (Alliance) has a contract with a Pharmacy Benefit Manager (PBM) to administer many of the pharmacy services operations. The PBM contract shall indicate that they will comply with all applicable laws and regulations related to providing Pharmacy Services to the Alliance enrollees.

PROCEDURE

Alliance is responsible for the lawful and compliant administration of the Medicare Parts C and D benefits under their contracts with CMS, regardless of whether the sponsor has delegated some of that responsibility to FDRs. The sponsor must develop a strategy to monitor and audit its first-tier entities to ensure that they are in compliance with all applicable laws and regulations, and to ensure that the first tier entities are monitoring the compliance of the entities with which they contract (the sponsors' "downstream" entities). Alliance must also monitor any related entities to ensure those entities are compliant with all applicable laws and regulations.

PROCESS

1. Alliance (or third-party contractor) shall conduct an annual audit of the contracted PBM.

2. PBM shall be audited based on contractual services provided to Alliance and per the audit guidelines stated in the contract.

a. Provider Communications (including Technical Call Center)
b. Member Call Center
c. Marketing (including EOBs and Formulary website)
d. Medicare Prescription Payment Plan
e. Pharmacy Network Management
f. Claims Adjudication Management
g. Fraud, Waste, and Abuse (FWA) Training
h. Drug Utilization Monitoring
i. Formulary, Transition Process and P & T Committee
j. Medication Therapy Management
k. Benefits and Beneficiary Protections
l. Compliance Plan
m. Prescription Drug Event

3. A Request for Information (RFI) will be provided to the PBM 30 days before the mutually agreed upon audit dates. A delegated function audit tool will be utilized to determine compliance with Medicare and state regulations.

4. Audit results will be reviewed by appropriate Alliance staff.

5. Upon receipt of all audit documentation, auditors will meet with the PBM audit team. Findings will be categorized as:

a. Compliant
b. Immediate Corrective Action Required (ICAR)
c. Corrective Action Required (CAR)
d. Observation Requiring Corrective Action (ORCA)
e. Observation
f. Invalid Data Submission (IDS)

6. ICAR findings will require response and corrective action plan within 3 business days. All other findings will require regularly scheduled meetings to address issues and solutions. Alliance will conduct more frequent audits based on non-compliant process and performance guarantee failures.

DEFINITIONS / ACRONYMS

EOB- Explanation of Benefits
P & T Committee- Pharmacy and Therapeutics Committee

Draft

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Compliance Department

RELATED POLICIES AND PROCEDURES

[List related Policies]

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

[List revision dates starting with original effective date – this is the date that revisions were approved at AOC, and is a running list of approval dates from AOC]

REFERENCES

42 CFR §423.504(b)(4)(vi)(F)
42 CFR §422.503(b)(4)(vi)(F)
Medicare Prescription Drug Benefit Manual (PDBM), Chapter 9, Section 50.2.6.1,

MONITORING

Alliance Pharmacy Department Staff will include results of ongoing monitoring in monthly Delegated Function Oversight/Monitoring statistics.

draft

ALAMEDA Alliance FOR HEALTH

Health care you can count on.
Service you can trust.

POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-021
Policy Name	Medicare Part D Best Available Evidence (BAE)
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	DSNP
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

Alameda Alliance for Health (Alliance) will provide its enrollees access to Part D drugs at the correct LIS cost-sharing when presented with evidence of LIS eligibility, even if Alliance and MARx system do not yet reflect their eligibility.

PROCEDURE

1 Alliance/PBM pharmacy help desk will be staffed with trained individuals prepared to assist pharmacists and enrollees to receive the documentation (e.g. by fax or email) so that system changes to correct cost-sharing levels can be implemented as soon as possible. Alliance/PBM will notify the pharmacy when changes have been made if they cannot make necessary system changes immediately upon confirming and/or receiving the appropriate documentation.

PROCESS

Effective August 3, 2007, Reed & Associates, CPAs (Reed) was designated by the Centers for Medicare & Medicaid Services (CMS) as the national contractor responsible for processing retroactive transactions for all Medicare Advantage Organizations, Part D Sponsors, Cost-based Plans, PACE Organizations, and Medicare-Medicaid Plans (MMPs). Under the terms of this contract, Reed validates and processes all retroactive transactions involving enrollment including those covered by this Standard Operating Procedure (SOP). All transactions submitted by Organizations must be in accordance with the processes outlined in this SOP as well as the latest CMS Guidance.

Collaboration

Compliance with LIS Standard Operating Procedure (SOP)

The guidelines for Alliance submitting documentation requesting a change in a beneficiary's Low Income Subsidy (LIS) level are written in accordance with CMS Chapter 13. The Best Available Evidence (BAE) section is written specifically in accordance with Chapter 13 70.5.2 and 70.5.3.

These guidelines are intended to assist Alliance in their compliance with RPC's Submission Procedure. Any transactions submitted by Alliance that do not comply with the guidelines may not be accepted. Careful adherence to these guidelines will ensure that transactions submitted to the RPC can be processed timely and as requested.

Low Income Subsidy (LIS) Overview

- The Medicare Modernization Act (MMA) allows beneficiaries to receive extra help (subsidy) with Part D prescription drug costs.
- This extra help takes the form of subsidies paid by the Federal Government to the drug plan in which the Medicare beneficiary enrolls.
- The subsidy provides assistance with the premium, deductible, and co-payments of the program.
- When a beneficiary's deemed status is not accurate in CMS' systems, Part D sponsors are required to submit their LIS Deeming request to the Retroactive Processing Contractor (Reed & Associates).
- Alliance must submit all valid manual LIS deeming requests to the RPC following the guidance contained in this SOP.

Timing of Manual LIS Status Correction

As described in Chapter 13 70.5.4 (Transmitting and Timing of Manual LIS Status Correction), prior to submitting a manual correction request to the RPC, CMS recommends allowing a reasonable time for updated information to be automatically entered into CMS' systems and reported to Allaince. The recommended delay is a minimum of 30 days and a maximum of 60 days, as it is likely that a significant portion of those who qualify under BAE policy in one month will be deemed for LIS via the normal process within the next several weeks.

Instructions for Submission to RPC

Alliance must submit all manual LIS deeming update transactions to the RPC following the specific guidance contained in this SOP. If Alliance has questions regarding the submission of transactions, they should contact the RPC's Client Services Department (clientservices@reedassociates.org).

Alliance should expect that transactions are processed and reported in the order received by the RPC. The general process is noted below:

A. Alliance submit the following to the RPC:
   a. A cover letter;
   b. The RPC submission spreadsheet; and
   c. BAE for each beneficiary identified in the retroactive transactions.

B. The RPC will import the transactions from the eRPT system into the RPC tracking system and, if necessary, issue error reports to Alliance within five (5) calendar days.

C. The RPC will review the transactions and, if applicable, make changes in CMS' systems within 35 days of the receipt date. A final disposition report (FDR) will be issued to Alliance communicating the results of RPC's review. Alliance should carefully monitor CMS' systems, RPC FDRs, Transaction Reply Reports (TRRs) and Monthly Membership Reports (MMRs) to ensure that all requested transactions have been processed.

D. Alliance must resubmit transactions to the RPC within 45 days of the issuance of the FDR if the original request was not processed as requested.

E. If Alliance believes that a transaction has not been processed within the 35-day timeframe, they should contact the RPC's Client Services Department to make a Transaction Inquiry. Instructions for transaction inquiries can be found in the section titled *Transaction Inquiries by Organization***.** (Attachment I)

Submissions that meet all the requirements explained in this SOP should be sent via a "Submission Package" in the Electronic Retroactive Processing Transmission (eRPT) system (https://portal.cms.gov/) .
Alliance should ensure that all Submission Packages sent to the RPC have been reviewed for accuracy and completeness. Any packages received by the RPC that do not adhere to the guidelines in this SOP will not be processed.

Submission Packaging Instructions:

a. Cover Letter

A cover letter must accompany all transactions submitted to the RPC. This letter should, at a minimum, contain the applicable contract number(s) (i.e., H#, S#, R#, E#) and a Certification Statement signed by an official representing the Organization. Below is an example of appropriate language for the Certification Statement:

*"I certify, as an authorized representative of the Organization, that the information submitted to the Retroactive Processing Contractor on <**date**> is accurate and complete. Supporting documentation is being maintained at the Organization for each request."*

Alliance must retain the original supporting documentation for the requested transactions as they may be required to produce it during a CMS audit.

The cover letter should also include any special circumstances or instructions Alliance believes may be necessary to assist the RPC in processing the submitted transactions timely and accurately. For example, if the submission contains transactions that require RO Approval or special handling instructions from an Account Manager, this information should be stated in the cover letter for the RPC to immediately identify.

b. Submission Spreadsheet

Retroactive transactions must be listed by Alliance on the Excel submission spreadsheet template. The completed spreadsheet must be saved in an "xls" or an "xlsx" file format and sent via a "Submission Package" in order to be uploaded into the eRPT system (https://portal.cms.gov/) .

The submission spreadsheet template is available on the RPC's website at (https://www.reedassociates.org/rpc-submission-toolkit/).

The formatting of the submission spreadsheet template, including tab names, column headers, column order, cell placement and cell formatting, must not be changed or altered in any way, or the spreadsheet may not import properly. Additionally, Alliance should note that there are drop-down menus for several of the columns which require very specific responses.

If Alliance automates the spreadsheet completion process, the RPC suggests that you review all spreadsheet components carefully (especially the required responses for the drop-down menus) to avoid errors in importing the spreadsheets and reviewing the transactions. The RPC cannot import transactions that do not meet the formatting requirements of the submission spreadsheet.

Specific instructions for how to complete each column of the spreadsheet are included on the spreadsheet itself. Basic instructions are listed below the column headers.

Please utilize the following table to provide the RPC with the correct information in the *Dual Eligible Status* and *Institutional Status* columns as it relates to the LIS status level being requested:

Dual Eligible Status (Medicaid Status Level)	Institutional or HCBS Status	LIS Level	Co-Payment Amount
Partial	No/Unknown	Level 1	High
Full	No/Unknown	Level 2	Low
Full	Yes	Level 3	None

Table 1 - LIS Deeming Copayment Levels

Please contact the RPC's Client Services Department with additional questions on how to complete the spreadsheet.

c. Documentation Required

- Retroactive transactions covered by this SOP are not subject to the Enrollment Data Validation review process.

- All Organizations must electronically submit the supporting documentation for each transaction covered by this SOP to the RPC as PDF files via a "Submission Package" in the eRPT system (https://portal.cms.gov/) .

- Alliance should only submit documentation that is required for processing. Documentation which has not been approved by CMS will not facilitate processing.

- In order for the electronic documentation to be accurately matched to the request listed on the submission spreadsheet, the documentation for each request must be sent in individual PDF files. Each request must include the RPC LIS Documentation Worksheet along with the specific documents required for manual LIS Deeming updates. The worksheet can be found on the RPC's website at https://www.reedassociates.org/rpc-submission-toolkit/.

Enrollees with Best Available Evidence (BAE) Documentation

All documents listed below are valid for the purpose of establishing the correct cost-sharing and effective date for individuals who should be deemed eligible for LIS. They are the only documents permissible for submission to the Retroactive Processing Contractor (Reed) for an LIS deeming update.

Level 1 Partial/No

Acceptable BAE pertaining to Level 1 P/N (CMS Chapter 13 70.5.2)

- A copy of the beneficiary's Medicaid card that includes the beneficiary's name and eligibility date during a month after June of the previous calendar year
- A copy of a state document that confirms active Medicaid status during a month after June of the previous calendar year
- A print-out from the State electronic enrollment file showing Medicaid status during a month after June of the previous calendar year
- A screen print from the State's Medicaid systems showing Medicaid status during a month after June of the previous calendar year
- Other documentation provided by the state showing Medicaid status during a month after June of the previous calendar year
- A letter from the Social Security Administration (SSA) showing that the individual receives Supplemental Security Income (SSI) (CMS Chapter 13 70.6, 70.6.1, 70.6.2)
- An application filed by Deemed Eligible confirming the beneficiary is "automatically eligible for extra help." (SSA publication HI03094.605)
- Alliance may also prepare a report of contact as evidence of a beneficiary's status as a full benefit dual eligible individual, institutionalized individual, and/or Home & Community Based Services (HBCS) recipient when Alliance makes a verification call to the State Medicaid Agency. The report of contact must include the date of the verification call and the name, title, and telephone number of the state staff person who verified the Medicaid status for a month after June of the previous calendar year.
- If for some reason none of the above is available, Alliance can submit a CTM (Complaint Tracking Module). If that is submitted, proceed to that section for processing instructions.

To substantiate P/N LIS Level 1
BAE Documentation must reflect one or all of bullet's a-c (below) during a month after June of the previous calendar year (as defined by CMS Chapter 13 70.5.2):

a) Indicates Medicaid benefits as Limited; and/or
b) Member is eligible for SSI; and/or
c) Medicare Savings Program (QMB, SLMB, QI/QI1, QDWI)

Level 2 Full/No

Acceptable BAE pertaining to Level 2 F/N (CMS Chapter 13 70.5.2)

- A copy of the beneficiary's Medicaid card that includes the beneficiary's name and eligibility date for a month after June of the previous calendar year
- A copy of a state document that confirms active Medicaid status during a month after June of the previous calendar year
- A print-out from the State electronic enrollment file showing Medicaid status during a month after June of the previous calendar year
- A screen print from the State's Medicaid systems showing Medicaid status during a month after June of the previous calendar year
- Other documentation provided by the state showing Medicaid status during a month after June of the previous calendar year
- A letter from SSA showing that the individual receives SSI (CMS Chapter 13 70.6, 70.6.1, 70.6.2)
- An application filed by Deemed Eligible confirming the beneficiary is "automatically eligible for extra help." (SSA publication HI03094.605)
- Alliance may also prepare a report of contact as evidence of a beneficiary's status as a full benefit dual eligible individual, institutionalized individual, and/or HCBS recipient when the sponsor makes a verification call to the State Medicaid Agency. The report of contact must include the date of the verification call and the name, title, and telephone number of the state staff person who verified the Medicaid status for a month after June of the previous calendar year.
- If for some reason none of the above is available, sponsors/plans can submit a CTM. If that is submitted, proceed to that section for processing instructions.

To substantiate F/N Level 2 BAE Documentation must demonstrate Full Comprehensive Medicaid Eligibility during a month after June of the previous calendar year (as defined by CMS Chapter 13 70.5.2).

NOTE: QMB PLUS and SLMB PLUS are Full Comprehensive Medicaid, therefore LIS 2.

LIS 3 Full / Yes

Acceptable BAE pertaining to Level 3 F/Y (CMS Chapter 13 70.5.2)

(For LIS Level 3 Full/Yes, the beneficiary must be Full Comprehensive Medicaid (Full) AND Institutionalized or receiving Home and Community Based Services (Yes)

- Remittance from the facility showing Medicaid payment on behalf of the beneficiary for a full calendar month after June of the previous calendar year.
- Copy of a state document that confirms Medicaid payment on behalf of the individual to the facility for a full calendar month after June of the previous calendar year

- Screen print from the State's Medicaid systems showing the individual's institutional status based on at least a full calendar month stay for Medicaid payment purposes for a month after June of the previous calendar year.
- Effective as of a date specified by the Secretary, but no earlier than January 1, 2017, a copy of:
    - State-issued Notice of Action, Notice of Determination, or Notice of Enrollment that includes the beneficiary's name and HCBS eligibility date during a month after June of the previous calendar year;
    - State -approved HCBS Service Plan that includes the beneficiary's name and effective date beginning a month after June of the previous calendar year;
    - State-issued prior authorization approval letter for HCBS that includes the beneficiary's name and effective date beginning during a month after June of the previous calendar year;
    - Other documentation provided by the State showing HCBS eligibility status during a month after June of the previous calendar year; or,
    - A state-issued document, such as remittance advice, confirming payment for HCBS, including the beneficiary's name and the dates of HCBS.
- State-issued document, such as remittance advice, confirming payment for HCBS, including the beneficiary's name and the dates of HCBS. The sponsor may also prepare a report of contact as evidence of a beneficiary's status as a full benefit dual eligible individual, institutionalized individual, and/or HCBS recipient when Alliance makes a verification call to the State Medicaid Agency. The report of contact must include the date of the verification call and the name, title, and telephone number of the state staff person who verified the Medicaid status for a month after June of the previous calendar year.

- If for some reason none of the above is available, sponsors/plans can submit a CTM. If that is submitted, proceed to that section for processing instructions.

Complaint Tracking Module (CMS, Chapter 13 70.5.3)

When BAE is not available the CTM (Complaint Tracking Module) is another method that may be used to substantiate a Subsidy Level Request on behalf of the beneficiary. To provide expedited service on behalf of Medicare beneficiaries. Alliance will enter BAE assistance requests into the CTM on behalf of the enrollee.

CMS reviews and completes a resolution section indicating LIS level and effective dates. After receiving the CTM case, CMS will attempt to confirm with the appropriate state Medicaid agency whether the beneficiary is eligible for LIS. The CMS Account Manager reports findings to the plan. Alliance submits those findings to RPC so that appropriate subsidy levels can be updated in ELMO.

Submitting to the CTM

1. The plan will record a CTM entry.
Lead: CMS
Category: Premiums and Costs
Subcategory: Beneficiary needs assistance with acquiring Medicaid eligibility information (EX)

Absent unusual circumstances, plans are to enter cases within one business day of being notified that the beneficiary claims to be subsidy eligible but cannot provide the plan with acceptable Best Available Evidence (BAE).
When entering, include all the following information in the "Complaint Summary":
• Medicare Beneficiary Identifier (MBI)
• Beneficiary's First and Last Name
• Beneficiary's Address
• Beneficiary's Date of Birth
• Issue Level: Immediate Need, Urgent, No Issue Level.
• Any additional information germane to the beneficiary's matter.

These cases will be reflected as "1.50" in the plan data extract.
2. After receiving the CTM case, CMS will:

a. Attempt to confirm with the appropriate state Medicaid agency whether the beneficiary is eligible for the low-income subsidy (LIS).

b. If CMS can confirm, the case will be changed to "Plan Lead" and re-categorized as "Premiums and Costs - Beneficiary needs assistance with acquiring Medicaid eligibility
information (EX)" category/subcategory for plan review/action. These cases will be reflected as "2.50" in the plan data extract. Additional information will be placed in the "Comments" section of the case and will include as applicable:

• Resolution
• Start of Medicaid/ Medicaid Institutional Status (MM/CCYY)
• Dual Eligible Status (Full/Partial)
• Institutional Status (Yes/No/ Unknown)
• LIS Co-Pay Level
• Any additional information germane to the beneficiary's matter.

c. If CMS cannot confirm, the case will be changed to "Plan Lead" and re-categorized to 2.50. The "comments section" will note the following: CMS has been unable to confirm LIS status with Name/State. Refer the beneficiary to Medicaid.gov and educate them on how to navigate the website to select About Us > Get Help with Medicaid & CHIP > Select State in which they reside. Then, they can obtain information on eligibility, enrollment, or check the status of an existing application.

3. When updates are provided, the plan will ensure its internal systems to reflect LIS status if appropriate and submit a request for correction to CMS' contractor in accordance with the procedures outlined in Chapter 13, Section 70.5.4 of the CMS Prescription Drug Benefit Manual. If CMS determines the beneficiary ineligible for LIS, no system updates are to be initiated.

4. As soon as the plan receives confirmation from CMS that a beneficiary is subsidy eligible (consistent with the direction in Chapter 13, Section 70.5.3 of the CMS Prescription Drug Benefit Manual), plans are to:

a. **Provide Drug Coverage at Correct Cost-Share:** Must immediately provide the beneficiary access to covered Part D drugs at a reduced cost-sharing level no greater than the higher of the LIS cost-sharing levels for full subsidy eligibles, or at zero cost-sharing if CMS also verifies the beneficiary's institutional status.

b. **Contact Beneficiary:** Attempt to notify the beneficiary of the results of the CMS review within one business day of receiving those results. If a plan is unable to reach the beneficiary as a result of this initial attempt, it must attempt to notify the beneficiary until it succeeds or until it has attempted to do so a total of four times. The fourth attempt, if necessary, shall be in writing, using one of two CMS Model Notices listed in Chapter 13 of the CMS Prescription Drug Benefit Manual.

i. If a request for a subsidy was made on the beneficiary's behalf by an advocate or authorized representative, it shall be sufficient for the plan to contact that advocate or representative. If, however, the only request made on the beneficiary's behalf was by a pharmacist, the plan must also contact the

beneficiary directly. After informing the beneficiary, or their representative, of the outcome, the plan is to close the case. After informing the beneficiary, or their representative, of the outcome, the plan is to close the case.

c. **Notice of Eligibility:** If CMS determines that the beneficiary is LIS eligible, plans are to send the "Determination of LIS Eligibility" Model Notice provided as Attachment A. If CMS determines that the beneficiary is not LIS eligible, or is unable to confirm the beneficiary's LIS status, plans are to use the "Determination of LIS Ineligibility" Model Notice provided as Attachment B. See the February 17, 2017 HPMS Memorandum, "Best Available Evidence Process Update" for attachments.

d. **Disagreement with Decision:** Should the beneficiary disagree with the outcome, the plan should submit a Plan Request to refer the matter back to CMS with appropriate CTM notes. A CMS caseworker will attempt to contact the beneficiary, affirm the outcome, and close the case.

NOTE:

- This process is not intended to serve as a general alternative to the subsidy eligibility confirmation process. Thus, it does not permit pharmacies or any other parties to send beneficiary records directly to the plan for research in the absence of a request for assistance from the beneficiary (or other individual on the beneficiary's behalf) or in lieu of making reasonable efforts to acquire the documentation from, or on behalf of, the beneficiary.

- In rare circumstances, a beneficiary's record may be incorrect in CMS' systems after they have applied for and been awarded the Part D extra help through the Social Security Administration. In these instances, make certain the beneficiary is able to access their Part D plan benefit. You may use this process to advise CMS when our systems need to be updated since corrections cannot be submitted to the RPC for processing.

In order to process the deeming request as submitted, RPC must receive documentation that includes all of the necessary elements of a CTM as listed below. These elements must support the request in order to be processed as requested.

Necessary Elements of a CTM

- Complaint Tracking ID#
- CMS Account Manager name
- Beneficiary
- Start of Medicaid/Medicaid Institutional Status (Effective Date)
- Dual Eligible Status (Full/Partial)
- Institutional Status (Yes/No/Unknown)
- LIS Co-Pay Level

RPC Importing Transactions & Error Reports

The RPC will import the transactions into the tracking system and update the status of the Submission Package in eRPT to "In Process" within five (5) calendar days. Any errors that are noted during the importation process will also be communicated to Alliiance via eRPT as a "Response Document" at that time.

The status of the Submission Package in eRPT and the error report(s) uploaded to the Submission Package should be carefully monitored by Alliance to ensure that all of the transactions are received by the RPC and imported properly.

A Final Disposition Report (FDR) will not be issued for the transactions that receive an error message during the importation process. Transactions that cause an error message and are subsequently resubmitted to the RPC are not considered to be resubmissions because they were never processed due to importation errors.

RPC Issuance of Final Disposition Reports (FDRs)

Valid retroactive transactions will be processed by the contractor within 35 days of receipt. If the RPC determines that it *should* and *can* make the requested changes, the retroactive change will be made in CMS' systems. Payment adjustments will be made accordingly as CMS processes the changes. Note that payment adjustments are not directly handled by the RPC.

After processing the adjustments, the RPC will provide Alliance with a Final Disposition Report (FDR) via eRPT to the Organization. The FDR communicates the disposition of the requests to Alliance. The disposition codes used by the RPC are available on the RPC's website (https://www.reedassociates.org/rpc-submission-toolkit/).

Alliance must have ongoing membership reconciliation processes that include data comparisons of Alliance information to all relevant CMS/RPC files and reports including Final Disposition Reports (FDRs), Transaction Reply Reports (TRRs) and Monthly Membership Reports (MMRs).

If the request cannot be processed for any reason, the materials submitted to the RPC will not be returned to Alliance; however, the disposition code provided by the RPC on the FDR will indicate why the submission, in whole or in part, could not be completed. The disposition code descriptions should be read very carefully to ensure that each transaction can be properly resubmitted and processed by the RPC. Instructions for resubmissions are detailed in the section *Resubmissions by Organizations*.

If Alliance has concerns or questions regarding the determination made by the RPC, they should first contact the RPC's Client Services Department by using the Transaction Inquiry form described in the section Transaction Inquiries by Organization (Attachment 1). If a transaction is found to have been processed incorrectly by the RPC, then Reed's Quality Assurance Department will work with the RPC Processing team to correct the transaction. For transactions or other matters that cannot be resolved by the RPC, Alliance should contact their local Account Manager for further assistance.

Resubmissions by Alliance

Following the issuance of the Final Disposition Report (FDR), Alliance may determine (by reviewing the disposition codes provided on the FDRs) that transactions were not processed by the RPC. Once the error is identified and resolved, Alliance may file a resubmission request for previously denied retroactive transactions.

Please note a FDR is not issued for records that are not successfully imported by the RPC. Therefore, the second submission of those transactions to the RPC would not be considered a resubmission transaction. Alliance should submit those transactions following the normal procedures since they were never originally entered into the system as a valid transaction.

In general, all the steps outlined in section A of the *Instructions for Submission to the RPC* must be followed for a resubmission (including all documentation which supports the request). Additional requirements for resubmissions to be imported and processed are listed below.

A. Resubmission transactions must be sent to the RPC within 45 days of receiving the original FDR for the request. It is highly recommended that Alliance reconcile the FDRs to CMS' Systems prior to resubmitting transactions. Alliance can then submit a master submission for all discrepant retroactive transactions.
B. Resubmission transactions must be listed on the Excel submission spreadsheet template following the standard submission process described in Section A.

C. On the documentation worksheet, Alliance should clearly state that the transaction is a resubmission and is not a duplicate transaction. Not stating this in the documentation worksheet could delay or negate the RPC's review of the requested transaction.

D. Documentation requirements for resubmissions are identical to the documentation requirements detailed above; however, if a transaction was not processed due to a missing document, Alliance must submit the documentation from the first request plus the requested documentation to ensure that the transaction is processed.

If the resubmission has been denied multiple times, it is strongly recommended that the Alliance contact the responsible Account Manager for additional guidance and/or a case- specific approval.

Transaction Inquiries by Organization

To follow up on specific previously submitted adjustment transactions, an inquiry may be submitted by email to clientservices@reedassociates.org, via "Transaction Inquiry" in eRPT, or telephone to our Client Services Department: (402) 315-3660. For inquiries sent via eRPT, Alliance is advised to complete the RPC Transaction Inquiry Excel template as instructed below.

Note: Alliance should not submit duplicate transactions unless the RPC specifically requests that duplicate information be submitted. All other general processing inquiries that are not case specific can be made via e-mail or by phone.

RPC's Client Services Department:

Reed & Associates, CPAs – CMS RPC
Attn: Client Services Department
11717 Burt Street, Suite 103
Omaha, NE 68154
Phone: (402) 315-3660
Email: clientservices@reedassociates.org

Furthermore, all system issues and questions regarding the eRPT application should be forwarded to the MAPD Help Desk (email: MAPDHelp@cms.hhs.gov; phone: 1-800-927-8069). Although the RPC relies heavily on the eRPT application, its development and maintenance is managed by another CMS contractor. Therefore, the RPC can only provide limited support regarding the application.

Note: Alliance member services, pharmacy services and/or PBM may carry out needed support and tasks included in this policy.

DEFINITIONS / ACRONYMS

BAE - Best Available Evidence
CMS - The Centers for Medicare and Medicaid
CTM - complaint tracking Module
eRPT – Electronic Retroactive Processing Transmission
FDR- Final Disposition Report
LIS - Low-Income Subsidy
MARx -Medicare Advantage and Prescription Drug system
MMR – Monthly Membership Report
RPC – Retroactive Processing contractor
TRC -Transaction Reply Code
TRR - Transaction Reply Report

AFFECTED DEPARTMENTS/PARTIES

Pharmacy PBM (PerformRx)
Pharmacy Services
Member Services

RELATED POLICIES AND PROCEDURES

None

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

New

REFERENCES

Medicare Prescription Drug Benefit Manual Chapter 13 - Premium and Cost-Sharing Subsidies for Low-Income Individuals, October 1, 2018
Reed & Associates, CPA: CMS-Retroactive Enrollment & Payment Validation, Retroactive Processing Contractor RPC, March 1, 2021

[List references such as regulatory citations]

MONITORING

Alliance Pharmacy Department Staff will include results of ongoing monitoring in monthly Delegated Function Oversight/Monitoring statistics.

Collaboration

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Attachment I

To follow up on specific previously submitted adjustment transactions, an inquiry may be submitted by email to clientservices@reedassociates.org, via "Transaction Inquiry" in eRPT, or telephone to our Client Services Department: (402) 315-3660. For inquiries sent via eRPT, Alliance is advised to complete the RPC Transaction Inquiry Excel template as instructed below.

Completing the RPC Transaction Inquiry Excel Template:

A. Input the following information associated with the submitted transaction:
   a. Inquiry Type (select the type of inquiry for this transaction)
   b. Explanation (If you selected "Question on Rejection" or "Other," please include a brief explanation on your inquiry)
   c. Beneficiary ID (beneficiary's Beneficiary ID)
   d. First Name (beneficiary's first name)
   e. Last Name (beneficiary's last name)
   f. Contract Number (contract number associated with the transaction)
   g. PBP Number (if appropriate)
   h. Transaction type (e.g. Enrollment, LIS, Reinstatement, etc...)
   i. Effective Date
   j. RPC Receipt Date (the day eRPT provided the notification the RPC downloaded the package)
   k. The eRPT Package ID for the Submission Package

B Create a Transaction Inquiry package in eRPT, upload the completed RPC Transaction Inquiry, and select "Submit" to send it to the RPC for review.

2	Organization Name					Contact Name:			
3	Mailing Address					Phone #:			
4	City, State, Zip Code					E-Mail Address:			
6	Beneficiary ID	First Name	Last Name	Contract #	PBP Number	Transaction Type	Effective Date	RPC Receipt Date	Package ID
7	*Beneficiary's MBI*	*Beneficiary's First Name*	*Beneficiary's Last Name*	*Contract # associated with transaction*	*If applicable*	*Choose from list. (e.g. Enrollment, LIS, Reinstatement, etc.)*	*Effective Date*	*Date RPC received transaction*	*From the Initial eRPT Submission Package*

The RPC Transaction Inquiry Template is available on the RPC's website (http://www.reedassociates.org/) in the **RPC Client Services** section.

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ALAMEDA Alliance FOR HEALTH

Health care you can count on.
Service you can trust.

POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-022
Policy Name	Medicare Part D Complaint Tracking Module (CTM)
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	DSNP
Effective Date	TBD
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

The Complaints Tracking Module is an electronic system maintained by CMS to record and track complaints submitted to CMS about Medicare health and drug plans from beneficiaries and others. Alameda Alliance for Health (Alliance) will respond to complaints uploaded by CMS, resolve or respond to complaints in accordance with federal guidance.

PROCEDURE

Alliance is strongly committed to the timely resolution of complaints received through CMS CTM. Alliance is also committed to regular communication with CMS staff to appropriately resolve individual complaints and engage in broader discussions designed to address root causes of complaints against Alliance.

PROCESS

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1.0 **Daily Checking of CTM**

1.1 Compliance Module (will be checked twice a day – once in the morning and once in the afternoon):

a. Log onto CMS Health Plan Management System (HPMS)
b. From the HPMS Home Page, select "Monitoring – Complaints Tracking"
c. From the Complaints Tracking Home Page, select "My Open Complaints"
d. For each open complaint, Compliance shall conduct daily checks for new CMS case worker notes and attachments.
e. Compliance will document details, such as the date and time of each check, on the CTM Checking Log (Excel file).

2.0 **Logging Complaints Received Through CTM**

2.1 For each complaint received through CTM, Compliance shall document the complaint in the following internal logs:

2.1.1 CTM General Log (Excel file)

a. Complainant/Enrollee's name
    - Compliance will log the name of the complainant. If the complainant is not an Alliance member, Compliance will log the complainant and the enrollee name(s).
b. Compliance will verify the contract ID
c. Compliance will view attachments and add additional supporting documents to the complaint in CTM by going to the "Intake Information" screen (see "CTM Plan User Manual" on HPMS for more details).

2.1.2 CTM complaint issue level

a. At least 95% of Immediate Need Complaints must be resolved within 2 calendar days.
b. At least 95% of Urgent Complaints must be resolved within 7 calendar days.
c. At least 95% of No Issue Level Complaints must be resolved within 30 calendar days.
d. CMS reserves the right to classify any complaint that does not fit the definitions for Immediate Need or Urgent.

2.1.3 Date complaint received by Alliance

a. Compliance will log the date in which the complaint was added to the CTM.

2.1.4 Date complaint closed

a. Compliance will log the date in which the complaint was closed by CMS. v. Complaint ID number
b. Compliance will log the complaint ID number as given by CMS.

2.1.5 Complaint type

a. Compliance will log the complaint type as categorized by CMS.

2.1.6 Complaint summary

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a. Compliance will log the initial summary of the complaint as provided by CMS. Additional information may be added as needed to understand the nature of the complaint, but the resolution will not affect the contents of the initial summary.

b. Alliance will verify any prior complaints from enrollee and if the prior complaint(s) is a duplicate and has already been resolved, Alliance should verify the enrollee was informed of the initial resolution. If the enrollee acknowledges the previous resolution was communicated to them, compliance should close the open complaint and note it was a repeat complaint in the resolution notes.

- If the prior complaint(s) are still open, but Alliance is working to resolve the issue or Alliance has not yet begun to investigate the issue, the plan should close the older complaint and reference the CTM number of the new complaint in the resolution notes.

- If the first complaint is a sufficiently distinct issue than the second complaint, Alliance is to keep both complaints open until they are resolved.

2.1.7 Complaint resolution

a. Compliance will log all communications between internal departments, members, providers, and CMS case workers as the communication occurs.

b. Compliance will log any casework notes and the complaint resolution with a dated timestamp from the HPMS website.

2.2 Annual CTM Tracking and Trending Log (Excel file)

2.3 Compliance will download and save a copy of the CTM complaint to the complainant's account. (determine Alliance process)

3.0 **Notifying Internal Departments**

3.1 For each complaint received from CTM, Compliance will send out a notification via email to all relevant internal departments, notifying in subject line: CMS CTM and attaching a copy of the CTM. The email shall document:

a. Complainant/Member's name
b. Complaint category & sub-category
c. Complaint issue level
d. Complaint resolution deadline
e. Complaint summary
f. Department specific instructions on resolving the complaint

3.2 Compliance will cc: Member Services to contact enrollee and let them know that Alliance has received their complaint and is working to resolve the issue. Any additional information received during the call with the enrollee should be sent to the Compliance contact and documented in the enrollee's call history.

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4.0 **CTM Scenarios/Issues**

4.1 Please refer to the most recent CTM Plan Standard Operational Procedures (SOP) guide released by CMS for a list of possible CTM scenarios/issues and steps to take for resolution. The SOP can be located at: https://www.hhs.gov/guidance/document/ctm-plan-sop.

5,0 **Complaint Resolution**

5.1 Upon resolution and before the complaint deadline, Compliance shall draft a complaint resolution, detailing steps taken by Alliance to resolve the complaint.

5.2 Compliance will upload the complaint resolution and supporting documentation to HPMS. Please refer to the most recent CTM SOP for suggested examples of Plan CTM Resolution Notes.

6.0 **Notifying Internal Departments of Complaint Resolution**

6.1 Once the complaint is closed, Compliance shall notify all relevant internal departments via email. The email will inform the departments that the complaint has been closed and Compliance will provide a short summary of the complaint resolution.

6.2 Compliance will also ask Member Services to contact the enrollee to notify him or her of the resolution, if applicable.

For general questions about handling a CTM complaint and casework operating procedures, Alliance will consult the SOP or contact the HPMS Help Desk at 1-800-220-2028 or HPMS@cms.hhs.gov.

For technical data questions related to the Alliance's CTM performance, Alliance will contact ctm@cms.hhs.gov.

DEFINITIONS / ACRONYMS

CTM- Complaint Tracking Module
HPMS - Health Plan Management System
SOP - Standard Operating Procedure

AFFECTED DEPARTMENTS/PARTIES

Member Services/Call Center
Pharmacy Services

RELATED POLICIES AND PROCEDURES

None

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RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

New

REFERENCES

HPMS memo: Medicare Advantage & Part D Program Complaints Tracking Module User's Manual (Plan Version, May 15, 2006

HPMS memo: Updated Complaints Tracking Module (CTM) Standard Operating Procedures, February 24,2017

HPMS memo: Complaints Tracking Module (CTM) Plan Standard Operational Procedures (SOP) (Effective – May 30, 2019)

MONITORING

Alliance Pharmacy Department Staff will include results of ongoing monitoring in monthly Delegated Function Oversight/Monitoring statistics.

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ALAMEDA Alliance FOR HEALTH

Health care you can count on.
Service you can trust.

POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-D-025
Policy Name	Appointment of Representative (AOR)
Department Name	Compliance
Department Officer	Compliance Officer
Policy Owner	Compliance Officer
Line(s) of Business	Medicare Advantage
Effective Date	[Original date policy was approved by committee - MM/DD/YYYY – TBD for new policies]
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	TBD
Administrative Oversight Committee Approval Date	TBD

POLICY STATEMENT

Alameda Alliance for Health (Alliance) is committed to maintaining our enrollees Personal Health Information (PHI) and supporting the Standards for Privacy of Individually Identifiable Health Information (Privacy Rule) by requiring the Appointment of Representative (AOR) form or similar document to be completed and filed with Alliance for access to enrollee information.

PROCEDURE

The representative has all the rights and responsibilities of an enrollee including filing a grievance, obtaining a coverage request, or in dealing with any levels of the appeals process.

If an enrollee has identified a representative, all notices or other correspondence that must be sent to the enrollee per the regulations at 42 CFR Part 422 or 423 Subpart M must be sent to

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the enrollee's representative instead of to the enrollee. Alliance will send notices or correspondence to both the representative and enrollee (but are not required).

PROCESS

1. Who Can Act or be Appointed as a Representative and Requirement for Representation

1.1 Any individual appointed by the enrollee (e.g., relative friend, advocate attorney) The enrollee may submit Form CMS-1696, Appointment of Representative (AOR) or an equivalent written notice (hereinafter, collectively referred to as a representative form).

1.2 An individual authorized under state or other applicable law. This could include, but is not limited to:

- Court appointed guardian
- Individual with durable power of attorney
- A health care proxy
- A person designated under a health care consent statute
- Executor of an estate

1.3 Authorized individual must produce appropriate legal papers supporting his or her status under state or other applicable law. A representative form is not required.

2. Appointment of Representative (AOR) Form or Equivalent Written Notice

2.1 Alliance is prohibited from requiring enrollees to use a specific form to appoint a representative. The OMB-approved Form CMS-1696 (Attachment I) is preferred but not required. Alliance will not require more information in a written notice than what is provided with the AOR form. Written notice needs to include:

a. Name, address and telephone numbers of the enrollee and the individual being appointed.
b. Enrollee's Medicare Beneficiary Identifier (MBI) or Alliance's member identification number.
c. Appointed representative's professional status or relationship to the enrollee.
d. Explanation of the purpose and scope of the representation
e. A statement that the enrollee is authorizing the representative to act on their behalf for the claim(s) at issue, and a statement authorizing disclosure of individually identifying information to the representative.
f. Statement from representative accepting the appointment,
g. Is signed and dated by the enrollee and representative.

2.2 An AOR or written notice is valid for one year from the dated signatures, unless revoked prior to that date. A new AOR or written notice will need to be issued annually if the enrollee desires the representation to continue. If a grievance, coverage determination or appeal is initiated during the valid date of a AOR or written notice, and the AOR or notice expire before the issue is resolved, the representation will remain valid until the case is closed.

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2.3 If the enrollee limited the scope of the AOR or written notice by specifying MA or Part D only, an additional AOR or written notice will need to be issued by the enrollee to appoint a representative to represent the opposing benefits.

3.0 Missing or Defective Representative Form

3.1 MA plans and Part D plans are not required to process grievances when the person or entity making the grievance is not permitted by 42 CFR §§ 422.564 or 423.564. When a request for a grievance, initial determination, or level 1 appeal is filed by a person claiming to be a representative, but the party does not provide the valid representative documentation to show that the individual is authorized to act on the enrollee's behalf, Alliance should:

a. For expedited requests, follow procedures to ensure that expedited requests are not inappropriately delayed.

b. Inform the enrollee and purported representative, in writing, that the grievance, coverage request, or appeal is not valid until documentation is provided.

c. Make and document Alliance's reasonable efforts to secure the necessary representative documentation.

d. Alliance cannot issue a decision until or unless documentation of representation is received.

e. Alliance is not required to initiate the review until documentation is received but may begin the review pending documentation. The timeframe for a coverage request or appeal does not begin until documentation of representation is received.

f. If documentation is not received by the end of the appliable timeframe and any extension granted, Alliance must apply the following:

- Dismiss the request
- Notify enrollee (and appointed representative and asserting representative) in writing by mail or other communication the dismissal notice must include:
  - reason for dismissal
  - the right to request that the plan vacate the dismissal action; and
  - the right to request review of the dismissal. The notice should also explain how the invalid request can be cured and that the request will be processed if the enrollee or representative submits a properly executed form.

DEFINITIONS / ACRONYMS

AOR – Appointment of Representation
MBI – Medicare Beneficiary Identifier
OMB – Office of Management and Budget

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PHI – Personal Health Information

AFFECTED DEPARTMENTS/PARTIES

Pharmacy
Medical
Member Services
Appeals and Grievance

RELATED POLICIES AND PROCEDURES

[List related Policies]

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

[List related documents]

REVISION HISTORY

[List revision dates starting with original effective date – this is the date that revisions were approved at AOC, and is a running list of approval dates from AOC]

REFERENCES

Part C & D Enrollee Grievances, Organization/Coverage Determinations, ad Appeals Guidance, Section 20

MONITORING

Alliance Pharmacy Department Staff will include results of ongoing monitoring in monthly Delegated Function Oversight/Monitoring statistics.

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Attachment I

Department of Health and Human Services
Centers for Medicare & Medicaid Services

Form Approved
OMB No. 0938-0950
Expires: 08/31/2025

Appointment of Representative

Use this form to appoint a representative to act on your behalf for your claim, appeal, grievance or request. By signing this form and appointing this representative, you agree that the representative will be the main contact and have authority to make requests, present evidence, get information, and receive all communication about your action. This person may see your personal medical information. **All fields in Sections 1 and 2 are required unless marked optional.**

Section 1: Information about the person appointing the representative

This section must be completed by the patient, provider or other person appointing a representative.

Name	Medicare Number or National Provider Identifier
Mailing address	Phone number (with area code) ( ) -
City	State / ZIP code
Email (optional)	Fax (optional) ( ) -
Signature	Date signed (mm/dd/yyyy) / /

Section 2: Information about the representative

This section must be completed by the representative.

Representative name

Professional status or relationship to the person in Section 1 (attorney, relative, etc.)

Mailing address	Phone number (with area code) ( ) -
City	State / ZIP code
Email (optional)	Fax (optional) ( ) -

By signing below, you agree to act as a representative and certify that you haven't been disqualified, suspended, or prohibited from practice before the Department of Health and Human Services (HHS) or otherwise disqualified from acting as a representative. Any fee to be charged for acting as a representative may be subject to review and approval by the Secretary. If you're charging a fee, go to instructions on page 2.

Signature	Date signed (mm/dd/yyyy) / /

Representative must complete the sections below, if applicable (go to instructions on page 2)

Section 3: Waiver of fee for representation

Providers and suppliers who furnished the items or services at issue can't charge a fee for representation and must sign below to waive their fee. Representatives who choose to waive their fee for representation must also sign below.

I waive my right to charge and collect a fee for representing the person in Section 1 before the Secretary of HHS.

Signature	Date signed (mm/dd/yyyy) / /

Section 4: Waiver of payment for items or services at issue

If you're a provider or supplier and you furnished items or services to the patient you're representing, if the appeal involves a question of whether you or the patient didn't know, or couldn't reasonably be expected to know, that Medicare wouldn't cover the items or services.

I waive my right to collect payment from the patient for the items or services at issue in this appeal if a determination of liability under §1879(a)(2) of the Act is made.

Signature	Date signed (mm/dd/yyyy) / /

Form CMS-1696 (09/24) 1

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Alameda Alliance for Health
1240 South Loop Road
Alameda, CA 94502

PHARMACY & THERAPEUTICS COMMITTEE

Record of Committee Meeting Minutes

Tuesday, March 18, 2025 | 5:00pm – 7:00pm

Status	Voting Committee Members	Organization	Initials	Officer / Notes
P	Donna Carey, MD	Chief Medical Officer-Alliance	DC	Chairman
P	Nora Tomassian, Pharm D	Interim Director of Pharmacy Services	NT	Co-Chair
P	Rahel Negash, Pharm D	Pharmacy Services Supervisor – Alliance	RN	
P	Aaron Basrai, PharmD	Haller's Pharmacy	AB	BOG
P	Paul Bayard, MD	La Clinica de la Raza (CHCN)	PB	
P	Ivan Lee, MD	Private Practice	IL	
P	Bao Dao, MD	Epic Care	BD	
P	Charles Raynor, PharmD	Alameda County Behavioral Health Dept.	CR	

P=Present; PH=Call-in; A=Absent; CMO = Chief Medical Officer; DOPS=Director of Pharmacy Services; BOG = Board of Governors Representative

Status	Regular Guests	Organization	Initials	Role / Department
P	Iryna Makukh	PerformRx	IM	Pharmacy Formulary Management.
P	Liza Rosendale	PerformRx	LR	Clinical Program Manager
P	Pat DeHoratius	PerformRx	PD	Manager Formulary/DUR
P	Barrie Cheung	PerformRx	BC	Regional Pharmacy Director
P	Ramon Tran Tang, PharmD	Alameda Alliance	RT	Clinical Pharmacist
P	Jefferey Bencini, Pharm D	Alameda Alliance	JB	Clinical Pharmacist
P	Timothy Tong, Pharm D	Alameda Alliance	TT	Clinical Pharmacist
A	Beverly Juan, MD	Alameda Alliance	BJ	Medical Director
A	Darryl Crowder	Alameda Alliance	DC	Provider Relations
P	Bibek Sandhu, PharmD, MBA	PillarRX	SB	Consulting Pharmacist

Other Guests	

Follow-up Items:

Clerk of the Committee: Benita Ochoa

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

Agenda Item	Discussion Leader	Discussion Summary	Action	Notes
I) Call to Order	D. Carey	• Agenda Overview	Call to order at: 5:01PM	
II) Informational Updates	D. Carey N. Tomassian	Informational Update • 2025 Joint DHCS and DMHC Audit - DC: We had both DHCS and DMHC on site for a week. We have our exit conference that is scheduled for Thursday, so 2 days from now. - And we will get our preliminary findings from both, hopefully from both DHCS and DMHC. - And then we will, of course, work through any and all findings and we will bring back to this committee any findings that are relevant to the pharmacy team. • Recruitment for permanent director of Pharmacy Services - DC: Nora's final day as our Interim Senior Director of Pharmacy is Friday. - We are still in the midst of recruiting for the permanent Senior Director of Pharmacy Services, but we have some really good applicants, and we will finish up the 1st round of interviews on Friday. - Nora gets to go out with the bang by interviewing our final two candidates. - From there, we will select the top two candidates and then we'll do an interview with me and then we will select a senior director and hope they agree to all of our terms and what we're offering as a company. - I know that it took a little time and that was quite honestly because I needed to understand pharmacy and understand pharmacy services and understand what our team does now so that I can make sure that the senior director that comes in is what we need. - Also, initially the position was going to be a director of pharmacy services and thankfully with some advocacy, I got it increased up to a senior director, which I think is the level that is most appropriate for this role • DSNP P&P updates (listed in e-voting section) - NT: So as far as the P&P updates, we had kind of like last time, we have a few more policies and procedures for the DSNP line of business. - We already submitted for CMS; we've submitted our program. We are set to launch on January 1, 2026. But before we launch in 2026, although the program will start next year, there's a lot of prep work that needs to happen. And some of the prep work is obviously, you know, coming up with our P&P, selecting our PBM, selecting our different vendors and MTM vendors setting up everything. And so, there's a full workflow happening for the DSNP line of business open enrolment. And so, there's a full workflow happening for the DSNP line of business open enrolment. The formulary gets submitted. June is a very busy month for CMS. - So, formulary gets submitted in June, the formula gets reviewed by CMS over several stages, MTM program gets submitted in June as well, Bid gets submitted in June and then all of these get reviewed		

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by CMS and get approved in turn before open enrolment. Open enrolment is on October 15. This is why we start getting our members and we launch on January 1st, 2026. The policies are halfway done.

- I think we still have about 30 policies coming up, but these policies are going to be more targeted and shorter policies, but we won't kind of give them all to you at once. We're going to give them to you in several sessions. So maybe for the next P&T there will be about 10-15 policies, maybe more, and then the P&T after they will be all the remaining policies.
- DC: If I could just make one little caveat or so you're right, we are starting January 1, 2026. But well on that day we are trying to start with a bit of a kind of a pilot mentality. And that is because this is a new plan for us as you're aware. And so, the plan is to try to start it with a smaller number of members.
- And so, we are working with our delegate, our largest delegate CHCN and we're I think what the plan is now to select kind of a pod within each large clinical site.
- So, for example, Clinica will choose one of their sites to be the sort of de SNP site as well as the other clinics within CHCN. So, there'll be a pod in in most of those sites. You know, like Clinica Asian Health Services Lifelong, we'll choose a POD site for us to start DSNP and that is really two-fold.
- So, the initial enrollment is hoping to be somewhere around 1,500 and then you know within, you know, 5 or 6 months after we have sort of this experience under our belt to really open it up because we want to make sure that when we start the product line that we are doing it appropriately.
- We have all the staffing in place that we really do a good job. So, we've decided to start small and then build.

- Carveout Drug SOP - Pharmacy - P&T (non-voting item)

- NT: So, the next item on the agenda is something that we normally don't share with the P&T committee. So, the next item on the agenda is something that we normally don't share with the P&T committee. And it is something it's a, an SOP, a pharmacy SOP about carve out drugs. So, as you know, medical covers certain classes of drugs.
- They're carved out aside from the medications that are at the pharmacy, available at the pharmacy, there are classes of drug that even if they're administered by a physician, they're carved out to the state up until now, we did not have a constant or current a, a consistent process. Up until now, we did not have a constant or current a, a consistent process.
- And so, we would play catch up really the medications would be paid inadvertently and then we will try to catch up with it.
- So, with this process, we are going to be able to identify the drugs the moment that they get released, the J codes and then carve them out immediately. And that way the physicians went inadvertently. And that way the physicians went inadvertently. It's a non-voting item, but it's just a FYI.
- It is mostly a coordination between the pharmacy department and the department that does actual coding. So, it is mostly a timeliness issue. We want to make sure that we code those right.
- And if you're wondering which drug categories are there?
- Antiviral HIV drugs, hepatitis B drugs, alcohol and heroin, detoxification drugs, blood factors and antipsychotic drugs.

Questions:

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		Comments:		
III) Pharmacy Utilization	N. Tomassian	(All matters listed on the Consent Calendar are to be approved with one motion unless a member of the P&T Committee removes an item for separate action. Any consent calendar item for which separate action is requested shall be heard as the next Agenda item in closed session.)		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

Reports (Quarter 4, 2024)		**Top 50 Drugs by Cost (IHSS)**
		- The top 50 drugs accounted for **1,404 claims** for **839 members** and cost **$1,589,451,** which is a decrease of $101,770 in spend from the previous quarter.
		- Biktarvy remains at number one, claims having gone down by 3, and there is one more member since the previous quarter.
		- Ozempic is at numbers 2, 4 and 6, with 272 total claims for 137 members. There was an increase of 4 claims and of 20 members from the previous quarter.
		- Vemlidy is up to number 3 with 55 claims for 23 members. This medication is managed via the Hepatitis B MRG.
		- Rezurock is up to number 5 with 2 claims for 1 member. This medication is managed via the Agents for graft versus host disease MRG.
		
		Top 50 Drugs by Cost (Medi-Cal)
		- The top 50 drugs accounted for 42,049 claims for 36,406 members and cost $58,117,376.51, which is an increase of $1,795,296.87 in spend from the previous quarter.
		- The last quarter's total cost increase relative to the one before was over 3 million dollars
		- Biktravy remains at the number 1 spot with 889 claims for 727 members. An decrease of 28 claims from last quarter, although 37 more members filled the medication in the quarter
		- Ozempic also remains at the number 2 spot, with 2,141 claims for 1,601 members. This is a decrease of 171 claims from last quarter.
		- Jardiance is still at number 3 for the 25 mg strength with 1903 claims for 1759 members, but also at number 4 for the 10mg strength with 1952 claims for 1748 members. Total Jardiance claims for the 25mg strength has increased by 91 claims from last quarter and the total Jardiance claims for the 10mg strength has increased by 97 claims. This increased utilization reflects the expanded indication for Jardiance (Type 2 diabetes, prophylaxis heart failure in diabetes and non-diabetes patients and reduction of risk of GFR decline in ESRD patients). 86 more members are using Jardiance 25mg relative to the previous quarter and 67 more members are using Jardiance 10mg relative to the previous quarter.
		- Skyrizi is at the number 5 spot down from number 5, with 102 claims in 94 members, and same number of claims as last quarter.
		<u>Questions:</u>
		
		Top 50 PA Reviewed Drugs by Volume (IHSS)
		- Top 50 PA requests = 209. There were 316 total PA requests for quarter 4.
		  o 82 requests (39%) were approved. This approval rate is lower by 3% than was observed last quarter.
		  o 122 requests (59%) were denied or partially approved.		

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- Wegovy is at numbers 1, 6, 13 and 19 with 59 total requests and 17 approvals (29%).
  - Wegovy to reduce excess body weight requires a diagnosis of obesity or BMI ≥27 and at least one weight-related comorbidity (diabetes, hypertension, hyperlipidemia) or history of heart attack, despite diet and exercise, and trial and failure or inability to use Qsymia and Contrave.
  - Wegovy to reduce the risk of major adverse cardiovascular events requires a documentation that the patient is obese or has BMI ≥27, has an established cardiovascular disease (prior myocardial infarction, stroke or symptomatic peripheral arterial disease), patient is on standard of care treatment for CVD and does not have diabetes.
- Lidocaine 5% patch is at number 2 with 17 requests and 3 approvals (18%).
  - Lidocaine requires a diagnosis of neuropathic pain and a trial and failure of gabapentin or pregabalin and one other formulary alternative (e.g., duloxetine, venlafaxine, amitriptyline) used for neuropathic pain or morphine MME ≧ 50/day for 3 months.
- Vemlidy is at number 3 with 13 requests. There were 6 approvals (46%).
  - Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets.
- Jardiance is at numbers 4 & 5 with 18 total requests and 4 approvals (22%).
  - Jardiance requires trial and failure of one of the following: metformin, branded/generic drug containing metformin, branded angiotensin receptor/neprilysin inhibitor (ARNi), generic angiotensin-converting enzyme inhibitor (ACEi), generic angiotensin receptor blocker (ARB), generic mineralocorticoid receptor antagonist (MRA), or generic beta blocker.

Top 50 PA Reviewed Drugs by Volume (Medi-Cal)

- The top 50 drugs accounted for 211,954 claims for 189,479 members and cost of $5,148,097.19. This is an increase of 4,500 claims from last quarter and an increase of $154.474.78 compared to last quarter.
- Albuterol remains at the number 1 spot with 12,323 claims for 10,099 members. This is an increase of 1,356 claims from last quarter.
- Ibuprofen is at number 2, with 9,573 claims for 8,656 members. This is a decrease of 182 claims compared to the previous quarter.
- Diclofenac gel has risen from 5th spot to number 3 with 8,964 claims for 7709 members. This is an increase of 1,314 claims compared to last quarter and an upward trend for this topical product.
- Aspirin is back in the 4th spot with 8,784 claims and 8,118 unique members. This is a decrease of 290 claims compared to last quarter.
- Fluticasone has dropped from the number 4 to the number 5 spot with 8,076 claims for 7,213 members. There was a decrease of 287 claims from last quarter.

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IV) E-Voting Material/Consent Agenda

N. Tomassian
B. Ochoa

- **E-Voting Material/Consent Agenda**
- **The following items have been sent to the voting committee for review via E-voting**
- *Nora Tomassian, PharmD, Interim Pharmacy Director – Alameda Alliance*
- *Benita Ochoa, CPhT, Lead Pharmacy Technician – Alameda Alliance*
- *(All matters listed on the Consent Calendar are to be approved with one motion unless a member of the P&T Committee removes an item for separate action. Any consent calendar item for which separate action is requested shall be heard as the next Agenda item in closed session.)*

Monographs/Class Reviews	Changes
- Alcohol Use Disorder Agents Class Review	- No changes
- Direct Oral Anticoagulants Class Review	- No changes
- Fluoride Dental Preparations Class Review	- No changes
- Inhaled Corticosteroids Class Review	- No changes
- Leukotriene Inhibitors Class Review	- No changes
- Methergine Monograph	- No changes
Medication Request Guidelines	**Changes**
- Angiotensin II Receptor Blockers and Renin Inhibitors	- No changes
- Atovaquone (Mepron)	- No changes
- Tadalafil (Cialis) for BPH	- No changes
- Corlanor (ivabradine)	- No changes
- Injectable Anticoagulants	- No changes
- Elmiron (pentosane polysulfate sodium)	- No changes
- Ezetimibe (Zetia)	- No changes
- Inhaled Corticosteroids/Long-Acting Beta-Agonists (ICS/LABA) Combinations	- Remove discontinued AirDuo Digihaler
- Altoprev (lovastatin ER) and Fluvastatin, Fluvastatin ER	- No changes

Approved via e-voting:
Yes: 7
No: 0
Abstained: 0

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- Symlin (pramlintide)	- No changes		
		- Histamine H2 Receptor Antagonists	- No changes		
		- Brilinta (ticagrelor) tablet	- No changes		
		- GLP-1 Agonists	- No changes		
		- DPP-4 Inhibitors and Combinations	- No changes		
		- SGLT2 inhibitors and Combinations	- No changes, grammatical correction		
		- Parkinson's Disease Agents	- No changes		
		- PCSK-9 Monoclonal Antibodies (mAbs)	- Add preferred NDCs		
		- Linezolid	- No changes		
		- Pyridostigmine (Mestinon)	- No changes		
		- Long-Acting Muscarinic /Long-Acting Beta Agonist/ Corticosteroid inhaled Triple Combination Products	- No changes		
		- Corticosteroid Preparations to Treat Hemorrhoids	- No changes		
		- Savella (milnacipran) tablet	- No changes		
		- Travoprost (Travatan Z) ophthalmic drops	- No changes		
		- Arikayce (amikacin)	- No changes		
		- Antifibrotic Respiratory Tract Agents	- Update naming convention to reflect generic availability of Esbriet as pirfenidone		
		- Biologic Agents for Nasal Polyposis	- Update naming of referenced policies		
		- Verquvo	- No changes		
		- Siklos (hydroxyurea)	- No changes		
		- Presbyopia Agents	- No changes		
		- Zurzuvae	- No changes		
		- Dificid	- No changes		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

- **Physician Administered Drug (PAD) Guidelines**	- **Changes**
- Emergency Use Authorization (EUA) Drugs/Products for COVID-19	- No changes
- Primary Hyperoxaluria Agents	- No changes, minor formatting correction
- Tzield	- No changes
- Gene Therapy for Regular Red Blood Cell (RBC) Transfusion Dependent Beta-Thalassemia	- No changes, minor formatting correction
- Pompe Disease Agents	- No changes
- Adzynma	- No changes
Interim Formulary Updates	
- See p. 158 in packet	
Summary of Physician Administered Drug (PAD) Updates	
- See p. 159 in packet	
Pharmacy Policy & Procedure Updates	
- RX – 001 Pharmaceutical Operating Processes	- Update RxNova to Darwin claims system
- RX – 002 PA Review Process	- Q1 2025 Annual Review
- RX – 003 Exception Review Process	- Update external exception review process language
- RX – 004 Formulary Management	- Add language to support AB 1842 (4 category coverage requirement)
- RX – 005 P&T Committee Roles and Scope	- Update DUR reporting language to align w/QI Program Description
- RX – 006 Pharmacy Services Staff Description	- Q1 2025 Annual Review
- RX – 007 Pharmaceutical Patient Safety	- Q1 2025 Annual Review
- RX – 008 PBM Delegated Audit Oversight	- Q1 2025 Annual Review
- RX – 009 Emergency Supply Provision	- Q1 2025 Annual Review

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- RX – 010 Drug Utilization Management	- DUR Reports to UM and BOG alignment update		
		- RX – 011 Decision and Notification Requirements	- Q1 2025 Annual Review		
		- RX – 012 DU Policies – Pharmacy Portal UD Access	- Q1 2025 Annual Review		
		- RX-013 Medical Benefit Physician Facility-Administered Drugs (PAD) Prior Authorization Review	- Q1 2025 Annual Review		
		- RX-014 Physician Facility-Administered Drugs (PAD) Prior Authorization List Management _	- Q1 2025 Annual Review		
		- RX-015 Pharmaceutical Safe Use Monitoring of Physician Administered Drugs	- Q1 2025 Annual Review		
		- Rx-016 Self-Administered Drugs Requested Under Medical Benefit	- NEW Policy		
		D-SNP P&Ps (5 New)			
		- Continuity of Care			
		- Medicare Part D Hospice			
		- Medicare Part D Medication Therapy Management (MTM)			
		- PBM Delegated Function Oversight and Monitoring			
		- Vaccine Benefit			
		ED Oversight			
		- None			
		90 Day Maintenance List updates			
		- Q1 2025 Annual Review			
		P&T Meeting Minutes			
		- P&T Meeting Minutes Q4 December 17, 2024			

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

Interim Formulary Changes

These changes have been made to the Alliance's formulary recently. The changes were necessary to enhance the formulary.

Medication	Formulary Change
Carbamazepine Oral Tablet Chewable 200 MG	NF to F
Vivitrol Intramuscular Suspension Reconstituted 380 MG	NF to F
Sublocade Subcutaneous Solution Prefilled Syringe 100 MG/0.5ML	NF to F
Sublocade Subcutaneous Solution Prefilled Syringe 300 MG/1.5ML	NF to F
Buprenorphine HCl Sublingual Tablet Sublingual 8 MG	F-QL to F
Buprenorphine HCl Sublingual Tablet Sublingual 2 MG	F-QL to F
Lumakras Oral Tablet 240 MG	NF to F-PA
Lumakras Oral Tablet 320 MG	NF to F-PA
Differin External Gel 0.1 % OTC	F-PA to F
Labetalol HCl Oral Tablet 400 MG	NF to F
Simlandi (2 Syringe) Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	NF to F-QL (4 syringes per 28 days, Loading dose: 8 syringes)
Mesna Oral Tablet 400 MG	NF to F-AL (minimum age: 21 years)
Mesnex Oral Tablet 400 MG	F-AL to NF
Bismuth Subsalicylate Oral Tablet Chewable 262 MG	NF to F

The following changes have been made to the Alliance 's PAD PA list recently. These changes were necessary to evaluate medical necessity based on medical guidelines, utilization, and other information.

Physician Administered Drug (PAD) Prior authorization (PA) list Updates

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		<table><tr><th>HCPCS Code</th><th>HCPSC Description</th><th>Action</th></tr><tr><td>J0222</td><td>PATISIRAN (ONPATTRO)</td><td>Add PA Requirement</td></tr><tr><td>J0225</td><td>VUTRISIRAN (AMVUTTRA)</td><td>Add PA Requirement</td></tr><tr><td>J1411</td><td>ETRANACOGENE DEZAPARVOVEC (HEMGENIX)</td><td>Add PA Requirement</td></tr><tr><td>J1414</td><td>FIDANACOGENE ELEPARVOVEC (BEQVEZ)</td><td>Add PA Requirement</td></tr><tr><td>J3392</td><td>EXAGAMGLOGENE AUTOTEMCEL (CASGEVY)</td><td>Add PA Requirement</td></tr><tr><td>J3393</td><td>BETIBEGLOGENE AUTOTEMCEL (ZYNTEGLO)</td><td>Add PA Requirement</td></tr><tr><td>J3394</td><td>LOVOTIBEGLOGENE AUTOTEMCEL (LYFGENIA)</td><td>Add PA Requirement</td></tr><tr><td>J3398</td><td>VORETIGENE NEPARVOVEC-RZYL (LUXTURNA)</td><td>Add PA Requirement</td></tr><tr><td>J3401</td><td>BEREMEAGENE GEPERPAVEC-SVDT (VYJUVEK)</td><td>Add PA Requirement</td></tr><tr><td>Q2056</td><td>CILTACABTAGENE AUTOLEUCEL (CARVYKTI)</td><td>Add PA Requirement</td></tr><tr><td>Q2057</td><td>AFAMITRESGENE AUTOLEUCEL (TECELRA)</td><td>Add PA Requirement</td></tr></table>		
V) New Business	Iryna Makukh	**<u>Rx-016 Self-Administered Drugs Requested Under Medical Benefit</u>** - TT: So, at the Alliance, we are creating a new policy and procedure for self-administered drugs that are being requested under the medical benefit. What we're trying to achieve is to make sure self-administered drugs that are being billed under the medical benefit are medically necessary. So, if you can Scroll down a little bit, in our procedure, we kind of define self administered drugs based on the following. The FDA has approved self-administration at home and does not require administration in a healthcare setting by a medical provider. - Drug is not typically administered or directly supervised by a healthcare provider in an outpatient setting, the route administration. It could be oral, inhaled, intranasal, topical, rectal, subcutaneous, or a self-injectable intramuscular injection or it could be a prefilled syringe, an auto injector, tablet, capsule, Suppository, nasal spray, meter, dose inhaler, or a nebulized solution. - As well as we pay attention to standards of medical practice that allows self-administration, we also evaluate any established medical literature or compendia, including but not limited to FDA approved prescribing information the manufacturer provided, medical literature, peer review of medical	Move to approve: 1st: BD 2nd: AB	

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		literature, evidence-based practice guidelines, self-administration, utilization statistics, and compendia. - Drugs that are carved out of the Alliance Medical Benefit will not be covered. Examples of those are any drugs that are used for infertility, erectile dysfunction or cosmetic use or any of the medical fee for service drug classes such as HIV, AIDS, hemophilia, opiate and alcohol detoxification, antipsychotics and some of the antidepressants. - Medical necessity will be reviewed as a case by case basis. It's defined as reviewing the members' medical records and relevant documents provided by the provider. - Requests from providers to review medical necessity must include, but not limited to the diagnosis, current labs, notes, specialist consultations which document medical necessity of the drug, clinical documentation to support medical necessity of the need to administer the drug in a medical setting by a healthcare professional instead of a home setting. - Reasons why I covered injectable therapeutic alternative is not being used if a suitable indicate alternative drug exists as well as reasons why the member must receive the dose from a medical provider instead of receiving it from a pharmacy for administration at home, such as teaching self-administration, adjusting or titrating the dose, monitoring for immediate side effects, emergency or underlying medical condition that prevents self-administration of the drug. - NT: This is basically the criteria we're going to use to approve for this medication to be administered in office rather than the patient receiving it at the pharmacy. **Questions:** PB: Can I clarify please the carve out because there are, there are injectable antipsychotics and injectable, you know, HIV meds, injectable Prep is injectable naltrexone. Is that how is that dealt with in this scenario? NT: These are carved out to the state. medical fee for service pays for them. PB: They're paid for OK, at a medical fee for service. NT: They're not self-injectable. We're talking about specifically for those drugs that come in with a full, you know, self-injectable form. This is a medication that can be administered at the physician's office, but the same product, same strength, same indications and everything is available to be self-administered at a pharmacy. And when it's self-administered at a pharmacy, would prefer for the patient to receive it at the pharmacy rather than just going to the doctor's office. Unless one of the criteria here, unless they're starting a therapy, they're increasing the dose, they're getting used to the drug, etcetera. There we have also some criteria that he's going to go over for exceptions for when the member cannot self-inject. NT: So, there are some situations where the member cannot self-inject and for those situations who would be approving the physician administered drug? TT: Yeah, so we have it under 4-5. So, the provider would need to provide documentation of why it would need to be administered at the provider setting, such as teaching self-administration. So, adjusting or titrating the dose or they need a monitor for immediate side effects, it's an emergency or they have an underlying medical condition that prevents self-administration of the drug. And then we also have some other examples of what would be defined as medical necessity as met under 4.6. NT: Yeah, I was going to say, so this is going to be a new policy for us. We did not have a policy that outlined the detail of this. We are going to start implementing it. We will also first start by informing our physician network of this policy once it gets approved by this committee and we will inform everyone who has been prescribing medications to be administered in office if the product exists on the, you know, the		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

market. With that, we'll reach out to them, we'll explain about our policy and if there is a reason for the member to continue receiving at the physician's office, we'll enter an authorization to override this.

New MRG

Niemann-Pick Disease Type C

- So, for our new business, our first new policy is for a pneumonic disease type C and this policy is a result of the approval of two new drugs, Miplyffa and Aqneursa. The Newman Pick disease Type C is a rare, progressive genetic disorder characterized by an inability of the body to transport cholesterol and other fatty substances inside of cells, and this leads to the abnormal accumulation of these substances within various tissues of the body, including brain.
- NPC is apparent in childhood, but symptoms can manifest at any time. Patients often struggle with speech, swallowing, and feeding. NPC patients can also experience neurologic symptoms such as seizures and a progressive decline in intellectual function. This is a very rare disease, about one in 100,220 thousand live births. There were no FDA approved treatments prior to these two drugs.
- We just had enzyme inhibitors that were available, such as miglustat. So, the two new FDA approved treatments are Aknosa and Myplifa. Aknosa can be used as monotherapy or in combination with other treatments and Miplyffa is specifically approved for use in combination with mygostat.
- Both treatments are intended to treat the neurological symptoms of NPC.
- Myplifa is indicated for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients two years of age and older and Aqneursa is the only FDA approved stand-alone treatment for NPC. It is indicated for the treatment of neurological manifestations of NPC in adults and pediatric patients weighing at least 15 kilograms. Miplyffa is available as an oral capsule and dosing is weight based, and the price is $106,020.00 per month for maximum weight. Dosing of Miplyffa and Aqneursa is available as a 1-gram packet and dosing is also weight based and Aqneursa price is $57,642 per month based on maximum weight dosing per whack.
- The approval of Miplyffa was based on safety and efficacy data from a multi-centre randomized, double-blind, placebo-controlled 12 months trial in patients 2 to 19 years of age who had a molecularly confirmed diagnosis of NPC. Patients were randomized 2 to one to Miplyffa or placebo stratified by mygostat use.
- The Rescored for Domain and PC Clinical Severity Scale was used to measure the impact of treatment with Miplyffa versus placebo. In patients who received Miplyffa in combination with miglustat, 0.2-point decrease on the R4 DNPC scale was observed compared to an increase of 1.9 points in patients who received miglustat with placebo.
- The approval of Aqneursa was based on results from a phase three trial, which evaluated the effect of Aqneursa on neurological symptoms and functioning in 60 patients. Patients were four years of age and older with a confirmed diagnosis of NPC. The primary efficacy outcome was the functional scale for the assessment and rating of ataxia, which evaluates gait setting, stands and speech disturbance domains.
- And on average, patients who received NURSA received a greater improvement in FSRS 4 versus placebo.
- As for the criteria, prescriber must be a neurologist, geneticist or specialist in the treatment of pneumatic disease type C, since this is a very rare disease and should be managed by a specialist.

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		Concomitant use of Myplifa and ACNORSA should be excluded since both drugs are very expensive and there is no evidence to support synergistic effect or to assess safety when used together. - Age restrictions according to packet insert. - For coverage duration, we have six months as efficacy, but NORSA was assessed after six months, and my plethora was assessed after 12 months. But six months should be appropriate to evaluate progress and make sure that patient is using it correctly. - And for the initial authorization, we're asking for the diagnosis of NPC as confirmed by generic testing demonstrating one of the following mutations in both alleles of NPC 1 gene or NPC 2 gene or mutation in one allele of NPC one or NPC 2 and either a positive Philippine staining or elevated cholestein trial of the sterile levels. These were inclusion criteria for pivotal trial to confirm diagnosis of NPC. Most patients have a pathogenic mutation in both alleles of either NPC one or NPC 2. But in patients that only have a mutation in one allele, Philippine staining test and biomarker test can confirm the diagnosis. - Also, we're asking for a documentation that members have at least one neurological sign of NPC such as cognitive decline, ataxia, seizures, because according to guidelines treatment is not warranted for patients who have no neurologic manifestations because some remain asymptomatic for long periods of time. We also require documentation that member is ambulatory since in trial patients were ambulatory for Miplyffa. Prescriber must also attest that members will use it in combination with microstat. - That's per indication and members weight is required because dosing is based on weight and that request is for FDA approved dose and for reauthorization, we're looking for the documentation of positive clinical response to therapy such as improvement or stabilization and ambulation, find more skills swallowing or speech also members weight and that the request is for FDA approved dose. And that's all for this new criteria for NPC. **<u>Vyalev</u>** - Vyalev was recently approved and is indicated for the treatment of moral fluctuations in adults with advanced Parkinson's disease. Parkinson's disease as you know is that progressive neurodegenerative disease that develops slowly over time and that's as a result of degeneration of dopaminergic neurons. The primary motor related symptoms include tremors, rigidity, ekinesia, bradykinesia and postural instability. - As the disease progresses and dopamine producing neurons die, the dopamine concentration in the brain decreases, resulting in a decline in mortar and cognitive function. - According to Parkinson's Foundation, there are an estimated 1,000,000 people in the US living with Parkinson's disease. - Initial treatments include low dose carbidopa, levodopa, or a dopamine agonist. Initial treatments include low dose carbidopa, levodopa, or a dopamine agonist. Initial treatments include low dose carbidopa, levodopa, or a dopamine agonist. Providers may choose to increase the dose of levodopa or dopamine agonist, but this approach increases the risk of unwanted side effects such as dyskinesias and motor fluctuations. - Providers may choose to increase the dose of levodopa or dopamine agonist, but this approach increases the risk of unwanted side effects such as dyskinesias and motor fluctuations.		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- Vyalev is the 1st subcutaneous 24-hour. It is administered directly under the skin through a minimally invasive mode by avoiding digestive system. Infusion of levodopa-based therapy for the treatment of more fluctuations. - Vyalev is a pro drug combination of foscarbidopa and foslevadopa levodopa. It is administered directly under the skin through a minimally invasive mode by avoiding a digestive system. - It is expected to deliver a more consistent dose of levodopa to the brain and start working faster than the oral formulation of the medication, therefore reducing off time. - Additionally, Vyalev is to be utilized only in the advanced Parkinson's disease setting, which is estimated to be around 1 to 3% of all PD population offers a less invasive treatment option compared to Duopa, which is an anterol suspension administered via pack g- tube that requires surgery to place the tube. - The pump also allows for personalized dosing based on individual needs throughout the day. The approval was supported by the pivotal phase 312-week study evaluating the efficacy of continuous subcutaneous infusion of Vyalev in adult patients with advanced Parkinson's disease and compared to oral immediate release carbidopa, levodopa and also with a 52-week open label study which evaluated the long-term safety and efficacy. - The phase three study demonstrated that patients in the vile of arm showed superior improvement in more fluctuations with increased on time without troublesome dyskinesias and decreased off time compared with oral carbidopa, levodopa, IR. The price of Vyalev is $14,737 per month and that's based on maximum dose. - As for the criteria, concurrent use with a non-selective mild inhibitor such as phenolzene or tranilsipramine should be excluded because they're contraindicated in the TI. - Prescriber must be a neurologist or in consultation with a neurologist since violence should be used only in advanced Parkinson's disease. - Should be managed by a specialist for coverage. Duration of the initial and reauthorization request will be approved for 12 months. Duration of the initial and reauthorization request will be approved for 12 months. For initial authorization. We require diagnosis of advanced Parkinson's disease per indication. - Medication is prescribed at an FDA approved dose. We ask for prescribers at the station or documentation that the patient is experiencing persistent motor fluctuations despite optimized carbidopa, levodopa therapy and that's including a minimum of 2 1/2 hours of off time per day and the patient is taking at least 400 milligrams of levodopa per day. - And both these requirements included criteria in the trial. - Also, we ask for documented trial and failure or contraindication to at least two of the following adjunctive medication classes. This is a requirement from our anti Parkinson's agent’s policy just to make sure that patients are not responding or not candidates for other adjunctive therapies And for reauthorization. - We require documentation or provided at the station of positive clinical response such as increase in on time without troublesome dyskinesia and decreased off time and that the medication is prescribed at an FDA approved dose. - And this is all for the Vyalev criteria. - **<u>Zepbound for Moderate to Severe Obstructive Sleep Apnea</u>**		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- Zepbound Bound recently received a new indication for the treatment of moderate to severe obstructive sleep apnea in adults with obesity. - Zepbound bound as you know is a GIPGL P1 receptor agonist indicated in combination with a reduced calorie diet and increased physical activity to improve or say symptoms. - That's in addition to weight reduction indication. So obstructive sleep apnea or say is the most common sleep related breathing disorder. - It's occurring in 20 to 30% of males and 10 to 15% of females in North America. It's occurring in 20 to 30% of males and 10 to 15% of females in North America. AHI represents the average number of times per hour during sleep that a person experiences either apnea or a hypopnea. - Untreated OSA has many potential consequences, including excessive daytime sleepiness, impaired daytime function, metabolic dysfunction, and increased risk of cardiovascular disease and mortality, lifestyle modifications, and positive airway pressure. PAP therapy is the mainstay of therapy for adults with OSA. - PAP therapy prevents respiratory events, apneas and hypopneas by maintaining a positive pharyngeal transmural pressure and by increasing and expert very lung volume. - Two phase three randomized trials compared to tirzepatide with placebo for one year in 469 patients with obesity and or say one trial in patients who were unwilling or unable to use PAP therapy and the other trial in patients who are stable on PAP for at least three consecutive months in keeping with 16 to 17% weight loss. - Tirzepatide 10 to 15 milligram weekly halved the HI compared with placebo, with a decrease of 20 to 24 events per hour, and this benefit was observed as early as 20 weeks. - The price is $1086 per month per WAG and for the criteria. Provider must be a specialist in the treatment of sleep disorders or in consultation with a specialist in the treatment of sleep disorders. - Exclusion criteria are for requests for set bounce solely for diagnosis of weight reduction and maintenance for overweight or obesity because the weight loss indication is not covered under this policy. Concurrent use of any GLP one receptor agonist. - This is a limitation of use per label that Co administration with any GLP one agonist is not recommended. Also, personal history of type one or type 2 diabetes. Patients with diabetes were excluded from the CERN MOUNT or SAY trial. - Also, personal or family history of macular thyroid carcinoma and multiple endocranioplasia syndrome type 2. - Those are black box warnings in the label and age restrictions are according to packets insert or coverage duration. - The request will be approved for up to six months initially and 12 months for renewal requests. - Primary endpoint for reduction in HI was assessed at week 52, but this benefit was observed as early as 20 weeks per Pi. Therefore, 6 months is reasonable to check for clinical benefit and for initial authorization requested dose. We want to see that requested dose is appropriate for labeling the patient's body mass index is provided and is at least 30 kilograms per meter squared, which was inclusion criteria in the clinical trial. - Also, we're asking for the documentation of current diagnosis of moderate to severe obstructive sleep apnea per indication in the Pi and for the documentation of trial and failure regarding lifestyle changes and behavioral modification such as healthy diet and increased physical activity to reach ABMI of less than 30.		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

- This was also inclusion criteria in the trial that stated that the patient had a history of at least oneself reported unsuccessful dietary effort to lose body weight.
- We're also looking for results of sleep testing showing patient's apnea hypoknia index or AHI of at least 15 while currently on PAP therapy or results of sleep testing showing AHI of at least 15 and patient had a previous trial and failure of PAP therapy, or a medical reason is provided as to why the patient is not able to use PAP therapy. The AHI is a crucial diagnostic tool for OSA.
- It is used to determine the severity of the condition and guides treatment decisions.
- So, AHI of more or equal to 15 means that the patient has moderate OSA and that bound is indicated only from moderate to severe OSA.
- Also, if the patient is currently on PAP therapy and still has uncontrolled sleep apnea, it shows that PAP is not effective.
- So basically, these two conditions are to show appropriate indication and trial and failure of PAP therapy which is the mainstay of therapy for adults with OSA. And lastly, we require that the patient is not pregnant.
- This is not specifically contraindication in the label but not advised because people should not lose weight during pregnancy and there is some animal data suggesting teratogenicity for reauthorization. Our requested dose is appropriate for labeling. Looking for documentation of positive clinical response to therapy such as improvement of patients.
- AHI, improvement in daytime sleepiness, sleep arousal, snoring and that the patient is adhering to therapy as evidenced by claims demonstrating at least 80% of fill rate.
- We want to confirm that the members are adherent to ensure benefits of the medication since there is some evidence that people may be using these GOP one therapies intermittently. So, we included this requirement here as well.

Questions:

PB: So, this for Wegovy you can use that for weight loss, and you have to have a complication and sleep apnea is not one of those complications, correct. But or Zepbound bound, this would be a complication that would justify giving it, you know, because weight loss is the way that it's working, right. For the sleep apnea, that's presumably how it works.
IM: Yes, you're right. But Wegovy doesn't have this indication on the Zepbound for now.
NT: Yes, I guess they may go after it, right.
PB: And then you know, unfortunately lots of patients don't tolerate CPAP therapy very well.
And so, but I guess you, you just, we just need to tell you that that they couldn't make it work and that would be sufficient, correct.
IM: Yes, yes. They would have to show trial and failure.
PB: So, and is that the exclusion and you're excluding diabetes because they would be on a you would rather have it, they would be on Ozempic. Is that is that the reason you're excluding diabetes?
IM: Diabetes wasn't included in the trials for a say and if they had diabetes, they would be on Mounjaro.
PB: OK, got it.

New PAD

Vyalev

- We're including Vyalev criteria here also since it is usually started in the healthcare provider's office.

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- So just a new PAD for Vyalev as well. - And it's exactly the same criteria as the MRG criteria. So, there are no changes or additions for this PAD policy. - This is so that the patients can be trained on the proper use of the delivery system and of the drug prior to being able to use it at home. **Benchmark Analysis** - So as a yearly process, we worked on benchmark analysis and have the following recommendations. Pg.354 Out of all drug categories and classes, there were three that did not meet the benchmark, and the first one is for antiparasitic category. Antiprotosols drug class. So, we have 9 drugs currently on formulary and need to add 1 more agent in order to meet the benchmark of 10 drugs. - Their recommendation is to add tenutazole to 50 and 500 milligram tablets to formulary in order to meet the benchmark of 10 formulary medications in this drug class. - Other ethyportazoles that are not on formulary are listed here in the rationale section. - We decided to add Tenutazole because it is cost effective and commercially available formulation with several approved indications. - Pricing for 250 is around $1.28 to $4.00 per tablet and Mac pricing is dollar 49 and for 500 milligrams the Mac pricing is $2.63 per tablet. And the highest dose is for amoebic liver Abscess caused by anti-amoeba histolytic indication which is 20 tablets total. And we recommend adding to the result to formulary in order to meet this benchmark. - And the second category where we need to meet benchmark is for hormonal agents, anabolic steroids drug class - The recommendation here is to add 2 strengths of Bijuva oral capsule that's in order to meet the benchmark of one formulary medication in this drug class. - You can see that the only other agent in this class was oxandrolone. However, it is no longer on the market in active formulation. - So, we recommend adding Bijuva to formulary to meet the benchmark. - And scrolling down a little bit, the third category that needs formulary addition is ophthalmic agents, intraocular pressure lowering agents' class. - So, during Q 3 2024 P&T, it was recommended to remove apoplonidine ophthalmic solution .500 point 5% due to no utilization and adequate alternatives. However, we recommend adding it back to formulary to meet the benchmark for this drug class. - Ophthalmic intraocular pressure lowering agents that are not on formulary include brinzolamide and phospholin iodide, Repressa and brimonidine tymolo solution. However, adding apraclonidine is the most cost-effective solution to beat the benchmark. So, these are all recommendations based on our analysis of benchmark analysis for the formulary. **Questions/Comments:**		
VI) Class Reviews, Monographs, and Recommendations-	Iryna Makukh	**1. Multiple Sclerosis Agents Class Review** - So multiple sclerosis is the chronic central nervous system disease causing inflammation and demyelination in multifocal areas. Pg. 356		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- It may start with clinically isolated syndrome or CIS, which is the first clinical episode that is suggestive of a mass and then it can progress to the relapsing remitting MS or RRMS, which is the most common type of a mass. - Then it can progress to secondary progressive MS and that's characterized by a progressive worsening of disease between relapses and the worst stage is primary progressive miss where disease progresses with no remissions. - There are only two approved disease modifying therapies for PPMS, which is Ocrevus and Ocrevus Zunovo. And let's look at utilization on page 389. So, there were a total 7 claims for three members for a total cost of $22,866 and an average cost per claim of $3267. - The most highly utilized medications were glitiramide and teriflunomide with three claims each and followed by Vumerity with one claim. There were two prior authorization requests with one approval. - Overall, current guidelines recommend that everyone with a diagnosis of clinical definite RRMS should begin disease modifying therapy as considerable evidence has shown that earlier treatment is associated with better long-term outcomes. Let's go to page 387. - So, from self-administered DM TS we have platform injection therapies such as interferon beta and glatiramer acetate on formulary with PA. - Glatiramer acetate is an immunomodulator available as a generic and this one of the preferred agents of formulary. As for interferons, we have both intent from beta 1B and 1A on formulary with PA. - The main difference between interferons lies in the dosage and how often they're injected. Some are given once a week while others are injected more frequently. - Interferons showed reduced relapse, late rates and delay in onset of death disability. All interferons are on formulary with PA except for Avonex is currently on formulary without restrictions. - We have a recommendation here changing Avonex to formulary with PA to match its current status in the criteria and because other more cost-effective interferons are on formulary with PA. - Also, there was no utilization of these products and no other changes except for Avonex. - On the next page 388, we have oral therapies that include fumarates such as Tecfidera, which is available generically as dimethyl fumarate. - Dimethyl fumarate is a market leading twice daily oral therapy of choice for patients with RRMS, especially in initial treatment and that's due to its clean safety profile and clinical efficacy. - It is on formulary and is cost effective. - The fumarates such as Befiatram and Vumerity are on formulary with PA and are more costly. Other oral medications includes Fingersen 1 phosphate receptor modulators, teriflunomide and Mavenclad from S1P receptor modulators. Gilenya is available as a generic phenolimod and it had been the only approved S1P modulator until recently, and it competes directly with generic Tecfidera. - Tecfidera In the oral MS category we have generics and going with one formulary with PA. It is the most cost effective out of S1P modulators drug class. - The brand Gilenya and Cassandra ODT are non-formulary and FPA respectively and they are more expensive. - No changes are recommended here in this section. - The other S1P modulators include Mayzent, Zaposia and Pugvori. - There was no utilization of these agents and no changes since they're substantially more expensive than Finvolimot. - Teriflunomide is a generic for Aubagio is another or luminosuppressant that is effective in a mass treatment and is also very cost effective. It is all formulated with PA. There was some utilization and		

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		our recommendation here is removing the PA criteria and moving this agent to formulary without restrictions and adding it as an additional preferred agent in MRG policy. So let's look at the policy on page 390. - So, we changed terraflunomide from non-preferred to preferred agents to provide an additional cost-effective option for the treatment of a mass of a mass for members - Also in this criteria, we updated naming convention to reflect generic availability of Gilenya and Aubagio as fingolimod and teriflunomide and these were all changes needed for the criteria. - And moving back to the utilization on page 388. So, we have injectable monoclonal antibodies such as Casimta, Ocrevus, Lemtrada and Tysabri. They may be preferred for patients with more active disease and patients who value efficacy and who are considered risks more risk tolerant. Anti CD20 monoclonal antibodies also have gained traction over the last few years due to their high efficacy and favorable safety profile. Anti CD20 monoclonal antibodies that are indicated for a mass include Ocrevus, Casimta and Briumvi. The anti-CD 20 class of drugs I believe to be more potent than S1, PS and controlling MS - All three have similar efficacy of our Ocrevus is the market leader because it was first to market and also has both favorability and familiarity for neurologists. - Cassinta has a subcutaneous route of administration and is given once monthly and is on formulary with PA. - Both Ocrevus and Brionvi have to be administered by a healthcare professional as an IV infusion every six months and we do not recommend any changes for these agents. - The last two agents are on page on the next page 389 and these are symptomatic therapies. - Dalfampridine Ampyra which is a symptomatic agent indicated to improve walking speed for mass patients and actor which is used for treatment of a mass exacerbations. Both agents are on formulary with PA. - There was no utilization in the last quarter and the only other change recommended for this drug class is on page 394 and that's the change for healthcare provider administered IV disease modifying therapies for mass policy. - So here on three on Page 395, I just added teriflunomide as well as an additional agent to try and fail before the use of non-preferred products. And these are all recommendations for this class review. **Questions/Comments:**		

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2. Second Generation Antihistamines Class Review New MRG: Cobenfy

- We have some recommendations for second-generation antihistamines and that's on page 401. Those second-generation antihistamines treat allergy symptoms like allergic rhinitis, urticaria and allergic conjunctivitis.
-
- They are preferred over first-generation agents due to the lower incidence of adverse events. American Academy of Allergy, Asthma and Immunology allergic rhinitis guidelines do not prefer any second-generation antihistamine over another as first line and recommend monotherapy before combination therapy.
- Therefore, it is mostly appropriate to prepare agents based on cost and let's look at the utilization that's on page 428.
- So, there were a total of 331 claims for 234 members for total cost of $2113.00 and an average cost per claim of $6.39.
- The most highly utilized medication was Cetirizine tablet with 149 claims and followed by Loratadine tablet with 96 claims. There were no prioritization requests for this class. And from oral dosage forms on page 425 South here we have a comprehensive coverage of these agents.
- We have Cetirizine oral solution and tablets that's loratadine and loratadine tablets, fexofenadine and levocetirizan tablets and solution on formulary and overall, Alameda has a comprehensive coverage of cost-effective oral dosage forms of second-generation antihistamines, and we do not recommend any changes here from the combination products on the next page 426.
- So here we are using pseudoephedrine and loratadine. Pseudoephedrine is on formulary. On the next page 427 we have Clarinex D, which’s a brand. It's not formulary, it's more costly. So, no changes are recommended.
- Dexophenidine to the ephedrine 12- and 24-hour tablets are not formulary, but the risk criteria that least lists these drugs as formulary with step therapy required. Also, there was some utilization.
- So, we recommend adding fexofenadine to formulary with step to match the criteria and the step would require documentation of trial and failure or intolerance to loratadine sitirs in all level sitirs.
- In next for ophthalmic and nasal dosage forms, we have comprehensive coverage of most cost-effective agents.
- Azelastine ophthalmic drops are on formulary and cost effective.
- The potestine is on formulary, but it is substantially more costly and listed as FPA in the criteria for ophthalmic antihistamines. We recommend moving the potestine to formula with PA to match the criteria. Ketotipan drops are on formulary with pointy limit, Olopatadine 0.10.2 also on formulary with pointy limits. They're all cost effective products.
- On the next page 428, we have Pataday 0.7 that's a brand. It’s on formulary with PA because it is more expensive than generics above and no changes recommended for these agents.
- And the last items are nasal sprays, and we have as listing 0.1% spray on formulary and olapatadine is non formulary as I was seeing is more cost effective and we recommend no other changes to these agents. And these are all recommendations for this class review.

Questions/Comments:

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

3. Alyftrek Monograph

- So Allitrac is the newest cystic fibrosis trans membrane conductance regulator modulator or CFTR modulator in the disease modifying space for cystic fibrosis. Pg. 433
- Cystic fibrosis is rare life shortening generic disease affecting more than 40,000 people in the US with 1000 new cases diagnosed annually. CFS progressive multi organ disease that affects lungs and liver, pancreas and other organs. It is caused by a defective CFTR protein resulting from certain mutations in the CFTR gene.
- The most common mutation is F5O8 del mutation, however there are approximately 2000 known mutations
- The defective function of CFTR protein results in poor flow of salt and water into and out of the cells and the number of more organs and in the lungs.
- This leads to a buildup of abnormally thick sticky mucus, chronic lung infections and progressive lung damage. So Elftrac is the newest CFTR modulator.
- It is indicated for the treatment of cystic fibrosis in patients aged six years and older who have at least one F by way Dell mutation or another responsive mutation in the CFTR gene.
- An ALIF tract is a combination of three agents, the two week after which has unique once daily CFTR potentiator.
- Tasakaftar is the same CFTR corrector used in Trikafta and Syndecco and Fanzakaftar which is considered the next generation CFTR corrector.
- So ALIF tract in trials showed non inferiority to Trikafta. It showed non inferiority in change in percent predicted forced expiratory volume in one second, which is a measure of lung function.
- Allstrec also demonstrated increased efficacy in reducing sweat chloride levels compared to Trikafta, which is a biomarker of CFTR function and is used to diagnose CF Whether the additional reduction in sweat chloride levels will translate to improved clinical outcomes is not currently clear and requires further study, but the main advantage that Lftrack offers is the convenience of once daily dosing and efficacy in 31 additional CFTR gene mutations compared to Trikafta.
- Existing CFTR modulator therapies already covered mutation for approximately 90% of the cystic fibrosis patient population, meaning that impact in terms of newly eligible CF patients who can now benefit from CFTR modulator should be minimal.
- However, the convenient dosing schedule and potential for improved long term clinical benefit may drive interest from patients and providers to switch from other existing CFTR modulators.
- Alistrax price is $30,433 per month and this is approximately 7% more than Tricafta, which is a current market leader.
- We recommend updating prior authorization criteria for cystic fibrosis agents with this new therapy and adding it to formulary with APA requirement.
- The MRG criteria is on page 443 and here the only change that we're making to the policy is adding this new drug Altra.
- We do not currently recommend a step through Tricafta for patients eligible for both based on mutations as we do not have a full understanding if improvement in sweat chloride levels will lead to a better long term outcomes in cystic fibrosis.
- And these are all changes to the criteria.

Questions/Comments:

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

VII) Medication Request Guidelines	R. Negash	The committee has reviewed and discussed the following updates and additions to the Medication Review Guidelines (MRG) Guideline (Changes): **1. Corticosteroids for Duchenne Muscular Dystrophy (DMD)** - We can start with the pharmacy benefit MRGs. - It's on page 447. - So, the first policy is for the corticosteroids that are treating DMD. - And with this policy, we can see in the medication section that we're updating that generic availability since it's now Emflaza is available as a generic product. - And we're also listing in the PA review criteria section based on cost efficacy that requests for Agamree will require that generic Emflaza be used first. - And there's no other changes to this policy or negative impact based on utilization. - Are there any questions with this policy? - There's just those two changes, OK. - And feel free to let me know if there's questions. - I'll just keep moving. **Comments:** Guideline (Changes): **2. Agents for Atopic Dermatitis** - The next policy is on page 428 for atopic dermatitis. - So, if we Scroll down a little bit towards the bottom of the page, we can see the beginning of the policy. - And so, the changes here relate to formulary alignment and updating our criteria. - So, in the medication section we see for the first changes and two of them are to add Eucrisa to formulary PA and also add Rinvoq to formulary, excuse me, add Rinvoq to the non-formulary section. - And we're also having an addition of Adbry there. - And this is for a preferred pricing strategy. - If we Scroll down to the next page, we also see that we're adding four agents to the non-formulary section and these products are now available to treat DMD. - And so, we're adding it to our policy. - And we also see changes in the prescriber restriction section. - So here we're expanding the restriction to all products.	Move to approve: 1st: BD 2nd: AB	

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- So, we would look to see a specialist on all of these requests unless it's for a topical calcineurin inhibitor like tacrolimus or pimecrolimus.
- For coverage duration, we're adding two products there, it's Vtama and Zoryve.
- So, they would have that eight-week initial authorization limit and then up to six months thereafter for reauthorization.
- If we Scroll down to towards the bottom of the page, we're also adding three products in line with Eucrisa.
- And so here we see that these are all topical agents and the criteria for them includes atopic dermatitis and treatment failure of a corticosteroid, so it would be medium to high potency, and also treatment failure of a topical calcineurin inhibitor.
- And then requests that are specific for Opzelura, they would require that Eucrisa is used first.
- So Eucrisa would stand out of preferred status.
- If we move to the next page, we can see the criteria update for Adbry.
- So here, Adbry is replacing that oral Rinvoq.
- So, we'll have those two subcutaneous agents being reviewed under the same criteria.
- And then we see right under that Nemluvio is having its own criteria.
- This is the new indication for this product.
- And so, we have it here with treatment failure of one of the following and it would be either Eucrisa, Opzelura, Vtama or Zoryve.
- And right underneath that, we see again the Ebglyss with appropriate diagnosis that we would need to have and then also treatment failure of one of the preferred products.
- And then lastly, we have two agents that would have the same review criteria.
- They'd be Cibingo or Rinvoq as they're both indicated for refractory moderate to severe AD.
- And so here we would just look for treatment failure of a preferred systemic drug.
- So that could be some of the ones listed previously like Dupixent. And those are all of the changes for this policy.
- The reauthorization remains unchanged, the criteria for it, even though we're adding some new agents.
- OK, if there's no questions, I will go ahead and move to the next policy.

Comments:

Guideline (Changes): **3. Thrombocytopenia Agents**

- It's on page 452.
- And so, this is for Thrombocytopenia agents.
- And here we can see that there's just a couple red lines.
- So, the medication section, we're adding Alvaiz to our list of formulary PA required products.

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		- And then in the coverage duration area, we're adding it to include up to 12 months of approval along in line with Promacta and Nplate. - And then towards the bottom, we see that Alvaiz is being added throughout the policy as it is indicated. - So, the first indication is the Chronic immune (idiopathic) thrombocytopenia (ITP) and Promacta would be preferred over this agent based on cost efficacy. - And as we scroll through the next page, we see Alvaiz added as appropriate and indicated also for severe aplastic anemia and then again for thrombocytopenia in patients who have Hep C, and Promacta tablets are preferred in each of these conditions. - And there's no other changes on this policy. - Any questions? **Comments:** PB: Alvaiz? It's the same generic medication, right? Is it a different formulation? Did I miss? It's the same generic as Promacta? IM: This is this is the same generic. Yeah, that's correct. Just a different salt form. But the indications differ a little bit such as age restrictions are a little different between them. That's the whole difference. DB: Good question, if it's generic wouldn't it be more preferred formulary over the brand product? Why is it the Promacta brand product is still preferred? IM: This is not exactly like a generic. This is not a generic. It's just the same active ingredient with a different salt form. This is not. It's not interchangeable with Promacta now. RN: Yes. And thank you. Thank you, Iryna. Also, the indications for the Alvaiz are not exactly the same. So, for Promacta it's indicated for aplastic anemia that is severe as first line treatment and the Alvaiz is not. RN: Any other questions on this policy? OK. RN: Thank you for those questions. Guideline (Changes): **4. Pulmonary Biologics for Asthma and Eosinophilic Conditions** - And we'll move to 455. - That's our next MRG here. - And so as you can see, we're changing the name of this policy based on a new indication for Dupixent since it's now indicated for COPD maintenance treatment. - And so you also see that change in the exclusion criteria. - We're putting respiratory instead of asthma to be more accurate and include all the indications. - And then under prescriber restrictions, we're adding language to include a consultation with any of the specialists when we when we receive requests for these medications, so that we're making sure to include appropriate that we have appropriate review. - And if we move to page 456, you can see the Dupixent policy language. - So, we're looking for appropriate diagnosis of COPD. - We're also going to look for blood eosinophil count of at least 300.		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

- And then we're looking for post bronchodilator FEV_1/FVC ratio and it would be less than 0.7.
- And we would also be looking for FEV_1 30% to 70%.
- And also to note, these parameters are based on the pivotal trials and the baseline characteristics.
- And so, we're adding our criteria to match that.
- And there we would also be looking for a trial and failure of triple therapy.
- And so that would be defined as a member continuing to experience significant symptoms despite use of an inhaled long-acting muscarinic antagonist plus long-acting beta 2 agonist and an inhaled corticosteroid.
- We'd also be looking for one of the following: at least two exacerbations in the last 12 months with a systemic corticosteroid and then or they could have at least one exacerbation in the last 12 months that resulted in hospitalization.
- And then of course, we're looking for the appropriate dose when we get these requests.
- If we move to page 457, we can see that we're also adding Fasenra to the EGPA indication and we're showing here that we would have requests for Nucala to try Fasenra.
- So Fasenra would be preferred based on cost efficacy.
- And then in the reauthorization area, we would simply add the COPD language to include that Dupixent indication.
- And if as we scroll through the policy, we'll see that there's no other changes related to criteria review.
- Any questions on this policy?

Comments:

Guideline (Changes): **5. Anti-Obesity Medications**

- The last policy listed here for the pharmacy benefit is the anti-obesity medications [p. 459].
- And we're just adding language here to include the exclusion criteria to make sure that we're approving safe and effective care for patients as sometimes they might have family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.
- So, if we get requests and we see that they have these, the requests would not be approved since it's contraindicated, a black box warning actually.
- And then there's no other changes on this policy.
- And if there's no other questions, I will turn it over to Iryna to go over the PAD policies that start on Page 462.

Comments:

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

VIII) Physician Administered Drug (PAD) Policies	Iryna Makukh	Guideline (Changes): **1. Rituximab** - Pg. 464 Not many recommendations here but just adding age requirements to pemphigus vulgaris and GPA/MPA indications for consistency. - So here pemphigus vulgaris rituximab is indicated for patients 18 years of age and older and for GPA/MPA indication is indicated for patients 2 years of age and older. - Another recommendation for GPA/MPA diagnosis is that we recommend removing the requirement for diagnosis classification of either severe or non-severe disease since Euler guidelines do not use non-severe and severe language because this puts patients at risk of being under treated. So, the Euler guidelines now use organ threatening or non-organ threatening language instead. - However, rituximab is now recommended regardless of organ status. - So, we recommend removing the requirement of trial and failure of methotrexate or cyclophosphamide for non-sever disease since per Euler guidelines, rituximab is recommended regardless of disease severity over methotrexate because it showed higher rates of sustained remission and lower glucocorticoid exposure. - Also, rituximab is preferred over cyclophosphamide in relapsing disease. - These are all the changes for this policy just based on the guidelines. Any questions? **Comments:** PB: It threw me off a little bit at the beginning of this, where it says oncology indications because you're really talking about its rheumatologic utilization, not oncology. Correct? The very first page on 462. IM: Right, we're not changing anything for oncology indications. Everything is appropriate. PB: Ok. IM: Yeah, so we're only making changes to the GPA/MPA diagnosis. PB: Ok, alright thank you. Guideline (Changes): **2. Ophthalmic indications for bevacizumab** - Pg. 466 We recommend removing the requirements for trial and failure of a biosimilar before Avastin because the American Academy of Ophthalmology strongly recommends against including these in step therapy regimens or as a replacement for the reference product bevacizumab because of the absence of sufficient clinical studies for these biosimilars for the eye disease. - The Academy has stated that neither available biosimilar has been studied for ophthalmic indications and that their inactive ingredients have not been approved for use in the eye - Also, they state that ophthalmic use of these products could create safety risks because of a small variation in excipients can lead to significant and even potentially blinding inflammatory complications when injected intravitreally. So, that's the one recommendation.	Approve	

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- The only other change here is just adding two indications for bevacizumab for ophthalmic use that we are missing from the policy. Any questions on this?

Comments:
N/A

Guideline (Changes): **3. Immunoglobulin Therapy (IVIG)**

- Pg. 467 We recommend adding Alyglo IVIG that is indicated for the treatment of primary humoral immunodeficiency in adults. This includes humoral immune defect in congenital immunoglobulin anemia, a common variable of immunodeficiency, x linked immunoglobulin anemia was called Eldrige syndrome, and severe combined immunodeficiency.
- All these indications are already addressed in the current criteria, so no other changes to the policy are needed. Just adding the missing product here.
- Also, on pg. 468 are minor grammatical corrections in acute idiopathic thrombocytopenic purpura indications, it should say inadequate increase, that's the correction.
- On pg. 469, we're correcting the dose for multiple motor neuropathy indication. The gamgar dose is 0.5 to 2.4 grams per kg per month per pi.
- Just these minor corrections and changes and no other changes to this policy.

Comments:
N/A

Guideline (Changes): **4. Reblozyl**

- Pg. 471 Our recommendations include changing initial authorization coverage duration to 6 months. This is to align better with the assessment of outcomes in clinical trials. The current timeline for authorization of 3 months is too soon when considering that the primary outcome for the phase three clinical trials was assessed over 24 weeks, which is 6 months.
- Additionally, for the MDS indication, the label says to discontinue only after 21 weeks if not effective, which well passed our initial 3 months authorization time frame.
- Also, in this policy we streamlined the red blood cell RBC abbreviations throughout the policy.
- Pg. 472 lastly for reauthorization section, we recommend changing the time frame for hemoglobin increase and reductions in RBC transfusions to 8-12 weeks as that was the definition of an erythroid response used in medalist and commence trials.
- For medalist trial erythroid response was defined as reduction in RBC transfusion burden of at least 4 RBC units over 8 weeks or response was defined as a mean hemoglobin increase of at least 1.5 grams per deciliter also over 8 weeks.
- So, we're just changing the timeframe to be more appropriate and aligned with clinical trials.
- These were the only changes to this policy. Any questions?

Comments:
N/A

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

		Guideline (Changes): **5. Zulresso** - We recommend retiring this criteria since Zulresso was discontinued. Sage therapeutics announced in its third quarter of 2024 earnings report that it will discontinue the Zulresso effective December 31st, 2024, because the company plans to focus its resources on that commercialization of Zurzuvae. - Zurzuvae is a once daily oral medication for the treatment of adults with postpartum depression while Zulresso was IV. - So, we recommend retiring this criteria. Any questions? - These are all the PD that I had. This is all for new business, I don't know if you want to vote. **Comments:** NT: I was going to ask whether we could vote on all of them, but we reviewed new MRG, MRG changes, new drugs, we reviewed class reviews, we reviewed benchmark analysis, we reviewed all those recommendations. Can I get a motion to approve these recommendations?		
IX) Informational Updates on New Developments in Pharmacy	Iryna Makukh	New Product Review • New Products were discussed.		

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

BRAND NAME	GENERIC NAME/DOSAGE FORM	RECOMMENDATION
Vyalev	foscarbidopa and foslevodopa subcutaneous solution 240-12 mg/ml	Non-formulary (see new MRG policy)
Vyloy	zolbetuximab-clzb intravenous solution reconstituted 100 mg	Non-formulary
Erzofri	paliperidone palmitate intramuscular suspension prefilled syringe 39mg/0.25ml, 78mg/0.5ml, 117mg/0.75ml, 156mg/ml, 234mg/1.5ml, 351mg/2.25ml	Non-formulary
Ebglyss	lebrikizumab subcutaneous solution auto-injector 250 mg/2ml	Non-formulary (see updated MRG policy)
Pavblu	Aflibercept-ayyh intravitreal solution and prefilled syringe 2mg/0.05ml	Non-formulary
Itovebi	Inavolisib 3mg, 9mg oral tablet	Non-formulary
Hympavzi	marstacimab-hncq subcutaneous solution auto-injector 150 mg/ml	Non-formulary
Lumakras	Sotorasib oral tablet 240mg	Non-formulary
Augtyro	Repotrectinib 160mg oral capsule	Non-formulary

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

			Aurlumyn	Iloprost intravenous solution 100 mcg/ml	Non-formulary			
			Azmiro	Testosterone cypionate intramuscular solution prefilled syringe 200 mg/ml	Non-formulary			
			Opipza	Aripiprazole oral film 2mg, 5mg, 10mg	Non-formulary			
			Emrosi	Minocycline hydrochloride oral capsule extended release 24 hour 40mg	Non-formulary			
			Revuforj	Revumenib oral tablet 110mg, 160mg	Non-formulary			
			Aucatzyl	Obecabtagene autoleucel intravenous suspension 410000000 cells	Non-formulary			
			Danziten	Nilotinib 71mg, 95mg oral tablet	Non-formulary			
			Ziihera	zanidatamab-hrii intravenous solution reconstituted 300 mg	Non-formulary			
			Nypozi	Filgrastim-txid injection solution prefilled syringe 300 mcg/0.5ml, 480mcg/0.8ml	Non-formulary			
			Attruby	Acoramidis oral tablet therapy pack 356 mg	Non-formulary			

Docusign Envelope ID: 2CFA24A5-CAB5-411B-802B-584441919610

			Simlandi	Adalimumab-ryvk (2 Syringe) Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	F-QL (Already added via CRF) (QL: 4 syringes/28 days, LD: 8 syringes)			
			Boruzu	Bortezomib Injection Solution 3.5 MG/1.4ML	Non-formulary			
			Hercessi	Trastuzumab-strf intravaneous solution reconstituted 150mg, 420mg	Non-formulary			
			Axtle	Pemetrexed dipotassium intravenous solution 100mg, 500mg	Non-formulary			
			Imkeldi	Imatinib mesylate oral solution 80mg/ml	Non-formulary			
			Bimzelx	Bimekizumab-bkzx 320mg/ml auto injector and syringe	Non-formulary			
			Qlosi	Pilocarpine HCl ophthalmic solution 0.4%	Non-formulary			
			Wezlana	Ustekinumab-auub subcutaneous solution 45 mg/0.5ml Ustekinumab-auub intravenous solution 130 mg/26ml Ustekinumab-auub subcutaneous solution prefilled syringe 45 mg/0.5ml Ustekinumab-auub subcutaneous solution	Non-formulary			

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				prefilled syringe 90 mg/ml				
			Alyftrek	vanzacaftor/ tezacaftor/ deutivacator oral tablet 4-20-50mg, 10-50-125mg	Add to F-PA (see updated MRG criteria)			
			Crenessity	crinecerfont oral capsule 50mg, 100mg crinecerfont oral solution 50mg/ml	Non-formulary			
			Bizengri	zenocutuzumab-zbco (750 mg dose) intravenous solution therapy pack 375 mg/18.75mL	Non-formulary			
			Tryngolza	Olezarsen subcutaneous solution auto-injector 80 mg/0.8ml	Non-formulary			
			Opdivo Qvantig	Nivolumab and hyaluronidase-nvhy subcutaneous solution 600-10000 mg-ut/5ml	Non-formulary			
			Kebilidi	Eladocagene exuparvovec-tneq injection suspension 280000000000 vg/0.5ml	Non-formulary			
			Gabarone	Gabapentin oral tablet 100mg, 400mg	Non-formulary			
			Adalimumab-adaz	Adalimumab-adaz subcutaneous solution auto-injector 80 mg/0.8ml	Non-formulary			
X) Old Business		**Pharmacists to prescribe Naloxone at POS** **Comments:**						

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		NT: So, the last item that we had on the agenda is something that we brought up last time, but we ran out of time. So, I think we still have time to review the Naloxone prescribing from the pharmacist. We were hoping to get P&T to approve 2 things: • To allow the pharmacist to prescribe and dispense at the point-of-sale Naloxone based on criteria established by the DHCS. • When we do an audit of these cases, we identify that certain pharmacies are not following those rules to stop the treatment and to recoup the treatment for the medication that we dispense. • So, we're hoping that the P&T committee will approve these. If you have questions let us know.		
XI) Public Comment	D. Carey	• No comment		
Adjournment	D. Carey	**Meeting adjourned at 6:52PM**	None	

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Rahel Negash
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Rahel Negash, PharmD
Supervisor, Pharmacy Services,
Alameda Alliance for Health

04/29/2025 | 4:15 PM PDT
Date

DocuSigned by:
Donna Carey
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Donna Carey, MD
Chief Medical Officer
Alameda Alliance for Health

04/30/2025 | 9:59 AM PDT
Date

New

Tryngolza	
Therapeutic Classes (AHFS)	Antilipemic Agents
Medications	Tryngolza (olezarsen)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be an endocrinologist, lipidologist, or cardiologist experienced in, or in consultation with a specialist experienced in, familial chylomicronemia syndrome (FCS)
Coverage Duration	If all of the criteria are met, the request will be approved for 6 months for initial requests, and 12 months for renewal requests. If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review

PA Review Criteria	**Initial Authorization:**
	• The member's most recent triglyceride level is ≥880 mg/dL (10 mmol/L)
	• The member is refractory to standard triglyceride lowering therapies (e.g., statins, fibrates, omega-3 fatty acids, and niacin)
	• The member has undergone genetic testing to confirm a diagnosis of FCS with ONE of the following results:
	  ○ The member has a pathogenic gene mutation in FCS-causing genes (e.g., *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*)
	  ○ The member has inconclusive genetic results and has documentation supporting the diagnosis of FCS by ONE of the following:
	  ▪ North America Familial Chylomicronemia Syndrome (NAFCS) score ≥ 45
	  ▪ FCS score ≥ 10
	  ▪ History of acute pancreatitis
	  ▪ History of recurrent abdominal pain without other known causes
	• Medication is prescribed at an FDA approved dose
	• The prescriber attests the member will follow a low-fat diet
	
	Re-Authorization:
	• Documentation of a positive clinical benefit (e.g., reduction in fasting triglyceride level from baseline, fewer acute pancreatitis events)
	• Medication is prescribed at an FDA approved dose
	• The prescriber attests the member will continue to follow a low-fat diet

Criteria Statement	Tryngolza is reserved for members who have a diagnosis of FCS, triglyceride level of ≥880 mg/dL (10mmol/L), are refractory to standard triglyceride lowering therapies, and will follow a low-fat diet.
Last P&T Review Date	6/2025

New

Crenessity	
Therapeutic Classes (AHFS)	Pituitary Agents
Medications	Crenessity (crinecerfont)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	• Patients with non-classic congenital adrenal hyperplasia (CAH) • Patients with adrenal insufficiency due to causes other than 21-hydroxylase deficiency
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescribed by, or in consultation with, an endocrinologist or other specialist experienced in managing congenital adrenal hyperplasia
Coverage Duration	If all of the criteria are met, the request will be approved for 6 months for initial requests, and 12 months for renewal requests. If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review
PA Review Criteria	**Initial Authorization:** • Medically confirmed diagnosis of classic 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) • Patient is currently on stable regimen of glucocorticoid therapy at a supraphysiological dose (i.e. >13 mg/m2/day in hydrocortisone dose equivalents for adults and >12 mg/m2/day in hydrocortisone dose equivalents for pediatric patients 4-17 years old) • Medication is prescribed at an FDA approved dose according to package insert (patient's current weight must be provided) • For all adults and pediatric patients weighing ≥55 kg or patients weighing ≥20 kg if CYP3A4 dose adjustment is required: capsule formulation is requested, or documentation is provided that patient is unable to swallow capsule whole • Dosing requests for capsule formulations will employ strategies to minimize the total number of capsules used daily (i.e. "doubling up" on lower strength capsules to achieve a higher dose when the requested dose strength exists will not be authorized) **Re-Authorization:** • Documentation is provided that patient has successfully achieved a reduction in glucocorticoid dosage from baseline. • Medication is prescribed at an FDA approved dose according to package insert (patient's current weight must be provided) • For all adults and pediatric patients weighing ≥55 kg or patients weighing ≥20 kg if CYP3A4 dose adjustment is required: capsule formulation is requested, or documentation is provided that patient is unable to swallow capsule whole • Dosing requests for capsule formulations will employ strategies to minimize the total number of capsules used daily (i.e. "doubling up" on lower strength capsules to achieve a higher dose when the requested dose strength exists will not be authorized)
Criteria Statement	Crenessity is reserved for members who have a confirmed diagnosis of classic 21-hydroxylase deficiency CAH, and who are currently on stable regimen of glucocorticoid therapy at a supraphysiological dose.
Last P&T Review Date	6/2025

New

H. Pylori Treatment Medications	
Therapeutic Classes (AHFS)	Antiulcer Agents and Acid Suppressants, miscellaneous
Medications	Formulary, PA required Talicia (omeprazole/rifabutin/amoxicillin) Voquezna Dual Pak (vonoprazan/amoxicillin) Voquezna Triple Pak (vonoprazan/amoxicillin/clarithromycin) Non-Formulary, PA required Pylera (bismuth subcitrate/metronidazole/tetracycline) bismuth/metronidazole/tetracycline (Pylera) Omeclamox-Pak (omeprazole/amoxicillin/clarithromycin)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescribed by, or in consultation with, a gastroenterologist, infectious disease specialist, or other specialist with expertise in the treatment of H. pylori infection
Coverage Duration	If all of the criteria are met, the request will be approved for up to 14 days If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review
PA Review Criteria	**Initial Authorization:** • Patient has a confirmed H. pylori positive infection • Patient has a trial and failure of a generic, guideline recommended, first-line regimen for H. pylori infection such as bismuth quadruple therapy (PPI + bismuth subsalicylate + tetracycline + metronidazole), or a medical reason is provided it would be inappropriate • Requested dose is appropriate per labeling Renewal requests for treatment of H.pylori infection will not be approved.
Criteria Statement	Pylera, Talicia, Voquezna dual/triple Pak, and Omeclamox-Pak are reserved for members who have H. pylori infection, tried and failed or had a medical reason not to use bismuth quadruple therapy.
Last P&T Review Date	6/2025

New

MEK Inhibitors for Neurofibromatosis Type 1 (NF1)	
Therapeutic Classes (AHFS)	Antineoplastic Agents
Medications	Gomekli (mirdametinib), Koselugo (selumetinib)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Prior use of a MEK inhibitor
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age According to package insert
Prescriber Restrictions	N/A
Coverage Duration	If all of the criteria are met, the request will be approved for 6 months for initial requests, and 12 months for renewal requests. If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review
PA Review Criteria	**Initial Authorization:** • Documentation of neurofibromatosis type 1 (NF1) with symptomatic plexiform neurofibromas (PN) not amenable to complete resection • Drug will be given as monotherapy • Medication is prescribed at an FDA approved dose **Re-Authorization:** • Documentation or provider attestation of positive clinical response (i.e. no evidence of progressive disease) • Medication is prescribed at an FDA approved dose
Criteria Statement	Gomekli and Koselugo are reserved for members who have a confirmed diagnosis of NF1 with symptomatic PN not amenable to complete resection, and drug will be given as monotherapy.
Last P&T Review Date	6/2025

New

Kebilidi	
Medications	Kebilidi (eladocagene exuparvovec-tneq)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Previous treatment with gene therapy
Required Clinical Information	See “Other Criteria” below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a geneticist or neurologist
Coverage Duration	If all the criteria are met, the request will be approved for one treatment per lifetime (4 infusions)
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization** • Medication is prescribed at an FDA approved dose • Documentation of genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency evidenced by biallelic mutations in the *DDC* gene (copy of genetic test submitted with request) • Documentation of skull maturity confirmed by neuroimaging • Patient has classic clinical characteristics (e.g. oculogyric crises, hypotonia, developmental delay) of AADC deficiency that are not well-managed by symptomatic control drugs (i.e. dopamine agonists, monoamine oxidase inhibitor, pyridoxine, etc.) If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review
Last Review Date	6/2025

New

Agents for graft versus host disease	
Medications	Niktimvo (axatilimab-csfr) Ryoncil (remestemcel-L-rknd)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "Other Criteria" below
Age Restrictions	According to package insert Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a hematologist, oncologist, or other specialist in the treatment of hematopoietic cell transplants
Coverage Duration	Niktimvo: If all of the criteria are met, the request will be approved for a 3 month duration for initial requests and a 6 month duration for reauthorization requests. Ryoncil: If all of the criteria are met, the initial request will be approved for a 2 month duration (12 infusions total). The reauthorization request will be approved for a 1 month duration (8 infusions total).
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Niktimvo
	  ○ Member has a diagnosis of chronic graft versus host disease
	  ○ Member has tried and failed at least two lines of systemic immunosuppressive therapy (e.g., corticosteroids, calcineurin inhibitors, mycophenolate mofetil, ibrutinib, ruxolitinib), one of which must be a systemic corticosteroid, or documentation is provided as to why a systemic corticosteroid cannot be used
	  ○ The drug is prescribed at an FDA-approved dose
	  ○ Member's weight is provided (indicated for ≥40kg weight)
	• Ryoncil
	  ○ Member has a diagnosis of acute graft versus host disease
	  ○ Member has tried and failed or cannot use a systemic corticosteroid or documentation is provided as to why a systemic corticosteroid cannot be used
	  ○ Medication is prescribed at an FDA approved dose
	  ○ Member's weight is provided
	
	Re-Authorization:
	• Documentation is provided that the member has achieved a clinical benefit from medication (e.g., symptom improvement, reduction in corticosteroid dose)
	• Medication is prescribed at an FDA-approved dose
	• For Ryoncil requests: documentation is provided that member has a recurrence of GvHD after achieving a complete response with initial therapy of Ryoncil
	
	If all of the above criteria are not met for initial or re-authorization, the request is referred to a Clinical Reviewer for medical necessity review

Last Review Date	6/2025

New

Fertility Agents	
Medications	Cetrotide (cetrorelix), ganirelix (Fyremadel), choriogonadotropin alfa (Pregnyl), chorionic gonadotropin (Novarel), Ovidrel (choriogonadotropin alfa), Follistim AQ (follitropin beta), Gonal-F, Gonal-F RFF, Gonal-F RFF Rediject (follitropin alfa), Menopur (menotropins) Any other newly approved medication for fertility
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Pregnancy
Required Clinical Information	See "Other Criteria" below
Age Restrictions	N/A
Prescriber Restrictions	Prescriber is experienced in fertility treatment, such as OB/GYN, fertility specialist, endocrinologist, etc.
Coverage Duration	If all the criteria are met, the request will be approved for 12 months If the request is for in vitro fertilization, the request will be approved for up to 3 cycles
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Medication is prescribed for an FDA-approved indication for treatment of infertility
	• Medication is prescribed at an FDA-approved or compendia supported dose and duration of therapy
	• Requests for Novarel or Ovidrel:
	  ○ Documentation of a trial and therapy failure, intolerance, or medical reason why patient cannot use Pregnyl
	• Requests for Cetrotide:
	  ○ Documentation of a trial and therapy failure, intolerance, or medical reason why patient cannot use ganirelix
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review

Last Review Date	6/2025

Tryngolza	
Medications	Tryngolza (olezarsen)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "Other Criteria" below
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be an endocrinologist, lipidologist, or cardiologist experienced in, or in consultation with a specialist experienced in, familial chylomicronemia syndrome (FCS)
Coverage Duration	If all the criteria are met, the request will be approved for 6 months for initial requests, and 12 months for renewal requests.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• The member's most recent triglyceride level is ≥880 mg/dL (10 mmol/L)
	• The member is refractory to standard triglyceride lowering therapies (e.g., statins, fibrates, omega-3 fatty acids, and niacin)
	• The member has undergone genetic testing to confirm a diagnosis of FCS with ONE of the following results:
	  ○ The member has a pathogenic gene mutation in FCS-causing genes (e.g., *LPL*, *GPIHBP1*, *APOA5*, *APOC2*, or *LMF1*)
	  ○ The member has inconclusive genetic results and has documentation supporting the diagnosis of FCS by ONE of the following:
	  ▪ North America Familial Chylomicronemia Syndrome (NAFCS) score ≥ 45
	  ▪ FCS score ≥ 10
	  ▪ History of acute pancreatitis
	  ▪ History of recurrent abdominal pain without other known causes
	• Medication is prescribed at an FDA approved dose
	• The prescriber attests the member will follow a low-fat diet
	
	Re-Authorization:
	• Documentation of a positive clinical benefit (e.g., reduction in fasting triglyceride level from baseline, fewer acute pancreatitis events)
	• Medication is prescribed at an FDA approved dose
	• The prescriber attests the member will continue to follow a low-fat diet
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review

Last Review Date	6/2025

Alzheimer's Disease

Executive Summary

Class Overview

Alzheimer's disease (AD) is the most common form of dementia in older adults accounting for 60 to 80 percent of cases. In the United States in 2011, there were approximately 4.5 million prevalent cases of clinical AD in persons over 65 years. The prevalence is expected to more than triple (from 2011 estimates) by the year 2050 to 13.8 million cases in the US. AD is hypothesized to be caused, in part, by amyloid β deposition in the brain leading to synaptic dysfunction and neurodegeneration. Mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) genes may underlie early-onset AD which presents before age 65. Early-onset AD may also occur sporadically. The cause of late-onset AD is more complex influenced by genetic, epigenetic, and environmental factors. Memory impairment is the most common symptom of AD, followed by executive function and problem-solving deficits and behavioral or psychological symptoms. Other symptoms include apraxia, olfactory dysfunction, sleep disturbance, and seizures. The average life expectancy after a diagnosis of AD has been reported to be between 8 and 10 years, but this may vary based on disease progression. Survival also relates to age at onset of symptoms.

AD drugs primarily fall into two categories: medications that potentially delay disease progression, and medications that treat cognitive AD symptoms. Several organizations define AD stages with different terms, although each describes decline of cognitive function and changes in behavior. In 2024 the Alzheimer's Association Workgroup released revised criteria for the diagnosis and staging of AD. The revised criteria highlight that AD is defined by its unique neuropathologic findings; therefore, detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease. Older guidelines primarily provide recommendations for treatment of AD in three stages – mild (early), moderate (middle), and severe (late). Cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists are indicated for the treatment of AD. Guidelines recommend ChEIs as first-line treatment for mild to moderate disease with no specific agent preference. Selection should be individualized to the patient based on dosage form, tolerability, and side effects. The only available NMDA antagonist, memantine (Namenda®), is recommended for moderate to severe disease. Amyloid directed monoclonal antibodies (Kisunla™ and Leqembi®) are disease-modifying agents that may change the course of disease if initiated early in treatment. There are other agents that treat behavioral and psychological symptoms associated with AD, but this class review will primarily focus on the cognitive symptoms and related drugs associated with AD.

Utilization Findings

There were 5 claims for 4 members, for a total cost of $79.93 and an average cost per claim of $15.99. The most highly utilized medication was donepezil tablet, with 3 claims, followed by memantine tablets with 2 claims. There were no prior authorization requests.

Recommendations

- Add Zunveyl (benzgalantamine) to PA criteria as a 3rd line agent (PA required)
    - New cholinesterase inhibitor indicated for the treatment of mild to moderate dementia of the Alzheimer's type in adults

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Clinical Summary

Alzheimer's disease (AD) is an irreversible and progressive dementia characterized by memory loss, impaired executive function, and behavioral and psychological symptoms. AD affects an estimated 55 million people worldwide and is the most common cause of dementia among older adults. AD is the fifth-leading cause of death in Americans aged 65 and older. Inherited forms of AD may occur in younger patients who exhibit autosomal dominant gene mutations that alter beta-amyloid protein production or metabolism, but this is rare. The pathogenesis of AD is not fully understood. The prevailing theory involves the overproduction and decreased clearance of amyloid beta peptides that are produced by the cleavage of a protein translated from the amyloid precursor protein gene. Neurotoxic plaques are formed due to extracellular amyloid beta deposition and neurofibrillary tangles, which are the result of intracellular accumulation of hyperphosphorylated tau protein. Patients also have a reduced volume of choline acetyl transferase, which leads to a decrease in acetylcholine synthesis and subsequent cortical cholinergic function.

Diagnosis is typically made based on symptomatology and criteria for diagnosis is provided by the National Institute on Aging and the Alzheimer's Association (NIA-AA), the standardized Mini-Mental Examination (sMMSE), and the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5). In 2024, the Alzheimer's Association Workgroup released revised criteria for the diagnosis and staging of AD. The fundamental principles highlight the importance of biomarker testing:

- It is necessary to separate syndrome (clinically identified impairment) from biology (etiology).
- AD is defined by its biology with the following implications.
- AD is defined by its unique neuropathologic findings; therefore, detection of AD neuropathologic change by biomarkers is equivalent to diagnosing the disease.
- AD exists on a continuum. The disease is first evident in vivo with the appearance of disease-specific Core biomarkers while people are asymptomatic. Pathophysiologic mechanisms involved with processing and clearance of protein fragments may be involved very early in the disease process, but these are not yet well understood.
- Symptoms are a result of the disease process and are not necessary to diagnose AD.
- Unimpaired individuals with abnormal biomarker test results are at risk for symptoms due to AD. They are not at risk for a disease they already have.
- Clinical syndromes commonly seen with AD may also be caused by disorders other than AD, and therefore clinical presentation alone is not diagnostic of AD.
- The same AD biology may result in different phenotypic presentations.

Neuropsychological testing and biomarker data may be used to confirm diagnosis. Several organizations define AD stages with different terms, although each describes decline of cognitive function and changes in behavior.

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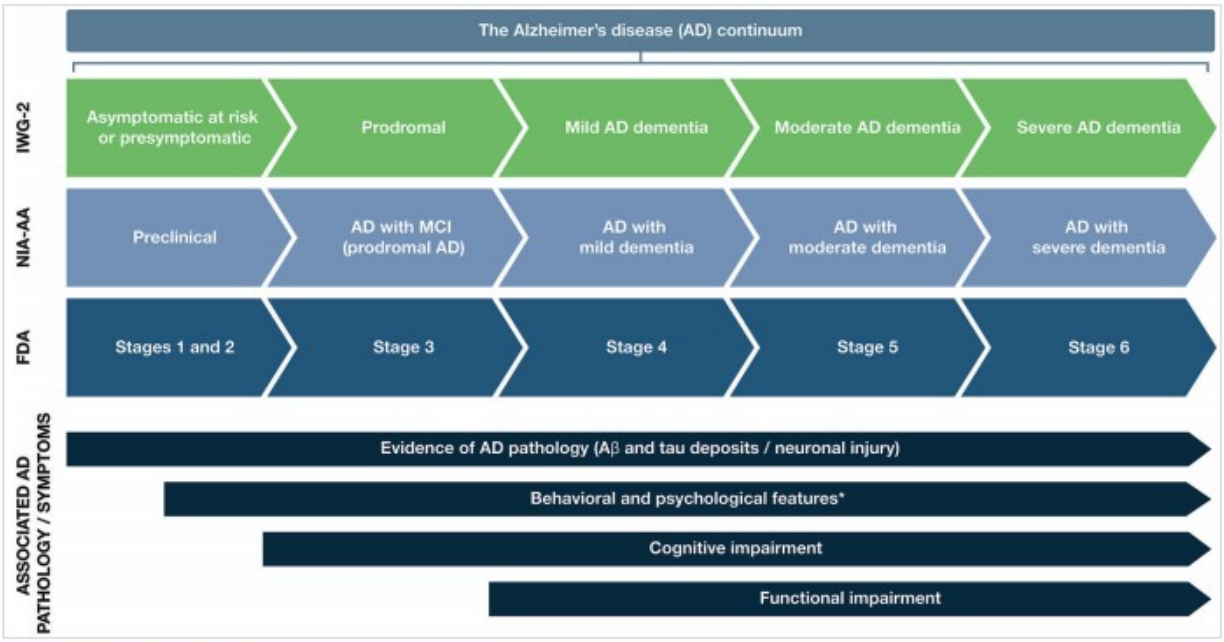
Variations in Nomenclature of Stages in the Alzheimer's Disease Continuum



Source: *J Prev Alz Dis*, 2021

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease, FDA, Food and Drug Administration; IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging: Alzheimer's Association

AD primarily progresses in three stages: mild (early stage), moderate (middle stage), and severe (late stage). As the disease progress, patients become more dependent on caregivers. Patients in the mild stage may have some functional dependence, whereas patients in the moderate stage may require assistance with driving, shopping, and decision-making. During the severe stage, patients are completely dependent on a caregiver. The treatment of AD involves disease modifying therapies and pharmacologic therapies aimed at symptom management. Treatment options consist of cholinesterase inhibitors (ChEIs), N-methyl-D-aspartate (NMDA) receptor antagonists, and amyloid directed monoclonal antibodies. ChEIs work by increasing cholinergic transmission, which results in a modest symptomatic benefit. NMDA receptor antagonists prevent the overstimulation of glutamate receptors, which are thought to contribute to neuronal toxicity and cell death. Amyloid directed monoclonal antibodies (Kisunla™ and Leqembi®) work by removing beta-amyloid, a protein that accumulates into plaques, from the brain. Clinical guidelines recommend ChEIs as first-line treatment for mild-to-moderate AD. These include donepezil (Aricept®, Adlarity®), galantamine, and rivastigmine (Exelon®). There is no preferred ChEI and therefore, selection should be individualized to the patient based on dosage form, tolerability, and adverse effects. Although this class review focuses on disease modifying treatment and cognitive symptom management, it should be noted that in May 2023, Rexulti® (brexpiprazole) became the first agent approved to treat agitation associated with dementia due to AD.

Donepezil is indicated for mild, moderate, or severe AD and is available as both an oral tablet, patch, and orally disintegrating tablet. Galantamine is indicated for mild to moderate AD and is available as immediate release tablets and solution and extended-release capsules. Zunveyl® (benzgalantamine) is the prodrug of galantamine and was approved in

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July 2024. Zunveyl® was designed to significantly reduce the adverse effects observed with the other acetylcholinesterase inhibitors, especially gastrointestinal side effects. Although Zunveyl® is expected to have an improved tolerability profile, this agent enters a crowded space with numerous low-cost generics already available. Zunveyl® is expected to be available in Q1 2025. Rivastigmine is available as an oral capsule and transdermal patch. Memantine (Namenda®), the only available NMDA receptor antagonist, is recommended for moderate-to-severe AD and is available in both immediate and extended-release tablets. Memantine-donepezil ER (Namzaric®) combines an NMDA receptor antagonist with a ChEI and is indicated for moderate to severe disease in patients already stabilized on donepezil 10 mg. Kisunla™ (donanemab-azbt) and Leqembi® (lecanemab-irmb) are amyloid beta-directed antibodies indicated for the treatment of AD. Treatment with these disease modifying agents should be initiated in patients with mild cognitive impairment or mild dementia stage of disease. Unlike Leqembi®, Kisunla™ was designed with “finite” dosing, meaning the drug can be discontinued once the amyloid beta plaques are cleared.

The first FDA approved amyloid directed monoclonal antibody was Aduhlem® (aducanumab) in 2021, followed by Leqembi® and Kisunla™ in 2023 and 2024, respectively. Although Aduhelm’s approval was a landmark event for the AD field, the steep cost and questionable efficacy of Aduhelm® caused controversy from the start of its approval journey. The manufacturer of Aduhelm®, Biogen, announced in January 2024 that it would be discontinuing the drug. According to Biogen, aducanumab was discontinued for the company "to reprioritize its resources in Alzheimer's disease.” Aduhelm® was officially off the market in November 2024. A work group convened by the Alzheimer's Association has released revised biology-based criteria for the diagnosis and staging of AD, including a new biomarker classification system that incorporates fluid and imaging biomarkers as well as an updated disease staging system. The work group organized AD biomarkers into three main categories: (1) core biomarkers of AD neuropathologic change (ADNPC), (2) nonspecific biomarkers that are important in AD but are also involved in other brain diseases, and (3) biomarkers of diseases or conditions that commonly coexist with AD. The approval of the amyloid directed therapies demonstrates the shifting landscape of AD treatment towards earlier intervention and biomarker-guided approaches in AD.

Extensive research and development into novel compounds for the treatment of AD is currently underway. Notable products include a new subcutaneous auto-injector formulation of Leqembi® with anticipated approval in August 2025, and an oral amyloid directed therapy, valiltramiprosate, which is in phase III of trials. Valiltramiprosate, also known as ALZ-801, has the potential to be the first-in-class oral disease modifying treatment for AD. Remternetug, also referred to as N3pG4 and LY3372993, is another amyloid directed inhibitor being investigated in subcutaneous and intravenous formulations. Remternetug, which has an estimated potential approval in 2027-2029, is designed similarly to Kisunla® with “finite” dosing. Novo Nordisk is investigating semaglutide as a potential add-on therapy to current AD therapies with primary study completion in late 2026. Other studies of interest include the AHEAD-3-45 and TRAILBLAZER-ALZ 3 trials which will investigate the use of Leqembi® and Kisunla™ in preclinical AD.

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Indications, Dosing and Administration

Medication	Indications	Dosing/Administration
Cholinesterase Inhibitors		
donepezil (Aricept®) 5 mg, 10 mg, 23 mg oral tablet donepezil 5 mg, 10 mg ODT Adlarity® (donepezil) 5mg/day, 10mg/day weekly patch	• Treatment of mild, moderate, or severe dementia of the Alzheimer type.	Oral: • Mild-to-moderate AD: 5 mg once daily, may increase to 10 mg once daily after 4 to 6 weeks. • Moderate-to-severe AD: 5 mg once daily, may increase to 10 mg once daily after 4 to 6 weeks, may increase to 23 mg once daily after > 3 months. Patch: • The recommended starting dosage is 5 mg/day. After 4 to 6 weeks, the dosage may be increased to the maximum recommended dosage of 10 mg/day. • If a patient has been on 5 mg/day oral donepezil for at least 4-6 weeks or on 10 mg/day of oral donepezil, the recommended starting dosage is 10 mg/day. • Administer Adlarity as one transdermal system applied to the skin once weekly.
galantamine 4 mg, 8mg, 12 mg oral tablet galantamine 4mg/ml oral solution galantamine ER 8mg, 16mg, 24mg oral capsule	• Treatment of mild-to-moderate dementia of Alzheimer's disease.	Mild-to-moderate AD: • IR tablet or solution: 4 mg twice daily for 4 weeks, increase to 8 mg twice daily for > 4 weeks, then may increase to 12 mg twice daily based on clinical benefit and tolerability; range: 16-24 mg daily in two divided doses. • Extended-release: 8 mg once daily for 4 weeks, increase to 16 mg once daily for > 4 weeks, then may increase to 24 mg once daily based on clinical benefit and tolerability; range: 16-24 mg once daily.
Rivastigmine 1.5 mg, 3 mg, 4.5 mg, 6 mg oral capsule rivastigmine (Exelon®) 4.6 mg/24 hour, 9.5 mg/24 hour, 13.3 mg/24 hour transdermal patch	Oral: • Treatment of mild to moderate dementia of the Alzheimer type. • Treatment of mild to moderate dementia associated with Parkinson disease. Transdermal:	Mild-to-moderate AD and Parkinson-related dementia: • Oral: 1.5 mg twice daily for 2 weeks (AD) or 4 weeks (PD), may increase by 3 mg daily every 2 weeks based on tolerability; Max: 6 mg twice daily. • Transdermal patch: Apply 4.6 mg/24 hours patch once daily, after 4 weeks may increase to 9.5 mg/24 hours

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Medication	Indications	Dosing/Administration
	• Treatment of mild, moderate, and severe dementia of the Alzheimer type. • Treatment of mild to moderate dementia associated with Parkinson disease.	patch, then to 13.3 mg/24 hours patch; Max: 13.3 mg/24 hours. Severe AD: • Transdermal patch: Apply 4.6 mg/24 hours patch once daily, after 4 weeks may increase to 9.5 mg/24 hours patch, then to 13.3 mg/24 hours patch; Max: 13.3 mg/24 hours. • Low body weight: Careful titration and monitoring should be performed in patients with low body weight (< 50 kg).
NMDA Antagonists		
memantine (Namenda® Titration Pak) 5 mg-10 mg dose pack memantine 2 mg/mL oral solution memantine 5 mg, 10 mg oral tablet memantine ER 7 mg, 14 mg, 21 mg, 28 mg oral capsule	• Treatment of moderate to severe dementia of the Alzheimer type.	Moderate-to-severe AD: • Immediate release: 5 mg daily, increase by 5 mg daily to a target dose of 20 mg daily; wait at least 1 week between dose changes; doses > 5 mg daily should be given in two divided doses. • Extended release: 7 mg once daily, increase by 7 mg daily to a target maximum dose of 28 mg once daily; wait at least 1 week between dose changes. • Dose reductions are recommended in severe renal impairment (CrCl 5-29 ml/min).
Combination Products		
memantine hcl/donepezil hcl (Namzaric®) 7mg-10mg, 21mg-10mg, 14mg-10mg, 28mg-10mg oral capsule	• Treatment of moderate to severe dementia of the Alzheimer type in patients stabilized on donepezil 10 mg once daily.	Moderate to severe AD: • Patients stabilized on donepezil 10 mg once daily and not currently on memantine: 7/10 mg once daily in the evening. Increase in increments of memantine ER 7 mg at intervals > 1 week to maintenance dose of memantine ER 28 mg/donepezil 10 mg once daily; max 28/10 mg daily. • Patients stabilized on memantine (10 mg twice daily or 28 mg ER once daily) and donepezil 10 mg: 28/10 mg once daily in the evening. • Dose reductions are recommended in severe renal impairment (CrCl 5-29 ml/min).
Amyloid Directed Monoclonal Antibodies		

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Medication	Indications	Dosing/Administration
Kisunla™ 320mg/20ml vial	• Treatment of Alzheimer's disease. Treatment with Kisunla should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in the clinical trials.	• 700 mg every four weeks for three doses, then 1400 mg every four weeks
Leqembi® 200mg/2ml, 500mg/5ml vial	• Treatment of Alzheimer's disease. Treatment with Leqembi should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials.	• 10 mg/kg once every 2 weeks administered as an intravenous infusion over approximately one hour ○ After 18 months, the regimen of 10 mg/kg once every two weeks may be continued, or a transition to the maintenance dosing regimen of 10 mg/kg once every 4 weeks may be considered

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Boxed Warnings and Contraindications

Medication	Boxed Warnings	Contraindications
Cholinesterase Inhibitors		
donepezil (Aricept®) 5 mg, 10 mg, 23 mg oral tablet donepezil 5 mg, 10 mg ODT Adlarity® (donepezil) 5mg/day, 10mg/day weekly patch	None	Known hypersensitivity to donepezil or to piperidine derivatives; History of allergic contact dermatitis with use of Adlarity.
galantamine 4 mg, 8mg, 12 mg oral tablet galantamine 4mg/ml oral solution galantamine ER 8mg, 16mg, 24mg oral capsule	None	Hypersensitivity to any component of the formulation.
Rivastigmine 1.5 mg, 3 mg, 4.5 mg, 6 mg oral capsule rivastigmine (Exelon®) 4.6 mg/24-hour, 9.5 mg/24 hour, 13.3 mg/24 hour transdermal patch	None	Hypersensitivity to rivastigmine, other carbamate derivatives, or any component of the formulation; history of application-site reactions with rivastigmine patch.
NMDA Antagonists		
memantine (Namenda® Titration Pak) 5 mg-10 mg dose pack memantine 2 mg/mL oral solution memantine 5 mg, 10 mg oral tablet memantine ER 7 mg, 14 mg, 21 mg, 28 mg oral capsule	None	Hypersensitivity to memantine or any component of the formulation.
Combination Products		
memantine hcl/donepezil hcl (Namzaric®) 7mg-10mg, 21mg-10mg, 14mg-10mg, 28mg-10mg oral capsule	None	Hypersensitivity to memantine, donepezil, piperidine derivatives, or any component of the formulation.

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Medication	Boxed Warnings	Contraindications
Amyloid Directed Monoclonal Antibodies		
Kisunla™ 320mg/20ml vial	Amyloid related imaging abnormalities	Hypersensitivity to donanemab-azbt or to any of the excipients.
Leqembi® 200mg/2ml, 500mg/5ml vial	Amyloid related imaging abnormalities	Hypersensitivity to lecanemab-irmb or to any of the excipients.

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Warnings/Precautions

Medication	Warnings/Precautions
Cholinesterase Inhibitors	
donepezil (Aricept®) 5 mg, 10 mg, 23 mg oral tablet donepezil 5 mg, 10 mg ODT Adlarity® (donepezil) 5mg/day, 10mg/day weekly patch	**Concerns related to adverse effects**: • Altered cardiac conduction • Anorexia/weight loss • GI effects: diarrhea, nausea, and/or vomiting • Neuroleptic malignant syndrome • Rhabdomyolysis • Application site reactions (Adlarity) **Disease-related concerns:** • Peptic ulcer disease • Respiratory disease • Seizure disorder • Urinary tract obstruction **Special populations:** • Low-weight patients: Patients weighing <55 kg may experience more nausea, vomiting, and weight loss than patients ≥55 kg **Concurrent drug therapy issues:** • Drug-drug interactions **Dosage form specific issues:** • Aspartame: Some products may contain aspartame, which is metabolized to phenylalanine and must be avoided (or used with caution) in patients with phenylketonuria.
galantamine 4 mg, 8mg, 12 mg oral tablet galantamine 4mg/ml oral solution galantamine ER 8mg, 16mg, 24mg oral capsule	**Concerns related to adverse effects:** • CNS depression • Skin reactions • Vagotonic effects • Weight loss **Disease-related concerns:** • Cardiac conduction abnormalities • Hepatic impairment • Peptic ulcer disease • Renal impairment • Respiratory disease • Seizure disorder • Urinary tract obstruction **Concurrent drug therapy issues:** • Drug-drug interactions **Special populations:** • Elderly: Limited safety data in patients ≥85 years of age
Rivastigmine 1.5 mg, 3 mg, 4.5 mg, 6 mg oral capsule rivastigmine (Exelon®) 4.6 mg/24-hour, 9.5 mg/24 hour,	**Concerns related to adverse effects:** • Allergic dermatitis • CNS depression • Extrapyramidal effects

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Medication	Warnings/Precautions
13.3 mg/24 hour transdermal patch	• GI effects • Vagotonic effects **Disease-related concerns:** • Peptic ulcer disease • Respiratory disease • Seizure disorder • Urinary tract obstruction **Concurrent drug therapy issues:** • Drug-drug interactions **Special populations:** • Body weight (low/high): Systemic exposure may be increased in patients <50 kg and decreased in patients >100 kg. Consider dose reduction if toxicities develop in patients <50 kg (oral and transdermal). • Smokers: Nicotine increases the clearance of rivastigmine by 23%. **Dosage form specific issues:** • Transdermal patch: May contain conducting metal (eg, aluminum); remove patch prior to MRI. **Other warnings/precautions:** • Appropriate use: Postmarketing cases of overdose (including rare fatalities) have been reported in association with medication errors/improper use of rivastigmine transdermal patches. No more than 1 patch should be applied daily and existing patch must be removed prior to applying new patch. • Initiation/interruption of therapy: Should be started at lowest dose and titrated; if treatment is interrupted for >3 days, reinstate at the lowest daily dose.
NMDA Antagonists	
memantine (Namenda® Titration Pak) 5 mg-10 mg dose pack memantine 2 mg/mL oral solution memantine 5 mg, 10 mg oral tablet memantine ER 7 mg, 14 mg, 21 mg, 28 mg oral capsule	**Concerns related to adverse effects:** • Hypersensitivity **Disease-related concerns:** • Cardiovascular disease • Hepatic impairment • Ophthalmic disease • Renal impairment • Seizure disorder **Other warnings/precautions:** • Urine pH: Clearance is significantly reduced by alkaline urine; use caution with medications, dietary changes, or patient conditions which may alter urine pH.
Combination Products	
memantine hcl/donepezil hcl (Namzaric®) 7mg-10mg, 21mg-10mg, 14mg-10mg, 28mg-10mg oral capsule	**Concerns related to adverse effects:** • Cardiovascular effects • GI effects • Neuroleptic malignant syndrome • Rhabdomyolysis

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Medication	Warnings/Precautions
	Disease-related concerns: • Cardiac conduction abnormalities • Peptic ulcer disease • Renal impairment • Respiratory disease • Seizure disorder • Urinary tract obstruction **Concurrent drug therapy issues:** • Drug-drug interactions **Other warnings/precautions:** • Urine pH: Clearance is significantly reduced by alkaline urine; use caution with medications, dietary changes, or patient conditions which may alter urine pH.
Amyloid Directed Monoclonal Antibodies	
Kisunla™ 320mg/20ml vial	**Concerns related to adverse effects:** • Infusion-related reactions • Amyloid related imaging abnormality-hemosiderin deposition superficial siderosis • Amyloid related imaging abnormality- hemosiderin deposition microhemorrhages • Amyloid related imaging abnormality – edema/effusion • Headache **Disease-related concerns:** • Incidence of intracerebral hemorrhage
Leqembi® 200mg/2ml, 500mg/5ml vial	**Concerns related to adverse effects:** • Infusion-related reactions • Amyloid related imaging abnormality- hemosiderin deposition microhemorrhages • Amyloid related imaging abnormality – edema/effusion • Headache **Disease-related concerns:** • Incidence of intracerebral hemorrhage

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Practice Guidelines

Jaqua EE, Tran MN, Hanna M. Alzheimer Disease: Treatment of Cognitive and Functional Symptoms. American Family Physician. 2024 Sep;110(3):281-293. PMID: 39283851.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	Evidence rating	Comments
Music therapy can be recommended to minimally improve behavioral disruption, mood, and cognition in patients with mild cognitive impairment or dementia.[14,15]	B	Systematic reviews of limited studies
Donepezil (Aricept) shows minor improvements in cognitive function, activities of daily living, and overall clinician-rated clinical state. Benefits of the 23-mg daily dosage are not significantly greater than those of the 10-mg daily dosage.[42]	A	Systematic review of RCT
Brexpiprazole (Rexulti) is approved for agitation caused by Alzheimer disease, and risperidone is more effective than placebo for acutely treating neuropsychiatric symptoms in people with dementia; however, antipsychotics should not be used routinely because of an elevated risk of mortality.[47,50,51]	B	Systematic review of RCTs, and a single RCT on brexpiprazole
Monoclonal antibody treatments have not demonstrated a meaningful benefit in patient-centered outcomes such as cognition; despite U.S. Food and Drug Administration approval, there are safety concerns, including amyloid-related imaging abnormalities.[23,25,54]	B	Meta-analysis of RCTs with a mix of disease-oriented and patient-oriented outcomes
There is no evidence that vitamin E benefits cognition in patients with mild cognitive impairment or dementia.[58]	B	Systematic review of RCTs

RCT = randomized controlled trial.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to https://www.aafp.org/afpsort.

Recommendation Definitions

Class/Level	Definition
A	Consistent, good-quality, patient-oriented evidence
B	Inconsistent or limited-quality patient-orientated evidence
C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Petersen RC, Lopez O, Armstrong MJ. Practice guideline update summary: Mild cognitive impairment Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90(3): 126-135.

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Section A: Recommendations for assessing for MCI
1. For patients for whom the patient or a close contact voices concern about memory impaired cognition, clinicians should assess for MCI and not assume the concerns are related to normal aging (Level B).
2. When performing a Medicare Annual Wellness Visit, clinicians should not rely on historical report of subjective memory concerns alone when assessing for cognitive impairment (Level B).
3. For patients for whom screening or assessing for MCI is appropriate, clinicians should use validated assessment tools to assess for cognitive impairment (Level B). For patients who test positive for MCI, clinicians should perform a more formal clinical assessment for diagnosis of MCI (Level B).
4. For patients with MCI, clinicians should assess for the presence of functional impairment related to cognition before giving a diagnosis of dementia (Level B).
5. For patients suspected to have MCI, clinicians who lack the necessary experience should refer these patients to a specialist with experience in cognition (Level B).
6. For patients diagnosed with MCI, clinicians should perform a medical evaluation for MCI risk factors that are potentially modifiable (Level B).
7. A. For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Level B).
7. B. For interested patients, clinicians may discuss the option of biomarker research or refer patients, or both, if feasible, to centers or organizations that can connect patients to this research (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).
8. For patients diagnosed with MCI, clinicians should perform serial assessments over time to monitor for changes in cognitive status (Level B).

Section B: Recommendations for Management of MCI
1. For patients diagnosed with MCI, clinicians should wean patients from medications that can contribute to cognitive impairment (where feasible and medically appropriate) and treat modifiable risk factors that may be contributing (Level B).
2. For patients diagnosed with MCI, clinicians should counsel the patients and families that there are no pharmacologic or dietary agents currently shown to have symptomatic cognitive benefit in MCI and that no medications are FDA-approved for this purpose (Level B).
3. A. For patients diagnosed with MCI, clinicians may choose not to offer cholinesterase inhibitors (Level B).
3. B. If clinicians choose to offer cholinesterase inhibitors, they must first discuss with patients the fact that this is an off-label prescription not currently backed by empirical evidence (Level A).
4. For patients diagnosed with MCI who are interested in pharmacologic treatment, clinicians may inform these patients of centers or organizations that can connect patients to clinical trials (e.g., subspecialty centers, Trial Match, ClinicalTrials.gov) (Level C).
5. For patients diagnosed with MCI, clinicians should recommend regular exercise (twice/week) as part of an overall approach to management (Level B).
6. For patients diagnosed with MCI, clinicians should discuss diagnosis and uncertainties regarding prognosis. Clinicians should counsel patients and families to discuss long-term planning topics such as advance directives, driving safety, finances, and estate planning (Level B).
7. Clinicians should assess for behavioral and neuropsychiatric symptoms in MCI and treat with both pharmacologic and nonpharmacologic approaches when indicated (Level B).
8. In patients with MCI, clinicians may recommend cognitive interventions (Level C).

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Recommendation Definitions

Class/Level	Definition
A	Consistent, good-quality, patient-oriented evidence
B	Inconsistent or limited-quality patient-orientated evidence
C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

Choosing Wisely: An initiative of the ABIM Foundation. (2017)
Alzheimer's disease or dementia related recommendations:

- Don't insert percutaneous feeding tubes in individuals with advanced dementia. Instead, offer oral assisted feedings.
- Don't prescribe antipsychotic medications for behavioral and psychological symptoms of dementia (BPSD) in individuals with dementia without an assessment for an underlying cause of the behavior.
- Don't assume a diagnosis of dementia in an older adult who presents with an altered mental status and/or symptoms of confusion without assessing for delirium or delirium superimposed on dementia using a brief, sensitive, validated assessment tool.
- Don't use physical or chemical restraints, outside of emergency situations, when caring for long-term care residents with dementia who display behavioral and psychological symptoms of distress; instead assess for unmet needs or environmental triggers and intervene using non-pharmacological approaches as the first approach to care whenever possible.
- Don't order APOE genetic testing as a predictive test for Alzheimer disease.
- Don't use antipsychotics as the first choice to treat behavioral and psychological symptoms of dementia.
- Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.
- Don't use PET imaging in the evaluation of patients with dementia unless the patient has been assessed by a specialist in this field.

Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Guideline watch (October 2014): practice guideline for the treatment of patients with Alzheimer's disease and other dementias.
Recommendations for mild-to-moderate disease:

- Cholinesterase inhibitors are recommended. Available products have shown modest benefits and similar rates of adverse effects.

Recommendations for moderate-to-severe disease:

- Memantine is recommended as it may provide modest benefit with few adverse effects.
- There is evidence to suggest that memantine in combination with donepezil is more efficacious than donepezil alone, however there is no evidence that the combination is better than memantine alone.
- Cholinesterase inhibitors may provide some symptomatic benefit in severe AD.

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Clinical Trials/Systematic Reviews/Meta-Analyses

Citation	Design	Endpoints
Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev. 2018 Jun 18;6:CD001190. doi: 10.1002/14651858.CD001190.pub3.	N=8257 patients in 30 studies Updated version of previous Cochrane review first published in 1996, most recent update in 2006.	Primary endpoints: To assess the clinical efficacy and safety of donepezil in people with mild, moderate or severe dementia due to Alzheimer's disease, to compare the efficacy and safety of different doses of donepezil, and to assess the effect of donepezil on healthcare resource use and costs.

Results:

- Studies were of short duration (6 months or less). Only 1 small trial lasted 52 weeks.
- The majority of the studies tested patients with mild to moderate disease.
- The main analysis compared the safety and efficacy of donepezil 10 mg/day with placebo at 24 to 26 weeks of treatment, and was associated with better outcomes for cognitive functions on several different scales (the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog, range 0 to 70) (mean difference (MD) -2.67, 95% confidence interval (CI) -3.31 to -2.02, 1130 participants, 5 studies), the Mini-Mental State Examination (MMSE) score (MD 1.05, 95% CI 0.73 to 1.37, 1757 participants, 7 studies) and the Severe Impairment Battery (SIB, range 0 to 100) (MD 5.92, 95% CI 4.53 to 7.31, 1348 participants, 5 studies)).
- Activities of daily living as measured by the Alzheimer's Disease Cooperative Study activities of daily living score for severe Alzheimer's disease (ADCS-ADL-sev) also showed improvement with use of donepezil vs placebo (MD 1.03, 95% CI 0.21 to 1.85, 733 participants, 3 studies).
- Some measures which did not show improvements with donepezil use vs placebo were behavioral symptoms measured by the Neuropsychiatric Inventory (NPI) (MD -1.62, 95% CI -3.43 to 0.19, 1035 participants, 4 studies) and the Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) scale (MD 0.4, 95% CI -1.28 to 2.08, 194 participants, 1 study).
- Quality of life measures showed no difference between donepezil and placebo.
- Participants receiving donepezil were more likely to withdraw from the studies before the end of treatment (24% versus 20%, OR 1.25, 95% CI 1.05 to 1.50, 2846 participants, 12 studies) or to experience an adverse event during the studies (72% vs 65%, OR 1.59, 95% 1.31 to 1.95, 2500 participants, 10 studies).
- There was no evidence of a difference between donepezil and placebo for patient total healthcare resource utilization.

Conclusion: The reviewers found small benefits in cognitive function, activities of daily living, and clinician-rated global clinical state in patients with mild, moderate, and severe Alzheimer's dementia wen treated with donepezil for periods of 12 or 24 weeks. Benefits were slightly larger on the 10 mg/day dose vs the 5 mg/day dose, but this improvement was not seen between the 10mg and 23 mg dose. Side effects and discontinuation rates were positively correlated with higher dosing.

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Citation	Design	Endpoints
Kishi T, Matsunaga S, Oya K, Nomura I, Ikuta T, Iwata N. Memantine for Alzheimer's disease: an updated systematic review and meta-analysis. J Alz Dis.2017;60 (2):401-25.	N=7567 patients in 11 trials Systematic review and meta-analysis including trials of memantine in AD.	Primary endpoints: cognitive function (CF) scores, behavioral disturbances (BD) scores, all-cause discontinuation

Results:

- Memantine demonstrated significant improvement in CF [standardized mean difference (SMD) = –0.24; p < 0.00001, I2 = 35%] compared with placebo.
- Behavioral disturbance scores were improved with memantine compared with placebo (SMD = –0.16; p = 0.01, I2 = 52%).
- In the sensitivity analysis including only patients with moderate to severe AD, memantine was superior to the placebo in reducing BD without considerable heterogeneity (SMD = –0.20; p = 0.003; I2 = 36%).
- Compared with ChEIs alone, memantine + ChEIs showed a greater reduction in BD (SMD = –0.20; p = 0.02; I2 = 77%) and a non-significant trend toward CF improvement. However, in the sensitivity analysis of double-blind, placebo-controlled studies only, memantine + ChEIs showed a significant reduction in BD compared with ChEIs without considerable heterogeneity (SMD = –0.11; p = 0.04; I2 = 40%).
- No differences were detected in all-cause discontinuation between the groups.

Conclusion: The meta-analyses suggest the credible efficacy and safety of memantine in treating AD when used alone or in combination with ChEIs.

Citation	Design	Endpoints
Campbell NL, Perkins AJ, Gao S, et al. Adherence and tolerability of Alzheimer's disease medications: a pragmatic randomized trial. J Am Geriatr Soc. 2017;65(7):1497-1504.	N=196 Pragmatic, randomized, open-label, comparative trial Participants were randomized to one of the following groups: • donepezil for 18 weeks • galantamine for 18 weeks • rivastigmine for 18 weeks	Primary endpoints: Caregiver-reported adherence, caregiver-reported adverse event

Results:

- Discontinuation rates after 18 weeks: donepezil 38.8%, galantamine 53%, rivastigmine 58.7% (p=0.063). The most common reasons for discontinuation were adverse events (73.1%) and cost (25.4%). No participants discontinued donepezil due to cost.
- Adverse events were reported by 81.2% of participants with no significant between-group differences.

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Conclusion: This pragmatic comparative trial showed high rates of adverse events and cost-related non-adherence with AChEIs. Interventions improving adherence and persistence to AChEIs may improve AD management.

Citation	Design	Endpoints
Chen R, Chan P, Chu H, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: a meta-analysis. PLoS One. 2017;12(8): e0183586	11 studies published between 2004 and 2015 PubMed, Medline, Embase, PsycINFO, and Cochrane databases were used to search for English and non-English articles for inclusion in the meta-analysis to evaluate the effect size and incidence of adverse drug reactions of different treatments. Inclusion criteria: · Peer-reviewed articles that included patients with AD · Studies that compared the effects of donepezil with the combination of memantine and donepezil Exclusion criteria: · Systematic reviews or meta-analyses · Quantitative research · Non-randomized trials · Experiment group combined with other treatment · Studies without full text · Several outcomes pooled together	• Primary endpoints: Comparison of the treatment effects of the control (donepezil) and combination treatment (donepezil + memantine) on cognitive functions and behavioral and psychological symptoms in dementia (BPSD) • Secondary endpoints: Global functions as assessed at final evaluation, adverse effects

Results:

Primary

- Nine articles were included in the analysis of overall cognitive function; the effect size as evaluated using Hedges' g was 0.378 (95% CI: 0.193±0.562, $p < .001$, and $I2 = 57.145$), indicating a moderate effect size and significant difference favoring combination treatment.
- Eight articles were included in the analysis to determine the treatment effect on BPSD. The effect size of BPSD as expressed through Hedges' g was ±0.878 (95% CI: −1.256 to −0.500, $p < .001$, and $I2 = 82.116$), achieving a significant difference favoring combination treatment. Patients with moderate to severe AD in the combination treatment group exhibited greater improvements in BPSD than did those in the control group.

Secondary

- Five articles were included in the current analysis for global functional evaluations. The effect size as expressed through Hedges' g was −0.585 (95% CI: −0.981 to −0.188, $p = .004$, and $I2 = 87.358$), achieving a significant difference favoring the combination group. Patients with moderate to severe AD in the combination treatment group exhibited greater improvements.
- Gastrointestinal and psychiatric adverse events were reported most often and no significant differences were observed between groups

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Conclusion: Combination therapy consisting of donepezil and memantine demonstrated superiority over donepezil in this meta-analysis when evaluating cognitive, BPSD, and global functions. Adverse events between monotherapy and combination therapy were similar.

Citation	Design	Endpoints
Schmidt R, Hover E, Bouwman FH, et al. European Federation of Neurological Societies (EFNS)-European Neurological Society (ENS)/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease: a systematic review and meta-analysis. Eur J Neurol. 2015;22(6):889-98.	• Systematic review and meta-analysis of randomized controlled trials • MEDLINE, EMBASE, PsycINFO, CINAHL, Lilacs and major trial/pharmaceutical industry trial registers were searched between January 2004 and January 2013. • Four trials including 1,549 AD patients met the criteria.	Primary endpoints: improvement in global clinical impression (GCI), cognition, behavior, activities of daily living (ADL), and adverse events

Results:

- The standardized mean difference for ChEI/memantine combination therapy versus ChEI monotherapy for the specified outcomes were as follows: GCI = -0.20 (95% CI:-0.31, -0.09); cognitive function= -0.27 (95% CI: -0.37, -0.17); behavioral = -0.19 (95% CI: -0.31, -0.07).
- Quality of evidence was low for ADL and panelists gave a weak recommendation
- A cost analysis between the two regimens was also conducted. Studies show patients with AD who have behavioral symptoms are associated with higher care costs than those with little to no behavioral change. The neuropsychiatric inventory (NPI) tool uses a point system (maximum score of 144) to assess annual care costs (1-point increase = US $247-409). The combination therapy resulted in a 3-point difference when compared to ChEI monotherapy, which translates into substantial cost savings.

Conclusion: Desirable effects of combined ChEI/memantine outweigh undesirable effect; no evidence for major differences in adverse events. The authors recommend the use of combination ChEI/memantine rather than ChEI alone, however the strength of recommendation is weak.

Citation	Design	Endpoints
Hyde C, Peters J, Bond M, et al. Evolution of the evidence on the effectiveness and cost-effectiveness of acetylcholinesterase inhibitors and	• This was a health technology assessment (HTA)/ systematic review of the effectiveness and cost-effectiveness of donepezil, galantamine, rivastigmine and memantine • The systematic review of effectiveness evaluated randomized controlled trials (RCTs) and systematic reviews of RCTs addressing the HTA question	Primary endpoints: effectiveness, a systematic review of cost-effectiveness, a critical appraisal of industry submissions and an original health economic model of cost-effectiveness.

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memantine for Alzheimer's disease: systematic review and economic model. Age Ageing. 2013; 42(1):14-20.	• Electronic databases were searched from January 2004 to March 2010 • Key findings were compared with the data utilized by the NICE Guidance 2007	
Results: The authors found that donepezil had the least amount of additional information concerning clinical effectiveness, but studies confirmed statistically significant benefits of donepezil across all the main outcomes. Galantamine studies provided more evidence to support the beneficial effect on function, behavior and global impact. Rivastigmine studies provided more evidence to support the beneficial effect on cognition, function and global impact. Memantine studies provided more evidence to support the beneficial effect on function and global impact. Authors noted that there was no new clinical effectiveness evidence on the impact on rates of institutionalization or time to institutionalization. Authors noted marked changes in cost-effectiveness and found that all drugs were more cost-effective compared with basic supportive care. **Conclusion**: Change in evidence between 2004 and 2010 is consistent with 2011 NICE guidelines; donepezil, galantamine, rivastigmine and memantine are effective in AD. Evidence on cost-effectiveness has improved, but more research is needed.		

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Formulary Placement, Utilization and Cost Experience (01-01-2025 to 03-31-2025)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Cholinesterase Inhibitors								
donepezil (Aricept®) 5 mg , 10 mg, 23 mg oral tablet	3	3	$10.41	$3.47	0	0 (0%)	F-5mg & 10mg NF-23mg	No change
donepezil 5 mg, 10 mg orally disintegrating tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Adlarity® (donepezil) 5mg/day, 10mg/day weekly patch	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
galantamine 4 mg, 8mg, 12 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
galantamine 4mg/ml oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
galantamine extended release (ER) 8mg, 16mg, 24mg oral capsule	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
rivastigmine 1.5 mg, 3 mg, 4.5 mg , 6 mg oral capsule	0	0	$0.00	$0.00	0	0 (0%)	F	No change
rivastigmine (Exelon®) 4.6 mg/24 hour, 9.5 mg/24 hour, 13.3 mg/24 hour transdermal patch	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
NMDA Antagonists								
memantine (Namenda® Titration Pak) 5 mg-10 mg dose pack	0	0	$0.00	$0.00	0	0 (0%)	F	No change
memantine 2 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
memantine 5 mg, 10 mg oral tablet	2	1	$69.52	$34.76	0	0 (0%)	F	No change
memantine extended release (ER) 7 mg, 14 mg, 21 mg, 28 mg oral capsule	0	0	$0.00	$0.00	0	0 (0%)	F-ST (donepezil & memantine)	No change

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Combination Products								
Namzaric® (memantine hcl/donepezil hcl) 7mg-10mg, 21mg-10mg oral capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
memantine hcl/donepezil hcl (Namzaric®) 14mg-10mg, 28mg-10mg oral capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Amyloid Directed Monoclonal Antibodies								
Kisunla™ 320mg/20ml vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Leqembi® 200mg/2ml, 500mg/5ml vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**5**	**4**	**$79.93**	**$15.99**	**0**	**0 (0%)**		

Key (as applicable) F = Formulary, no restrictions; F-QL = Formulary, quantity limit applies; F-AL = Formulary, age limit applies; F-ST = Formulary, step therapy applies; F-PA = Formulary, PA required; NF = Non-formulary; X = Excluded

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Prior Authorization Criteria

Recommendation: Add Zunveyl--new cholinesterase inhibitor indicated for the treatment of mild to moderate dementia of the Alzheimer's type in adults.

Cholinesterase Inhibitors	
Therapeutic Classes (AHFS)	Parasympathomimetic (cholinergic agents)
Medications	Formulary, PA required galantamine (Razadyne) tablets and solution galantamine (Razadyne ER) capsules rivastigmine (Exelon) patches Non-formulary, PA required Donepezil (Aricept) 23mg tablet Adlarity (donepezil) 5 mg/day weekly patch Zunveyl (benzgalantamine) tablets
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial/Re-Approval** If all conditions are met, the request will be approved for up to 12 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.

PA Review Criteria	Criteria for approval
	• Galantamine tablet, galantamine ER capsule, ~~or~~ donepezil (Aricept) 23mg tablet, or Zunveyl are approved when the following criteria is met:
	  ○ Documentation of a trial/failure/contraindication to rivastigmine capsule or donepezil (Aricept) 5mg or 10mg tablet
	• Rivastigmine (Exelon) patches and Adlarity (donepezil) patches are approved when the following criteria is met:
	  ○ Documentation of a compliance issue or intolerance with oral therapy
	• Galantamine solution is approved when ONE of the following criteria is met:
	  ○ Documentation of a trial/failure/contraindication to rivastigmine capsule or donepezil (Aricept)
	  ○ Documentation of difficulty or inability to swallow

Criteria Statement	Galantamine tablet, galantamine ER capsule, Zunveyl, or donepezil (Aricept) 23mg tablet are reserved for members who have used (or cannot/should not use) rivastigmine capsule or donepezil 5mg or 10mg tablet. Rivastigmine patches and Adlarity patches are reserved for members who have an intolerance to or compliance issue with oral therapy. Galantamine solution is reserved for members who have used (or cannot/should not use) rivastigmine capsule or donepezil OR have difficulty or inability to swallow.
Last P&T Review Date	~~6/2024~~6/2025

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No changes

Leqembi	
Medications	Leqembi (lecanemab-irmb)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	Patients with moderate to severe Alzheimer's Disease (AD) Patients with neurodegenerative disease caused by a condition other than AD
Required Clinical Information	See "other criteria"
Age Restrictions	age 50-90 years
Prescriber Restrictions	Prescriber must be a neurologist
Coverage Duration	For initial authorization: the request will be approved for 6 months For reauthorization: if all of the conditions are met, the request will be approved for 6 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of mild cognitive impairment (MCI) caused by AD or mild AD consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ Clinical Dementia Rating Global (CDR-G) score of 0.5-1.0 and a Memory Box score of 0.5 or greater
	  ○ Mini-Mental State Examination (MMSE) score ≥ 22 and ≤ 30
	  ○ Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) score at least 1 standard deviation below age-adjusted mean
	• The request is for an FDA approved dose
	• Documentation of BOTH of the following:
	  ○ Recent, within past year, positive results for the presence of beta-amyloid plaques on a positron emission tomography (PET) scan or cerebrospinal fluid testing
	  ○ Recent, within past year, baseline Magnetic Resonance Imaging (MRI) scan
	• Physician has assessed baseline disease severity utilizing an objective measure/tool (i.e., Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog-14], Alzheimer's Disease Cooperative Study-Activities of Daily Living Inventory-Mild Cognitive Impairment version [ADCS-ADL-MCI], Clinical Dementia Rating Sum of Boxes [CDR-SB], etc.)
	• No recent (past 1 year) history of stroke, seizures or transient ischemic attack (TIA), or findings on neuroimaging that indicate an increased risk for intracerebral hemorrhage.
	
	Reauthorization
	• The request is for an FDA approved dose

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	• Patient continues to have a diagnosis of mild cognitive impairment (MCI) caused by AD or mild AD consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ CDR-G score of 0.5-1.0 and a Memory Box score of 0.5 or greater
	  ○ MMSE score of 22-30
	  ○ Wechsler Memory Scale IV-Logical Memory (subscale) II (WMS-IV LMII) score at least 1 standard deviation below age-adjusted mean
	• Provider attestation of safety monitoring and management of amyloid related imaging abnormalities (ARIA) and intracerebral hemorrhage, as recommended per the manufacturer's prescribing information.
	• Documentation that member has experienced clinical benefit from the medication (such as: stabilization or decreased rate of decline in symptoms from baseline on CDR-SB, ADAS-Cog14, or ADCS MCI-ADL scales)
	• No recent (past 1 year) history of stroke, seizures or TIA
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~6/2024~~6/2025

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No changes

Kisunla (donanemab-azbt)	
Medications	Kisunla (donanemab-azbt)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Patients with moderate to severe Alzheimer's Disease (AD) Patients with neurodegenerative disease caused by a condition other than AD
Required Clinical Information	See "Other Criteria" below
Age Restrictions	Age 60-85 years
Prescriber Restrictions	Prescriber must be a neurologist
Coverage Duration	For initial authorization: the request will be approved in accordance with the FDA-indicated titration schedule for up to 6 months. For reauthorization: if all of the conditions are met, the request will be approved for 6 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of mild cognitive impairment (MCI) caused by AD or mild AD dementia consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ Clinical Dementia Rating Global (CDR-G) score of 0.5-1.0
	  ○ Mini-Mental State Examination (MMSE) score ≥ 20 and ≤ 28
	  ○ Montreal Cognitive Assessment (MoCA) score of ≥16
	• The request is for an FDA approved dose
	• Documentation of BOTH of the following:
	  ○ Recent, within past year, positive results for the presence of beta-amyloid plaques on a positron emission tomography (PET) scan or cerebrospinal fluid testing
	  ○ Recent, within past year, baseline Magnetic Resonance Imaging (MRI) scan
	• Physician has assessed baseline disease severity utilizing an objective measure/tool (i.e., integrated Alzheimer's Disease Rating Scale [iADRS], Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog], Alzheimer's Disease Cooperative Study-instrumental Activities of Daily Living [ADCS-iADL], Clinical Dementia Rating-Sum of Boxes [CDR-SB], etc.)
	• No recent (past 1 year) history of stroke, seizures or transient ischemic attack (TIA), or findings on neuroimaging that indicate an increased risk for intracerebral hemorrhage
	Reauthorization
	• The request is for an FDA approved dose
	• Patient continues to have a diagnosis of MCI caused by AD or mild AD dementia consistent with Stage 3 or Stage 4 Alzheimer's disease as evidenced by at least one of the following:
	  ○ CDR-G score of 0.5-1.0
	  ○ MMSE score of 20-28
	  ○ MoCA score of ≥16

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	• Provider attestation of safety monitoring and management of amyloid related imaging abnormalities (ARIA) and intracerebral hemorrhage, as recommended per the manufacturer's prescribing information • Documentation that member has experienced clinical benefit from the medication (i.e., stabilization or decreased rate of decline in symptoms from baseline on CDR-SB, iADRS, ADAS-Cog, or ADCS-iADL scales) • No recent (past 1 year) history of stroke, seizures or TIA If all of the above criteria are not met for initial or re-authorization, the request is referred to a Clinical Reviewer for medical necessity review
Last Review Date	~~12/2024~~6/2025

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Non-proprietary Name

Proprietary Name	Non-proprietary Name	Interchangeability
Stelara®	ustekinumab	N/A
Steqeyma®	ustekinumab-stba	N
Yesintek™	ustekinumab-kfce	N
Imuldosa®	ustekinumab-srlf	N
Otulfi®	ustekinumab-aauz	Y
Pyzchiva®	ustekinumab-ttwe	Y
Selarsdi®	ustekinumab-aekn	Y
Wezlana™	ustekinumab-auub	Y

Y=yes; N=no

Prescribing Information

		Stelara	Steqeyma	Yesintek	Imuldosa	Otulfi	Pyzchiva	Selarsdi	Wezlana
Indication	Adult and pediatric patients 6 years and older patients with moderate to severe PsO who are candidates for phototherapy or systemic therapy	√	√	√	√	√	√	√	√
	Adults and pediatric patients 6 years and older with active PsA	√	√	√	√	√	√	√	√
	Adults with moderately to severely active CD	√	√	√	√	√	√	√	√
	Adults with moderately to severely active UC	√	√	√	√	√	√	√	√
How Supplied	45 mg/0.5ml single-dose prefilled syringe	√	√	√	√	√	√	√	√
	90 mg/ml single-dose prefilled syringe	√	√	√	√	√	√	√	√

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		Stelara	Steqeyma	Yesintek	Imuldosa	Otulfi	Pyzchiva	Selarsdi	Wezlana
	45 mg/0.5ml single-dose vial	√		√					√
	130 mg/26ml single-dose vial	√	√	√	√	√	√	√	√

PsO = plaque psoriasis; PsA = psoriatic arthritis; CD = Crohn's Disease; UC = ulcerative colitis

Price and Formulary Recommendation

	Stelara	Steqeyma	Yesintek	Imuldosa	Otulfi	Pyzchiva Ustekinumab-ttwe	Selarsdi	Wezlana
Alameda Formulary Status	NF	NF	F-PA	NF	F-PA	NF	NF	NF
Price^	$29,151	$4,176	$3,000	TBD	$3,620	$5,830 $15,742	$4,176	$5,568 $27,564

*^Proprietary drug pricing is based on wholesale acquisition cost (WAC) and non-proprietary drug pricing is based on National Average Drug Acquisition Cost (NADAC) for dose of **90mg every 12 weeks.***

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Prior Authorization Criteria

Recommendation:

- Add Yesintek and Otulfi to F-PA and to the drug list section as Step 2 agents
- Add all other Stelara biosimilars to the drug list section as Step 3 agents

Specialty Biologic Agents	
Therapeutic Classes (AHFS)	Disease-Modifying Antirheumatic Agents
Medications	Step 1: Preferred (pays at point-of-sale) Hadlima (adalimumab-bwwd) Adalimumab-fkjp (Hulio) Adalimumab-aaty (Yuflyma)-- 80mg/0.8mL dose formulation available Simlandi (adalimumab-ryvk) Step 2: Preferred (PA required) Enbrel (etanercept) Simponi, Simponi Aria (golimumab) Infliximab Inflectra (infliximab-dyyb) Avsola (infliximab-axxq) Renflexis (infliximab-abda) Orencia (abatacept) Xeljanz, Xeljanz XR (tofacitinib) Kineret (anakinra) Otezla (Apremilast) Siliq (brodalumab) Kevzara (sarilumab) Tyenne (tocilizumab-aazg) Tofidence (tocilizumab-bavi) Olumiant (baricitinib) Entyvio (vedolizumab) Otulfi (ustekinumab-aauz) Yesintek (ustekinumab-kfce) Step 3: Non-Preferred (PA required) Humira (adalimumab) Stelara (ustekinumab) Skyrizi (risankizumab) Actemra (tocilizumab) Arcalyst (rilonacept) Ilaris (canakinumab) Tremfya (guselkumab) Remicade (infliximab) Cosentyx (secukinumab) Zeposia (ozanimod) Taltz (ixekizumab) Tysabri (natalizumab) Cimzia (certolizumab) Rinvoq (upadacitinib)

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	Ilumya (tildrakizumab-asmn) Sotyktu (deucravacitinib) Bimzelx (bimekizumab) Omvoh (mirikizumab) Zymfentra (infliximab) All adalimumab biosimilar agents not listed in step 1(ex. Amjevita, Cyltezo, Hyrimoz, Yuflyma, etc.) Litfulo (ritlecitinib) All Stelara biosimilars not listed in step 2 (ex. Steqeyma, Selarsdi, etc.) Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines. **** Non-FDA approved (i.e. off-label) uses; refer to the "Off-Label Use" policy****
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescribed by a specialist in the field to treat the member's respective medical condition
Coverage Duration	If all of the conditions are met, requests will be approved for 12 months.
PA Review Criteria	**Initial Authorization:** • The drug is being requested for an appropriate use (per the references outlined in "Covered Uses") • The dose requested is appropriate for the requested use (per the references outlined in "Covered Uses") • If the request is for a preferred Step 2 agent, documentation has been provided that the member has tried and failed or has a medical reason why (e.g. intolerance, contraindication) they cannot use a preferred Step 1 agent appropriate for the requested use (per the references outlined in "Covered Uses") • If the request is for a non-preferred Step 3 agent, documentation has been provided that the member has tried and failed or has a medical reason why (e.g. intolerance, contraindication) they cannot use one preferred step 1 agent and one preferred step 2 agent appropriate for the requested use (per the references outlined in covered uses) AND: • If the request is for a reference biologic drug with a biosimilar or interchangeable biologic drug (ex. Humira, Remicade, Stelara), documentation of one of the following: • The provider has verbally, or in writing, submitted a member-specific reason why the reference biologic is required based on the member's condition or treatment history; AND if the member had side effects or a reaction to the biosimilar or interchangeable biologic, the provider has completed and submitted an FDA MedWatch form to justify the member's need to avoid these drugs. MedWatch form must also be included with the prior authorization request. Form FDA 3500 – Voluntary Reporting

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	• The currently available biosimilar product does not have the same appropriate use (per the references outlined in "Covered Uses") as the reference biologic drug being requested *NOTE: • Requests for 80mg/0.8mL dose presentations of Humira or non-preferred biosimilar adalimumab agents, preferred biosimilar adalimumab-aaty 80mg/0.8mL should be used • Requests for Humira 10 mg/0.1 mL in pediatric patients may be approved without a trial of a step 1 or step 2 agent, when requested for an appropriate use (per the references outlined in "Covered Uses") **Reauthorization:** • Documentation submitted indicates that the member has obtained clinical benefit from the medication. • The drug is being requested for an appropriate use and dose (per the references outlined in "Covered Uses")
Criteria Statement	Step 2 preferred prior authorization required medications are reserved for members with an appropriate indication and dose, who have used (or cannot/should not use) a preferred step 1 medication. Step 3 non-preferred prior authorization required medications are reserved for members with an appropriate indication and dose, who have used (or cannot/should not use) a preferred step 1 medication and a step 2 preferred prior authorization required medication.
Last P&T Review Date	~~9/2024~~6/2025

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Alameda MRGs for review Q2 2025 P&T

Recommendation:

- Remove nortriptyline and duloxetine from the list of trial and failure agents because they are not in the guidelines, and only amitriptyline and venlafaxine are specifically mentioned in the guidelines

Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention	
Therapeutic Classes (AHFS)	CALCITONIN GENE-RELATED PEPTIDE ANTAGONISTS
Medications	Formulary, PA required Emgality (galcanezumab-gnlm) - PREFERRED Ajovy (fremanezumab-vfrm) - PREFERRED Non-Formulary, PA required Aimovig (erenumab-aooe) Vyepti (eptinezumab-jjmr) Nurtec ODT (rimegepant)- if the request is for acute treatment of migraine please refer to the Acute Migraine Treatments criteria Qulipta (atogepant) Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Criteria for Initial Authorization:** **Cluster Headache:** • Diagnosis of episodic cluster headache • Requested dose is within FDA approved dosing guidelines **Migraine Headache Prophylaxis:** • Diagnosis of episodic migraine or chronic migraine • Requested dose is within FDA approved dosing guidelines • Provider should note on the prior authorization request the number of headache days per month • Trial and failure (or a medical justification for not using e.g. hypersensitivity, baseline bradycardia or hypotension, adverse events experienced from previous trial, etc.) with at least one of the following: 1. Beta-adrenergic blockers 2. Topiramate or divalproex ER or DR 3. A tricyclic antidepressant (TCA) (e.g. amitriptyline ~~or nortriptyline~~) OR a serotonin norepinephrine reuptake inhibitor (SNRI) (e.g. venlafaxine ~~or duloxetine~~) 4. Frovatriptan, zolmitriptan or naratriptan (for menstrual migraine prophylaxis)

Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention	
	• If the medication request is for a Calcitonin Gene-Related Peptide Antagonist other than Emgality or Ajovy, the patient has a documented medical reason (intolerance, hypersensitivity, contraindication, treatment failure etc) for not using Emgality or Ajovy to treat their medical condition. **Criteria for Re-Authorization:** **Episodic Cluster Headache:** • Documented reduction in the frequency of headaches (clinical benefit). **Migraine:** • Greater than or equal to a 50% reduction in the number of headache days per month relative to pre-treatment baseline (clinical benefit) • The provider should note on the prior authorization request the number of headache days per month
Criteria Statement	Emgality and Ajovy are reserved for members requiring migraine prophylaxis and who have used (or cannot/should not use) one medication to prevent migraines including beta-adrenergic blockers, topiramate or divalproex ER or DR, a tricyclic antidepressant, or a serotonin norepinephrine reuptake inhibitor, or frovatriptan zolmitriptan, or naratriptan. Non-preferred CGRPs are reserved for members requiring migraine prophylaxis and who have used (or cannot/should not use) one medication to prevent migraines including beta-adrenergic blockers, topiramate or divalproex ER or DR, a tricyclic antidepressant, or a serotonin norepinephrine reuptake inhibitor, or frovatriptan, zolmitriptan, or naratriptan AND who cannot/ should not take Emgality or Ajovy. Emgality is reserved for members with a diagnosis of episodic cluster headaches.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation:

- Add requirements for coverage of prophylaxis for individuals at high risk of Hep B reactivation per new AGA guidelines on the prevention and treatment of Hep B reactivation in at risk individuals. Based on evidence and baseline risk assessment, the panel made a strong recommendation in favor of antiviral prophylaxis for individuals at high risk of HBV reactivation.
- Combine requirements for compensated and decompensated cirrhosis since there is a new recommendation per guidelines to treat patients with compensated cirrhosis with low level viremia (HBV DNA <2000 IU/mL) to reduce the risk of hepatic decompensation.

Hepatitis B Drugs		
Therapeutic Classes (AHFS)	Various	
Medications	Formulary Tenofovir disoproxil fumarate (Viread) 300 mg tablet Entecavir (Baraclude) 0.5, 1 mg tablets Formulary - PA required Baraclude (entecavir) 0.05 mg/ml solution Adefovir (Hepsera) 10 mg tablet Lamivudine (Epivir HBV) 100 mg tablet Lamivudine (Epivir HBV) 25 mg/5 ml solution Viread 150mg, 200mg, 250mg tablet Vemlidy (tenofovir alafenamide fumarate) 25 mg tablet Non-formulary Viread (Tenofovir disoproxil fumarate) 40mg/gm oral powder **Any other newly marketed agent**	
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.	
Exclusion Criteria	N/A	
Required Clinical Information	See "**PA Review Criteria**" below	
Age Restrictions	Check AAH active CCS cases for members < 21 years of age	
Prescriber Restrictions	N/A	
Coverage Duration	**Initial Approval**	For pregnant patients taking prophylaxis therapy for reduction of perinatal transmission of HBV: 6 months All other INITIAL requests: 12 months: Requests can be approved for up to a 90 day supply
	Later Approvals	For RENEWAL requests for patients undergoing chemotherapy: HBV prophylactic treatment is only approved for up to an additional 12 months upon completion of chemotherapy. For RENEWAL requests for patients requiring prophylaxis against HBV reactivation due to high-risk therapies: non-chemotherapy related agents may be approved for an additional 6 months after discontinuation of the high-risk therapy; or 12 months after discontinuation of b-cell depleting

	agents. Otherwise, RENEWAL requests for patients continuing use of high-risk therapies may be approved for 12 months. RENEWAL requests will not be considered for perinatal prophylaxis after 3 months postpartum All other RENEWAL requests:12 months Requests can be approved for up to a 90 day supply Partial approvals - For situations where lab values required for later approvals/ renewals are missing either in full or in part should be granted for 3 months. *If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**INITIAL CRITERIA for adult population:** • Diagnosis of Hepatitis B; AND • Medication is being prescribed at an appropriate FDA approved dose (for age and weight); AND • Requests for Vemlidy require trial and failure of, intolerance to, or inability to use entecavir (Baraclude) tablet AND • **For Immune-Active chronic hepatitis B (CHB)**: Elevation of ALT ≥2 ULN (above 50 U/L for females or 66 U/L for males) OR evidence of significant histological disease (significant inflammation and/or fibrosis); AND A) Elevated HBV DNA ≥ 2000 IU/mL (HBeAg negative); OR B) Elevated HBV DNA > 20,000 IU/mL (HBeAg positive). • **For Compensated or Decompensated Cirrhosis:** Presence of compensated or decompensated cirrhosis and detectable serum HBV DNA. • ~~**For Compensated Cirrhosis:**~~ ~~Presence of elevated HBV DNA ≥ 2000 IU/mL~~ • **Prophylaxis for Transplant Recipients with Hepatitis B:** A) Patient is HBsAg-positive and undergoing liver transplantation, regardless of HBeAg status or HBV-DNA level pre-transplant; OR B) Patient is HBsAg-negative and received a HBsAg-negative but anti-HBc–positive graft; OR C) Patient has received a HBsAg-positive (non-liver) organ transplant. • **Pregnant Women (for perinatal transmission prophylaxis only; patient does not meet other eligibility categories):** A) Patient is HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL; AND B) Patient is in the third trimester of pregnancy • **Undergoing Chemotherapy or Will Be Initiating Cytotoxic Chemotherapy**: A) Patient is HBsAg-positive, anti-HBc–positive regardless of baseline serum HBV DNA levels; OR B) Patient is HBsAg-negative, anti-HBc–positive; AND

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1) Receiving anti-CD20 antibody therapy (e.g., rituximab); OR
2) Undergoing stem cell transplantation.

- **Acute Symptomatic Hepatitis B**
  Patient has acute hepatitis B with acute liver failure OR has a protracted, severe course, as indicated by total bilirubin >3 mg/dL (or direct bilirubin >1.5 mg/dL), international normalized ratio >1.5, encephalopathy, or ascites.

- **Prophylaxis for Individuals at High Risk of Hepatitis B Reactivation:**
  A) Patient is HBsAg negative, anti-HBc positive and receiving B cell-depleting agents; OR
  B) Patient is HBsAg positive and receiving any of the following: anthracycline derivatives, anti-TNF therapy, anti-IL-6 therapy, B cell-depleting agents, CAR-t cell therapy, cytokine/integrin inhibitors, transcatheter arterial chemoembolization, tyrosine kinase inhibitors, janus kinase inhibitors, HCV co-infection undergoing direct-acting antivirals therapy, corticosteroid therapy of moderate-high dose and duration of ≥4 weeks.

***For adults, if request is for adefovir (Hepsera) or lamivudine (Epivir HBV), documentation of treatment failure or contraindication to entecavir (Baraclude) tablet AND tenofovir disoproxil fumarate (Viread) 300 mg tablet must be provided.**

***If request is for oral solution/oral powder, medical justification for use (i.e. difficulty swallowing) must be provided.**

INITIAL CRITERIA for Treatment of CHB in children (ages 2 to <18 years):

- Diagnosis of Hepatitis B; AND
- Medication is being prescribed at an appropriate FDA approved dose (for age and weight); AND
- Patient is HBeAg-positive with both:
  A) elevated ALT; AND
  B) measurable HBV-DNA levels

***For children, if request is for adefovir (Hepsera) or lamivudine (Epivir HBV), documentation of treatment failure or contraindication to entecavir (Baraclude) tablet or disoproxil fumarate (Viread) 300 mg tablet must be provided.**

For requests for Viread 150mg, 200mg, or 250mg tablet, documentation of weight required as rationale supporting why tenofovir disoproxil fumarate (Viread) 300 mg tablet cannot be used.

***If request is for oral solution/oral powder, medical justification for use (i.e. difficulty swallowing) must be provided.**

RENEWAL CRITERIA

- Documented response to treatment shown by reduced HBV DNA levels.
- If all other criteria are met but the necessary lab values have not been provided, a partial approval for 3 months may be granted. The partial approval should indicate what information is needed for ongoing approval.
  OR

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	• Patient continues to require prophylaxis for Hepatitis B reactivation due to continuation of high risk therapies, or recent discontinuation of high risk therapies (see Coverage Duration section above)
Criteria Statement	N/A
Last P&T Review Date	~~6/2024~~6/2025

Recommendation:

- Add new product Erzofri—extended release injectable paliperidone for the treatment of schizophrenia
- Remove Perseris and Zyprexa Relprevv as they have been discontinued

Injectable Atypical Antipsychotic Medications	
Therapeutic Classes (AHFS)	Antipsychotic agents
Medications	Formulary, Prior Authorization Required Risperidone microspheres ER (Risperdal Consta) Invega Sustenna (paliperidone palmitate) ~~Zyprexa Relprevv (olanzapine)~~ Abilify Maintena (aripiprazole) Non-Formulary Invega Trinza (paliperidone palmitate) Invega Hafyera (paliperidone palmitate) Aristada (aripiprazole lauroxil) Aristada Initio (aripiprazole lauroxil) ~~Perseris ER (risperidone)~~ Abilify Asimtufii (aripiprazole) Uzedy (risperidone) Rykindo (risperidone) Erzofri (paliperidone palmitate) Any other newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** If all conditions are met, the request will be approved for up to 6 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review. **Reauthorization** If all conditions are met, the request will be approved for up to 12 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	CRITERIA FOR INITIAL AUTHORIZATION • Member has claims history or physician attestation that member has tolerated treatment with the oral agent of the drug that is being requested • The member has a long-term history (>3 months) of uncertain compliance or noncompliance with oral anti-psychotic medications **OR** the member has a documented medical reason (i.e. documented treatment failure to maximum doses and/or has intolerable side effects or drug interactions) for not using oral formulary atypical antipsychotic medication **OR** the prescriber attests that the member has stated preference for injectable atypical antipsychotic therapy • Request is for FDA approved indication at an approved dose. • If request if for Aristada Initio, only a single dose will be approved if documentation has been provided that the member is initiating Aristada

	• If request is for Invega Trinza, documentation has been provided that the member has been stable on Invega Sustenna for 4 months, and at the same dose for the last 2 months • If the request is for Invega Hafyera, documentation has been provided that the member has been stable on Invega Sustenna for 4 months and at the same dose for the last 2 months OR has been stable on Invega Trinza for the last 3 months CRITERIA FOR REAUTHORIZATION • Member has been compliant with filling their medication (documentation via claims fill history or provider attestation) OR documentation was provided indicating why member missed dosing • Request is for FDA approved indication at an approved dose. • Documentation submitted indicating member is stable and tolerating medication.
Criteria Statement	Injectable antipsychotics are reserved for members who have used (or cannot/should not use) formulary oral atypical antipsychotic medications.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: Update criteria with buprenorphine (Subutex) sublingual tablet, Sublocade subcutaneous injection, and Vivitrol injection as formulary agents since they are available on formulary without restrictions to comply with Bill 1842.

Opioid Use Disorder (OUD) Agents	
Therapeutic Classes (AHFS)	Opiate Partial Agonists
Medications	Formulary: Buprenorphine (Subutex) sublingual tablet Sublocade (buprenorphine) subcutaneous injection Vivitrol (naltrexone) intramuscular injection Formulary (with quantity limit): ~~Buprenorphine (Subutex) sublingual tablet~~ Buprenorphine/naloxone (Suboxone) sublingual tablet Formulary, PA required: Buprenorphine/naloxone (Suboxone) film Zubsolv (buprenorphine/naloxone) sublingual tablet Non-formulary, PA required: ~~Sublocade (buprenorphine) subcutaneous injection~~ Brixadi (buprenorphine) Weekly or Monthly subcutaneous injection Any other newly marketed agent for opioid use disorder
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage duration	**Initial/Re-Approval:** If all conditions are met, the request will be approved for up to 12 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	**INTIAL CRITERIA** **Buprenorphine/naloxone (Suboxone) film or Zubsolv (buprenorphine/naloxone) sublingual tablet** • Patient has a diagnosis of opioid use disorder • Dosing maximum of 24mg/day of buprenorphine or equivalent is requested (Dosing above 24mg/day may be approved on a case by case basis • Documented trial and failure, contraindication, or intolerance to one of the following medications: buprenorphine (Subutex) tablet OR buprenorphine/naloxone (Suboxone) tablet is required ~~**Sublocade:**~~ ~~• Patient has a diagnosis of moderate to severe opioid use disorder~~ ~~• Documented trial and failure, contraindication, or intolerance to one of the following medications: buprenorphine (Subutex) tablet OR buprenorphine/naloxone (Suboxone) tablet is required~~ ~~• Patient has initiated treatment with an oral or transmucosal buprenorphine containing product at a daily dose of 8-24 mg buprenorphine for at least 7 days prior to initiating treatment~~

	~~• Patient will not be receiving supplemental oral, sublingual, or transmucosal buprenorphine.~~ **Brixadi:** • Patient has a diagnosis of moderate to severe opioid use disorder • Documented trial and failure, contraindication, or intolerance to one of the following medications: buprenorphine (Subutex) tablet OR buprenorphine/naloxone (Suboxone) tablet is required • Patient has initiated treatment with a single dose of at least 4mg of a transmucosal buprenorphine product or are already being treated with buprenorphine **RENEWAL CRITERIA** • Patient has a diagnosis of opioid use disorder • For buprenorphine/naloxone (Suboxone) film or Zubsolv (buprenorphine/naloxone) sublingual tablet, documentation must be provided for renewals after the first year that indicated prescriber has reevaluated the patient on an annual basis for a dosage lower than 24mg/day For requests above the quantity limit The provider has submitted a medical reason why the plan's quantity limit will be inadequate based on the member's condition and treatment history.
Criteria Statement	~~Sublocade (buprenorphine) subcutaneous injection,~~ Brixadi (buprenorphine) Weekly or Monthly subcutaneous injection, Zubsolv, and buprenorphine/naloxone (Suboxone) film are reserved for members who have used (or cannot use) buprenorphine (Subutex) tablets or buprenorphine/naloxone (Suboxone) tablets.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation:

- Add Lumryz to policy—indicated for the treatment of cataplexy and excessive daytime sleepiness (EDS) with narcolepsy in patients 7 years of age and older.
- Add armodafinil 200mg tablet to F-PA as it is missing from formulary.
- Add trial and failure or inability to use generic sodium oxybate before brand Xyrem, Lumryz and Xywav for cost containment, and add generic sodium oxybate to F-PA

Sleep Disorder Therapy	
Therapeutic Classes (AHFS)	Wakefulness-Promoting Agents, Central Nervous System Agents, Misc.
Medications	Formulary, PA required Armodafinil (Nuvigil) 50, 150, 200, 250 mg tablet Modafinil (Provigil) 100, 200 mg tablet Sodium oxybate (Xyrem) solution 500 mg/mL Non-Formulary, PA required Sunosi (solriamfetol) 75, 150 mg tablet Wakix (pitolisant) 4.45, 17.8 mg tablet ~~Sodium oxybate (Xyrem) solution~~ Xywav (oxybate salts) solution Lumryz (sodium oxybate) oral packet
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	See "**PA Review Criteria**" below
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Per prescribing information
Prescriber Restrictions	Sleep specialist, neurologist, psychiatrist, or other specialist in the treatment of the member's diagnosis (does not apply for diagnosis of shift-work disorder)
Coverage Duration	**Initial Approval** If the criteria are met, requests for modafinil or armodafinil will be approved for up to a 12 month duration. Requests for Sunosi or Wakix will be approved for up to 6 months. Requests for sodium oxybate (Xyrem), Lumryz, or Xywav will be approved for up to a 3 month duration. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review. **Later Approvals** If all conditions are met, the request will be approved for up to 12 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	**For all requests:** • Appropriate diagnosis/indication for requested medication • Medication is being prescribed at an FDA approved dose **Modafinil/armodafinil initial authorization:** • For a diagnosis of obstructive sleep apnea (OSA) documentation that the member has been compliant with or is unable to use positive airway pressure [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), or automatic positive airway pressure (APAP)]. • If request is for armodafinil, member must meet above criteria AND documentation of trial and failure, contraindication or intolerance to modafinil. **Sunosi initial authorization**: • Documented trial and failure of, or inability to use, modafinil or armodafinil

	• For members with OSA:
	  ○ Documentation that the member has been compliant with or is unable to use positive airway pressure (CPAP, BPAP, or APAP)
	
	Wakix initial authorization:
	• For a diagnosis of narcolepsy without cataplexy: documented trial and failure of (or medical reason for not using), BOTH of the following:
	  ○ Modafinil or armodafinil
	  ○ Sunosi (solriamfetol)
	• For a diagnosis of narcolepsy with cataplexy: documented trial and failure of, or medical reason for not using, the following:
	  ○ Dextroamphetamine
	
	Sodium oxybate (Xyrem), Lumryz, or Xywav initial authorization:
	• Medication is not being taken concurrently with sedative hypnotics
	• If member has a history of substance abuse, documentation has been provided that prescriber has referred the member for substance abuse disorder treatment.
	• For a diagnosis of narcolepsy without cataplexy:
	  ○ Documented trial and failure of, or a medical reason for not using, ALL of the following:
	  ▪ Modafinil or armodafinil
	  ▪ Sunosi (solriamfetol)
	  ▪ Wakix (pitolisant)
	  ○ For Xyrem, Xywav, or Lumryz: documented trial and failure of, ~~or~~ medical reason for not using generic sodium oxybate
	• For a diagnosis of narcolepsy with cataplexy:
	  ○ Documented trial and failure of each of, or a medical reason for not using BOTH of the following:
	  ▪ Dextroamphetamine
	  ▪ Wakix (pitolisant)
	  ○ For Xyrem, Xywav, or Lumryz: documented trial and failure of, ~~or~~ medical reason for not using generic sodium oxybate
	• For a diagnosis of idiopathic hypersomnia (Xywav only):
	  ○ Patient has a documented trial and failure of, or a medical reason for not using, the following:
	  ▪ Modafinil or armodafinil
	
	Criteria for reauthorization:
	• Documentation has been submitted indicating member has experienced a clinical benefit from treatment (e.g. improvement on Epworth Sleepiness Score)
	• For members with cataplexy: Documentation has been provided that there has been a reduction in frequency of cataplexy attacks.

Criteria Statement	Modafinil is reserved for members who have a diagnosis of obstructive sleep apnea, who use or have used (or cannot/should not use) positive airway pressure [continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), or automatic positive airway pressure (APAP)]. Armodafinil is reserved for members who have used (or cannot/should not use) modafinil For members with obstructive sleep apnea (OSA), Sunosi is reserved for those who have used (or cannot/should not use) positive airway pressure (CPAP, BPAP, or APAP) and modafinil/armodafinil. For members without OSA, Sunosi is reserved for those who have used (or cannot/should not use) modafinil/armodafinil.

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	Wakix is reserved for members who have a diagnosis of narcolepsy without cataplexy and have used (or cannot/should not use) modafinil/ armodafinil and Sunosi. Wakix is reserved for members who have a diagnosis of narcolepsy with cataplexy and have used (or cannot/should not use) dextroamphetamine. For members without cataplexy, sodium oxybate (Xyrem), Lumryz or Xywav are reserved for those who have used (or cannot/should not use) modafinil/armodafinil, Sunosi, and Wakix. For members with narcolepsy with cataplexy, sodium oxybate (Xyrem), Lumryz or Xywav are reserved for those who have used (or cannot/should not use) dextroamphetamine and Wakix. For members with idiopathic hypersomnia, Xywav is reserved for those who have used (or cannot/should not use) modafinil/armodafinil.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation:

- Remove Tegsedi because it was discontinued as a result of low sales per Akcea Pharmaceuticals
- Add new product Attruby to policy for the cardiomyopathy type as one of the preferred agents because of comparative pricing and efficacy
- Add Amvuttra to the cardiomyopathy indication as a result of approval of expanded indication. Add Amvuttra as a non-preferred agent for CM indication, because it is substantially more costly and there is no evidence of clinical advantage over the other agents.
- Remove the restriction of "no duplicate agents" portion of the policy and update it due to 30% of patients being mixed polyneuropathy-cardiomyopathy phenotypes or progressing from one predominant phenotype to a mixed over time. In these cases, if the severity of the condition is such that the patient meets clinical requirements for both indications, a dual agent approach is reasonable.

Transthyretin-mediated Amyloidosis Agents	
Therapeutic Classes (AHFS)	OTHER MISCELLANEOUS THERAPEUTIC AGENTS
Medications	**Preferred:** Polyneuropathy – Amvuttra (vutrisiran), Wainua (eplontersen) Cardiomyopathy – Vyndaqel (tafamidis meglumine), Vyndamax (tafamidis), Attruby (acoramidis) **Non-preferred**: ~~Polyneuropathy – Tegsedi (inoterson)~~ Cardiomyopathy – Amvuttra (vutrisiran) Or any other newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be neurologist, cardiologist, or specialist in the treatment of amyloidosis
Coverage Duration	If all the criteria are met, the initial request will be approved for 6 months. For continuation of therapy, the request will be approved for 6 months.
PA Review Criteria	**Initial Authorization**: • Regimen does not exceed FDA-approved dose/frequency • Patient has not undergone a liver or heart transplant • Requests for use of multiple agents (different mechanism of action) in this policy for mixed polyneuropathy-cardiomyopathy phenotypes will only be considered if patient meets clinical criteria requirements for each section • ~~Patient is not taking any of these agents concurrently: Tegsedi, Amvuttra, Vyndaqel, Vyndamax, or Wainua~~ **Polyneuropathy Type** If the request is for Amvuttra~~,~~ or Wainua~~, or Tegsedi:~~: • Patient has diagnosis of polyneuropathy of hereditary transthyretin-mediated amyloidosis as evidenced by documented transthyretin variant by genotyping • One of the following: ○ Patient has baseline polyneuropathy disability (PND) score ≤ IIIb

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	○ Patient has a baseline Familial Amyloid Polyneuropathy (FAP) Stage 1 or 2 ○ Patient has baseline neuropathy impairment (NIS) score ≥ 5 and ≤ 130 • Patient has clinical signs/symptoms of neuropathy • ~~For Tegsedi, patient has contraindication to/or previous trial and failure of use of Amvuttra or Wainua~~ **Cardiomyopathy Type** If the request is for Vyndaqel~~, or~~ Vyndamax, Attruby or Amvuttra: • Patient has a confirmed diagnosis of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis • Documented amyloid deposit by biopsy or positive technetium 99m pyrophosphate (Tc 99m PYP) cardiac imaging • Patient has New York Heart Association (NYHA) functional class I, II, or III heart failure symptoms~~.~~ • For Amvuttra, patient has contraindication to/or previous trial and failure or continued clinical progression with use of Vyndaqel, Vyndamax or Attruby **Re-authorization**: • Patient's regimen does not exceed FDA-approved dose/frequency for the agent • Patient has not undergone a liver or heart transplant • Requests for use of multiple agents (different mechanism of action) in this policy for mixed polyneuropathy-cardiomyopathy phenotypes will only be considered if patient meets clinical criteria requirements for each section • ~~Patient is not taking any of these agents concurrently: Tegsedi, Amvuttra, Wainua, Vyndaqel or Vyndamax~~ • Documented positive clinical response to therapy from baseline (stabilization/slowing of disease progression, improved neurological impairment, motor functions, improved NIS score, stabilization/reduced rate of decline in 6 minute walk test, etc.) • If the request is for Vyndaqel/Vyndamax/Attruby/Amvuttra ○ Patient has continued NYHA functional class I, II, or III heart failure symptoms
Criteria Statement	Amvuttra, Wainua~~, and Tegsedi~~ are reserved for members with a diagnosis of polyneuropathy of hereditary transthyretin-mediated amyloidosis who have not undergone a liver transplant, with clinical signs or symptoms of neuropathy. ~~Tegsedi is reserved for members who have used (or cannot/should not use) Amvuttra or Wainua.~~ Vyndaqel, ~~and~~ Vyndamax, Attruby, and Amvuttra are reserved for members with a diagnosis of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis who have documented amyloid deposit by biopsy or positive technetium 99m pyrophosphate (Tc 99m PYP) cardiac imaging and New York Heart Association (NYHA) functional class I, II, or III heart failure symptoms, who have not undergone a heart transplant. Additionally, Amvuttra is reserved for members who have used (or cannot/should not use) Vyndaqel, Vyndamax, or Attruby.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: Change examples of inhaled corticosteroids that can be swallowed to only list fluticasone propionate, as the latest guidelines from ACG specifically mention fluticasone propionate over other steroids.

Eohilia	
Therapeutic Classes (AHFS)	Glucocorticoids
Medications	Eohilia (budesonide)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age According to package insert
Prescriber Restrictions	Prescribed by gastroenterologist, allergist, immunologist, or other provider who specializes in the treatment of eosinophilic esophagitis (EoE)
Coverage Duration	If the criteria are met, the request will be approved for 3 months Reauthorization requests will not be approved as Eohilia has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review
PA Review Criteria	• Diagnosis of EoE as confirmed by esophageal biopsy indicating ≥15 eosinophils per high-power field (eos/hpf) • Member must have experienced dysphagia for at least 4 days over a 2-week period • Documented trial and failure, intolerance, or contraindication to one proton pump inhibitor (PPI) at a maximally tolerated dose for a minimum of 8 weeks • Documented trial and failure, intolerance, or contraindication to an inhaled corticosteroid that can be swallowed (i.e., fluticasone propionate~~, ciclesonide, mometasone, etc.~~) • Request is for an FDA-approved dose
Criteria Statement	Eohilia is reserved for members who have a diagnosis of eosinophilic esophagitis (EoE), who have experienced dysphagia and have tried and failed or were unable to use PPI at a maximally tolerated dose for at least 8 weeks and inhaled corticosteroid that can be swallowed.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: Update diagnosis requirements to align with PI as the indication for Spravato has changed slightly, and now Spravato can be used as a monotherapy in patients with treatment resistant depression.

Spravato (esketamine) Intranasal	
Therapeutic Classes (AHFS)	N/A
Medications	Spravato (esketamine) intranasal
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 4 weeks **Later Approvals** 6 months If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.

PA Review Criteria	**Initial Authorization:**
	• The member has a diagnosis of at least one of the following:
	  ○ Major depressive disorder with treatment-resistant depression.
	  ○ Major depressive disorder with acute suicidal ideation or behavior.
	• ~~Medication will be used in conjunction with an oral antidepressant.~~
	• Medication is being prescribed at an FDA approved dosage.
	• Requests for a diagnosis of major depressive disorder with acute suicidal ideation or behavior (not required for treatment resistant depression):
	  ○ Prescriber attests Spravato will be used in conjunction with an oral antidepressant.
	
	Additionally, if member has diagnosis for major depressive disorder with treatment-resistant depression only (i.e. without suicidal ideation or behavior):
	• Documented trial and failure of three preferred oral antidepressants (eg. SSRIs, SNRIs, TCAs) of at least a minimum effective dose for four (4) weeks or longer OR~~;~~ a medical justification as to why the patient cannot use preferred alternative(s).
	
	Re-authorization:
	• Medication is prescribed at an FDA-approved dosage.
	• Medication is being used in conjunction with an oral antidepressant (not required for diagnosis of treatment resistant depression).
	• Documentation was submitted indicating the member has clinically benefited from therapy.

Criteria Statement	Spravato is reserved for members who have treatment-resistant depression who have tried and failed (or cannot use) three other preferred oral antidepressants for 4 weeks or longer ~~and who will use Spravato along with another oral antidepressant~~. Spravato is reserved for members who have depression with acute suicidal ideation and who will use Spravato along with another oral antidepressant.
Last P&T Review Date	~~9/2024~~6/2025

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Recommendation:

- Change policy name to incorporate new hemophilia products.
- Add three new products: Hympavzi, Alhemo, and Qfitlia. Hympavzi is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with hemophilia A (congenital factor VIII deficiency) without factor VIII inhibitors, or hemophilia B (congenital factor IX deficiency) without factor IX inhibitors. Alhemo is indicated for hemophilia A with factor VIII inhibitors and hemophilia B with factor IX inhibitors. Qfitlia is indicated for hemophilia A or B with or without factor VIII or IX inhibitors.
- Change language in initial authorization section to encompass all drugs in the policy.
- Add trial and failure or intolerance to Hemlibra before Hympavzi, Alhemo, or Qfitlia for hemophilia A for cost containment.
- Add additional requirement for Qfitlia per boxed warnings in the labeling.
- Reword criteria statement to encompass all drugs in the policy.

~~Hemlibra (emicizumab-kxwh)~~Subcutaneous Treatments for Hemophilia	
Therapeutic Classes (AHFS)	Hemostatics
Medications	Hemlibra (emicizumab-kxwh), Hympavzi (marstacimab-hncq), Alhemo (concizumab-mtci), Qfitlia (fitusiran)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	N/A
Age Restrictions	N/A
Prescriber Restrictions	Prescriber must be a hematologist
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review** **Initial Authorization:** Documentation submitted indicates the following: • Documentation of patient's weight • Drug is being requested for an FDA-approved indication and the ~~D~~dose requested is within FDA approved limits • ~~Severe~~Diagnosis of hemophilia A or hemophilia B AND one of the following: o ~~—~~Member has tried Factor VIII or Factor IX products and is not well-managed due to limited venous access or treatment failure (attestation must be submitted from prescriber) o ~~—~~Request is for routine prophylaxis in patients with a diagnosis of ~~severe~~ hemophilia A or hemophilia B **WITH** ~~Factor VIII~~ inhibitors and history of spontaneous or traumatic bleeding episode

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	○ Request is for routine prophylaxis in patients with a diagnosis of ~~severe~~ hemophilia A or hemophilia B ***WITHOUT*** ~~Factor VIII~~ inhibitors and patient requires management with Factor VIII or Factor IX products at a total weekly dose of >100 U/kg (attestation must be submitted by prescriber) • If the request is for Hympavzi, Alhemo, or Qfitlia for hemophilia A, the member must also have a trial and failure or intolerance to Hemlibra ~~○~~• If the request is for Qfitlia, prescriber must also attest to monitor patient's antithrombin (AT) levels, signs and symptoms of thrombotic events, and signs and symptoms of acute and recurrent gallbladder disease as recommended per the manufacturer's prescribing information. **Re-Authorization:** • Documentation submitted indicates a clinical benefit was observed (e.g. reduction in bleeding episodes, improved quality of life) • Documentation of patient's weight • Dose requested is within FDA approved limits • If the request is for Qfitlia, prescriber must also attest to monitor patient's antithrombin (AT) levels, signs and symptoms of thrombotic events, and signs and symptoms of acute and recurrent gallbladder disease as recommended per the manufacturer's prescribing information.
Criteria Statement	Hemlibra, Hympavzi, Alhemo, and Qfitlia ~~is~~are reserved for patients who have a diagnosis of ~~severe~~ hemophilia A or B with one of the following: not a candidate for Factor VIII or Factor IX products due to limited venous access or treatment failure, routine prophylaxis in patients with ~~Factor VIII~~ inhibitors and spontaneous/traumatic bleeding episodes, or without ~~Factor VIII~~ inhibitors and requires management with Factor VIII or Factor IX products at a total weekly dose of >100 U/kg . Additionally, Hympavzi, Alhemo, and Qfitlia for hemophilia A require trial and failure, intolerance or inability to use Hemlibra.
Last P&T Review Date	~~6/2024~~6/2025

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Recommendation: Change policy to include coverage only for severe obesity for adults and pediatric patients

Anti-Obesity Medications	
Therapeutic Classes (AHFS)	GI drugs, miscellaneous; anorexigenic agents
Medications	Alli (orlistat) Xenical (orlistat) Phentermine (phentermine hcl) (Adipex-P) Phentermine (phentermine hcl) (Lomaira) Qsymia (phentermine/topiramate) Contrave (naltrexone/bupropion) Saxenda (liraglutide) Wegovy (semaglutide) Zepbound (tirzepatide) Any other newly marketed agent ****Please Note: If the request is for Wegovy to reduce the risk of major adverse cardiovascular events please refer to the Wegovy criteria*****
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial/Re-Approval** If all conditions are met, the request will be approved for up to 6 months. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	**INITIAL CRITERIA FOR APPROVAL** Phentermine HCL (Adipex-P) • Diagnosis of class III/severe obesity (including documentation of BMI ≥ ~~30~~40) ~~OR BMI ≥27 and at least one weight-related comorbidity (such as diabetes, controlled hypertension, hyperlipidemia etc) or history of heart attack, despite diet and exercise.~~ • For phentermine (Lomaira): trial and failure or medical reason for not using generic phentermine (Adipex-P) Alli: • Diagnosis of class III/severe obesity (including documentation of BMI ≥ ~~3~~40) ~~OR BMI ≥27 and at least one weight-related comorbidity (such as diabetes, controlled hypertension, hyperlipidemia etc.) or history of heart attack despite diet and exercise.~~ Qsymia • **For adults:** Diagnosis of class III/severe obesity (including documentation of BMI ≥ ~~3~~40) ~~OR BMI ≥27 and at least one weight-related comorbidity (such as diabetes, controlled hypertension, hyperlipidemia etc.) or history of heart attack, despite diet and exercise.~~ **OR** ○ **For pediatrics**: BMI ~~in the~~ of 120% of the ~~≥~~95th percentile standardized for age and sex or ≥35 kg/m^2

	▪ https://www.cdc.gov/healthyweight/bmi/calculator.html • Documented trial and failure, contraindication, or intolerance to use phentermine HCL (Adipex-P) and topiramate as separate ingredients Contrave • Diagnosis of class III/severe obesity (including documentation of BMI ≥ 340) ~~OR BMI ≥27 and at least one weight-related comorbidity (such as diabetes, controlled hypertension, hyperlipidemia etc.) or history of heart attack, despite diet and exercise.~~ • Documented trial and failure, contraindication, or intolerance to use Qsymia Saxenda, Wegovy, and Zepbound • Diagnosis of class III/severe obesity (including documentation of BMI ≥ 340) ~~OR BMI ≥27 and at least one weight-related comorbidity (such as diabetes, controlled hypertension, hyperlipidemia etc.) or history of heart attack, despite diet and exercise~~ • Documented trial and failure, contraindication, or intolerance to use Qsymia AND Contrave Xenical: • Diagnosis of class III/severe obesity (including documentation of BMI ≥ 340) ~~OR BMI ≥27 and at least one cardiovascular comorbidity (such as diabetes, controlled hypertension, history of heart attack, etc.) despite diet and exercise.~~ • Documented trial and failure, contraindication, or intolerance to Alli dosed at 120 mg (2 capsules) three times daily. **REAUTHORIZATION CRITERIA FOR APPROVAL** • Documented weight loss of 5% of body weight or more, compared with baseline • ~~If a weight-related comorbidity was previously noted, an objective improvement compared with baseline is documented (e.g. reduction in blood pressure, cholesterol, hemoglobin A1c, etc.)~~
Criteria Statement	Phentermine is reserved for members who have a diagnosis of class III/severe obesity~~are obese~~ with body mass index of ≥ 340 ~~or ≥ 27 with a comorbidity such as diabetes or hypertension~~. Generic Lomaira is reserved for members who have used (or cannot/should not use) generic Adipex-P. Alli is reserved for members who have a diagnosis of class III/severe obesity~~are obese~~ with a body mass index of ≥ 340 ~~or ≥ 27 with a comorbidity such as diabetes, hypertension, or heart attack~~. Qsymia is reserved for adult members who have a diagnosis of class III/severe obesity~~are obese~~ with a body mass index of ≥ 340 ~~or ≥ 27 with a comorbidity such as diabetes, hypertension, or heart attack~~ or pediatric members who are obese with a BMI of 120% ~~in~~of the ~~≥~~95th percentile standardized for age and sex or ≥35 kg/m^{2}and who have used (or cannot/should not use) phentermine and topiramate as separate ingredients. Contrave is reserved for members who have a diagnosis of class III/severe obesity~~are obese~~ with a body mass index of ≥ 340 ~~or ≥ 27 with a comorbidity such as diabetes, hypertension, or heart attack~~ and who have used (or cannot/should not use) Qsymia. Saxenda, Wegovy, and Zepbound are reserved for members who have a diagnosis of class III/severe obesity~~are obese~~ with a body mass index of ≥ 340 ~~or ≥ 27 with a~~

	~~comorbidity such as diabetes, hypertension, or heart attack~~ and who have used (or cannot/should not use) Qsymia and Contrave. Xenical is reserved for ~~obese~~ members who have a diagnosis of class III/severe obesity with a body mass index of ≥ ~~34~~0 ~~or ≥ 27 with a comorbidity such as diabetes, hypertension, or heart attack~~ and who have used (or cannot/should not use) Alli.
Last P&T Review Date	~~6/2024~~6/2025

Recommendation: Retire criteria to comply with AB 118 prescription exclusions section

Erectile Dysfunction Medications	
Therapeutic Classes (AHFS)	Phosphodiesterase type 5 inhibitors, vasodilating agents, miscellaneous
Medications	Sildenafil (Viagra), tadalafil (Cialis), vardenafil (Staxyn), vardenafil (Levitra), Stendra (avanafil), Caverject (alprostadil), Edex (alprostadil), Muse (alprostadil), IFE-BiMix (papaverine/phentolamine/water), Tri-Mix (papaverine/phentolamine/alprostadil) Any other medication for erectile dysfunction
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Prescriber is experienced in fertility treatment, such as OB/GYN, fertility specialist, endocrinologist, etc.
Coverage Duration	If the criteria are met, the request will be approved for 12 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Authorization criteria:**
	• Medication is prescribed for erectile dysfunction
	• Medication is prescribed at an FDA approved dose
	• The request is for **iatrogenic infertility** (infertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment)
	  ○ Requests for other causes of infertility or erectile dysfunction not associated with iatrogenic infertility will be denied
	• Requests for sildenafil (Viagra):
	  ○ Approve
	• Requests for medications other than sildenafil (Viagra):
	  ○ Documentation of a trial and therapy failure, intolerance, or medical reason why patient cannot use sildenafil (Viagra):

Criteria Statement	Medications used to treat erectile dysfunction are reserved for members who have a diagnosis of erectile dysfunction associated with iatrogenic infertility. Medications other than sildenafil (Viagra) are reserved for members who have used (or cannot/ should not use) sildenafil (Viagra).
Last P&T Review Date	9/2024

Recommendation: Remove iatrogenic infertility requirement from the criteria and extend coverage to any infertility causes to comply with SB 729 that requires coverage for the treatment of infertility for a maximum of 3 completed oocyte retrievals and removes the exclusion of in vitro fertilization.

Vaginal Progesterone	
Therapeutic Classes (AHFS)	Progestins
Medications	Non-formulary, prior authorization required: Crinone (micronized progesterone) gel Endometrin (micronized progesterone) vaginal insert
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Prescriber must be OB-GYN specialist
Coverage Duration	Prevention of spontaneous preterm delivery: • Crinone and Endometrin will be approved for 30 single use applicators/inserts per 30 days until the end of pregnancy Secondary Amenorrhea: • Crinone will be approved for up to 6 single use applicators Assisted Reproductive Technology (ART): • Crinone and Endometrin will be approved for: ~~12 months~~up to 3 cycles If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Prevention of Spontaneous Preterm Delivery:** • Current singleton pregnancy and short cervix • Patient has tried and failed, or has a contraindication or intolerance to micronized progesterone (Prometrium) capsules • If the request is for Crinone, the patient has tried and failed, has a contraindication or intolerance to, or other medical justification for not using Endometrin **Secondary Amenorrhea:** • Member has a diagnosis of secondary amenorrhea • Member has tried and failed, or has contraindication or intolerance to, oral progestin therapy (e.g. medroxyprogesterone acetate, norethindrone acetate tablets, micronized progesterone) • If the request is for Crinone 8% gel the patient has tried and failed, or has a contraindication or intolerance to, Crinone 4% gel. **Assisted Reproductive Technology (ART):** • The request is for ~~iatrogenic~~ infertility ~~(infertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment)~~ o ~~Requests for other causes of infertility will be denied~~ • Member requires intravaginal progesterone as part of an ART treatment plan
Criteria Statement	**Prevention of Spontaneous Preterm Delivery:** Endometrin is reserved for members who are currently pregnant with one child, who also have short cervix and have used (or cannot/ should not use) micronized progesterone (Prometrium) capsules. Crinone is reserved for members who are currently pregnant with one child, who also have short cervix, and who have used (or cannot/ should not use) micronized progesterone (Prometrium) capsules AND Endometrin.

	Secondary Amenorrhea: Crinone is reserved for members who have a diagnosis of secondary amenorrhea and have used (or cannot/ should not use) oral progestin therapy (e.g. medroxyprogesterone acetate, norethindrone acetate tablets, micronized progesterone). Crinone 8% gel is reserved for members who have used (or cannot/ should not use) Crinone 4% gel. **Assisted Reproductive Technology (ART):** Crinone and Endometrin are reserved for members who require assisted reproductive technology (ART), as a result of ~~iatrogenic~~ infertility ~~(infertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment)~~.
Last P&T Review Date	~~9/2024~~6/2025

Recommendation: Remove iatrogenic infertility requirement from the criteria and extend coverage to include in vitro fertilization to comply with SB 729 that requires coverage for the treatment of infertility for a maximum of 3 completed oocyte retrievals and removes the exclusion of in vitro fertilization.

Fertility Agents	
Therapeutic Classes (AHFS)	Estrogen agonists-antagonists, gonadotropins, antigonadotropins
Medications	Cetrotide (cetrorelix), ganirelix (Fyremadel), clomiphene (Serophene, Clomid), choriogonadotropin alfa (Pregnyl), chorionic gonadotropin (Novarel), Ovidrel (choriogonadotropin alfa), Follistim AQ (follitropin beta), Gonal-F, Gonal-F RFF, Gonal-F RFF Rediject (follitropin alfa), Menopur (menotropins) Any other newly approved medication for fertility ***Requests for non-fertility related indications: refer to the Non-Formulary and PA Required Medications without Drug-Specific Criteria**
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Pregnancy
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Prescriber is experienced in fertility treatment, such as OB/GYN, fertility specialist, endocrinologist, etc.
Coverage Duration	If the criteria are met, the request will be approved for 12 months If the request is for in vitro fertilization, the request will be approved for up to 3 cycles If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**For authorization of fertility agents:**
	• ~~The request is for **iatrogenic infertility** (infertility caused directly or indirectly by surgery, chemotherapy, radiation, or other medical treatment)~~
	  ○ ~~Requests for other causes of infertility will be denied~~
	• Medication is prescribed for an FDA-approved indication for treatment of infertility.
	• Medication is prescribed at an FDA approved or compendia supported dose and duration of therapy.
	• Requests for Novarel or Ovidrel:
	  ○ Documentation of a trial and therapy failure, intolerance, or medical reason why patient cannot use Pregnyl.
	• Requests for Cetrotide:
	  ○ Documentation of a trial and therapy failure, intolerance, or medical reason why patient cannot use ganirelix.

Criteria Statement	~~Medications used for infertility~~ Fertility agents are reserved for members who have a diagnosis of ~~iatrogenic~~ infertility. Novarel or Ovidrel are reserved for members who have used (or cannot/ should not use) Pregnyl. Cetrotide is reserved for members who have used (or cannot/ should not use) ganirelix.
Last P&T Review Date	~~9/2024~~6/2025

Recommendation: Add language to include newly launched biosimilars for Soliris (BKEMV and Epysqli) to policy

Complement Inhibitors for the Treatment of Paroxysmal Nocturnal Hemoglobinuria	
Therapeutic Classes (AHFS)	Complement Inhibitors
Medications	Fabhalta (iptacopan) capsule, Voydeya (danicopan) tablet
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age According to the package insert
Prescriber Restrictions	Prescriber must be a hematologist or oncologist
Coverage Duration	For Fabhalta: if the criteria are met, the initial request will be approved for up to 6 month duration; reauthorization requests will be approved for up to 12 months. For Voydeya: if the criteria are met, the initial request will be approved for up to 3 month duration; reauthorization requests will be approved for up to 6 months.
PA Review Criteria	**Initial Authorization:** • The request is for a dose that is FDA approved or in nationally recognized compendia in accordance with the patient's diagnosis, age and concomitant medical conditions • Documentation patient complies with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. • Documentation of diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by high sensitivity flow cytometry • For Fabhalta (iptacopan): Hemoglobin (Hgb) < 10 g/dL • For Voydeya (danicopan) o Member has been receiving ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV, Epysqli) or Ultomiris (ravulizumab) therapy for at least 6 months o Member has clinically evident extravascular hemolysis [defined as anemia (Hgb ≤9.5 gram/deciliter) with absolute reticulocyte count ≥120 x 10^9/liter] despite treatment with ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV, Epysqli) or Ultomiris (ravulizumab) o Voydeya (danicopan) will be used as add-on therapy to ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV, Epysqli) or Ultomiris (ravulizumab) **Re-Authorization:** • Provider has submitted documentation of clinical response to therapy (e.g., reduction in disease severity, improvement in quality of life scores, increase in Hgb, reduced need for blood transfusions, etc.) • The request is for a dose that is FDA approved or in nationally recognized compendia in accordance with the patient's diagnosis, age, and concomitant medical condition
Criteria Statement	Fabhalta is reserved for members who have a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by high sensitivity flow cytometry with a hemoglobin (Hgb) < 10 g/dL, who have complied with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria. Voydeya is reserved for members who have a diagnosis of PNH by high sensitivity flow cytometry with a Hgb ≤ 9.5 g/dL and absolute reticulocyte count ≥120 x 10^9/liter

	despite treatment with ~~Soliris~~ eculizumab (Soliris, BKEMV, Epysqli) or Ultomiris for at least 6 months, and will be used as an add-on therapy to ~~Soliris~~ eculizumab (Soliris, BKEMV, Epysqli) or Ultomiris.
Last P&T Review Date	~~9/2024~~6/2025

Recommendation: Add language to include newly launched biosimilars for Soliris (BKEMV and Epysqli) to policy

Complement Inhibitors for the Treatment of Myasthenia Gravis	
Therapeutic Classes (AHFS)	Complement Inhibitors
Medications	Zilbrysq (zilucoplan) subcutaneous injection
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age ≥ 18 years
Prescriber Restrictions	Prescribed by a neurologist or rheumatologist
Coverage Duration	Initial request: 6 months Continuation of therapy: 12 months If the conditions are not met, the request will be sent to a clinical reviewer for medical necessity review

PA Review Criteria	**Initial Authorization:**
	• Diagnosis of generalized myasthenia gravis (gMG)
	  ○ Patient has a positive serological test for Anti-AChR antibodies
	• Patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification of class II, III or IV
	• Patient has tried and failed, or has contraindication, to one of the following:
	  ○ Two (2) or more conventional therapies (i.e. acetylcholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressive therapies)
	  ○ Failed at least 1 conventional therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin
	• Medication is prescribed at an FDA approved dose
	• No concurrent use of Vyvgart, Vyvgart Hytrulo, Rystiggo, Soliris, BKEMV, Epysqli, or Ultomiris
	• Documentation patient complies with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal infections in patients receiving a complement inhibitor
	
	Re-Authorization:
	• Provider has submitted documentation of clinical response to therapy (e.g., reduction in disease severity, improvement in quality-of-life scores, MG-ADL scores, etc).
	• Medication is prescribed at an FDA approved dose.

Criteria Statement	Zilbrysq is reserved for members who have a diagnosis of generalized myasthenia gravis clinical classification of class II, III or IV and have tried and failed 2 or more conventional therapies or at least 1 conventional therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin, and who have complied with the ACIP current vaccination recommendations against meningococcal infections in patients receiving a complement inhibitor.
Last P&T Review Date	~~6/2024~~6/2025

Alameda Q2 2025 PADs for Review Changes

Recommendation:

- Add new drug Aucatzyl—CD 19-directed genetically modified autologous T cell immunotherapy indicated for the treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.
- Add coverage duration for Aucatzyl and update coverage duration section for more clarity, since one treatment regimen of Aucatzyl includes 2 infusions.
- Update Acute Lymphoblastic Leukemia (ALL) section with the new agent per indication and timeframe for post-transplant relapsed/refractory disease.
- Update Follicular Lymphoma (FL) and Mantle Cell Lymphoma (MCL) sections with Breyanzi that received an expanded indication for FL and MCL treatment, supported by NCCN guidelines as a third line agent.
- Correct miswording for Large B-cell Lymphoma section and formatting throughout the policy.
- Update Re-authorization section with Aucatzyl.

Anti-CD19 CAR-T Immunotherapies	
Medications	Kymriah (tisagenlecleucel) Yescarta (axicabtagene ciloleucel) Tecartus (brexucabtagene autoleucel) Breyanzi (lisocabtagene maraleucel) Aucatzyl (obecabtagene autoleucel)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Patients with primary central nervous system lymphoma
Required Clinical Information	See "Other Criteria" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	Prescriber must be an oncologist, hematologist or other appropriate specialist
Coverage Duration	If all the criteria are met, the initial request will be approved for a ~~one –time infusion~~single treatment regimen per lifetime. • Kymriah, Yescarta, Tecartus, Breyanzi: a one-time infusion • Aucatzyl: a split-dose infusion administered on day 1 and day 10 (± 2 days)
Maximum Billable Units	Variable
Other Criteria	**Initial authorization:** • Patient must not have received prior anti-CD19 CAR-T therapy. • Patient will be screened for HBV, HCV, and HIV in accordance with clinical guidelines. • Patient does not have an active infection or inflammatory disorder. • Patient has a life expectancy greater than 12 weeks. • Patient will not receive live virus vaccines for at least 6 weeks prior to the start of lymphodepleting chemotherapy and until immune recovery following treatment. • Use is supported by a labeled indication or NCCN guidelines **Leukemia** **For B-cell precursor Acute Lymphoblastic Leukemia (ALL):** • If the request is for Kymriah o Patient is 25 years of age or younger o ALL that is refractory or in second or later relapse as defined by: ▪ Second or greater bone marrow (BM) relapse or

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- Any BM relapse after allogeneic stem cell transplant (alloSCT) and greater than or equal to 6 months from SCT at the time of tisagenlecleucel infusion or
- Primary refractory, defined as not achieving complete remission (CR) after 2 cycles of a standard chemotherapy regimen, or chemorefractory, defined as not achieving CR after 1 cycle of standard chemotherapy for relapsed leukemia or
- Philadelphia chromosome–positive ALL intolerant of or with 2 failed lines of tyrosine kinase inhibitor (TKI) therapy or if TKI therapy is contraindicated or
- Ineligible for alloSCT due to comorbid disease, contraindications to alloSCT conditioning regimen, lack of a suitable donor, prior SCT, or declined alloSCT after documented discussion about the role of SCT with a physician

- If the request is for Tecartus or Aucatzyl
  - Patient is 18 years of age or older
  - ALL that is relapsed or refractory (one of the following):
    - Primary refractory disease
    - First relapse if first remission ≤ 12 months
    - Relapsed or refractory disease after 2 or more lines of systemic therapy
    - Relapsed or refractory disease after alloSCT, provided patient is at least 100 days afterfrom SCT at the time of brexucabtageneTecartus infusion or at least 3 months after SCT at the time of Aucatzyl infusion

For Chronic Lymphocytic Leukemia (CLL):

- If the request is for Breyanzi
  - Patient is 18 years of age orf older
  - Patient has relapsed/refractory disease defined as failure of two or more lines of therapy, including a Bruton tyrosine kinase (BTK) inhibitor AND a B-cell lymphoma 2 (BCL-2) inhibitor

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Non-Hodgkin's Lymphoma (NHL)

For Follicular Lymphoma (FL):

- If the request is for Kymriah, Breyanzi or Yescarta:
  - Patient is 18 years of age or older
  - Patient has relapsed/refractory disease defined as failure of two or more lines of systemic therapy

For Large B-cell Lymphoma (LBCL), Diffuse Large B-cell Lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, follicular lymphoma grade 3B, and DLBCL arising from follicular lymphoma or indolent lymphoma:

- If the request is for Breyanzi, Kymriah, or Yescarta
  - Patient is 18 years of age or older
  - For Breyanzi ONE of the following:
    - Patient is refractory to first-line chemoimmunotherapy or relapsed within 12 months of first-line chemoimmunotherapy
    - Patient is refractory to first-line chemoimmunotherapy or relapsed after first-line chemoimmunotherapy and is not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age

	▪ Patient has ~~failed~~relapsed or refractory disease after two or more lines of systemic therapy ○ For Kymriah: Patient has relapsed/refractory disease defined as failure of two or more lines of systemic therapy ○ For Yescarta ONE of the following: ▪ Patient is refractory to first-line chemoimmunotherapy or relapses within 12 months of first-line chemoimmunotherapy or ▪ Patient has failed two or more lines of systemic therapy **For Mantle Cell Lymphoma (MCL):** ~~• If the request is for Tecartus:~~ • Patient is 18 years of age or older • If the request is for Tecartus: ○ Patient has relapsed/refractory disease defined as failure of ~~BOTH~~all of the following ~~lines of therapy~~: ▪ Chemoimmunotherapy such as an anti-CD20 monoclonal antibody (e.g. Rituxan) + any chemotherapeutic agent ▪ Bruton Tyrosine Kinase (BTK) Inhibitor (e.g. Calquence, Imbruvica, Brukinsa) • If the request is for Breyanzi: ▪ Patient has relapsed or refractory disease who have received at least 2 prior lines of systemic therapy, including BTK inhibitor **For Small Lymphocytic Lymphoma (SLL):** • If the request is for Breyanzi ○ Patient is 18 years of age or older ○ Patient has received at least 2 prior lines of therapy including, a Bruton tyrosine kinase (BTK) inhibitor and a B-cell lymphoma 2 (BCL-2) inhibitor **Re-authorization:** • Treatment exceeding ~~1 dose~~a single treatment regimen per lifetime will not be authorized. ○ Kymriah, Yescarta, Tecartus, Breyanzi: a one-time infusion ○ Aucatzyl: a split-dose infusion administered on day 1 and day 10 (±~~2~~ days) If all of the above criteria are not met for initial or re-authorization, the request is referred to a Clinical Reviewer for medical necessity review
Last Review Date	~~6/2024~~6/2025

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Recommendation:

- Remove nortriptyline and duloxetine from the list of trial and failure agents because they are not in the guidelines, and only amitriptyline and venlafaxine are specifically mentioned in the guidelines

Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention	
Medications	Emgality (galcanezumab-gnlm) Aimovig (erenumab-aooe) Ajovy (fremanezumab-vfrm) Vyepti (eptinezumab-jjmr) Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	N/A
Coverage Duration	If the criteria are met, the initial request will be approved for up to a 6 month duration; reauthorization requests will be approved for up to 6 months.
Maximum Billable Units	Variable
Other Criteria	**Criteria for Initial Authorization:** **Cluster Headache:** • Request for Emgality (galcanezumab) for diagnosis of episodic cluster headache • Requested dose is within FDA approved dosing guidelines **Migraine Headache Prophylaxis:** • Requested dose is within FDA approved dosing guidelines • Provider should note on the prior authorization request the number of headache days per month • Trial and failure (or a medical justification for not using e.g. hypersensitivity, baseline bradycardia or hypotension, adverse events experienced from previous trial, etc.) with at least one of the following: ○ Beta-adrenergic blockers ○ Topiramate or divalproex ER or DR ○ A tricyclic antidepressant (TCA) (e.g. amitriptyline ~~or nortriptyline~~) OR a serotonin norepinephrine reuptake inhibitor (SNRI) (e.g. venlafaxine ~~or duloxetine~~) ○ Frovatriptan, zolmitriptan or naratriptan (for menstrual migraine prophylaxis) **Criteria for Re-Authorization:** **Episodic Cluster Headache:** Documented reduction in the frequency of headaches (clinical benefit). **Migraine:** • Greater than or equal to a 50% reduction in the number of headache days per month relative to pre-treatment baseline (clinical benefit)

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	• The provider should note on the prior authorization request the number of headache days per month If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~6/2024~~6/2025

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Recommendation:

- Add newly launched biosimilars for Soliris: BKEMV and Epysqli to policy
- Add trial and failure of Epysqli before Soliris or BKEMV for cost containment

Complement Inhibitors	
Medications	Soliris (eculizumab), Ultomiris (ravulizumab), Empaveli (pegcetacoplan), Syfovre (pegcetacoplan injection), Izervay (avacincaptad pegol injection), PiaSky (crovalimab-akkz), BKEMV (eculizumab-aeeb), Epysqli (eculizumab-aagh)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	Prescriber must be a hematologist, nephrologist, neurologist, oncologist, ophthalmologist, or other appropriate specialist.
Coverage Duration	If the criteria are met, the initial request will be approved as follows: For ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV. Epysqli), Ultomiris (ravulizumab), and Empaveli (pegcetacoplan): initial request will be approved for up to a 3 month duration; reauthorization requests will be approved for up to 6 months. For PiaSky (crovalimab-akkz): initial request will be approved for up to 6 months, reauthorization requests will be approved for up to 12 months. For Syfovre (pegcetacoplan injection): initial and reauthorization requests will be approved for up to 12 months. For Izervay (avacincaptad pegol injection): initial request will be approved for up to 12 month duration with no reauthorization.
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** • The request is age appropriate according to FDA approved package labeling or nationally recognized compendia; AND • The request is for a dose that is FDA approved or in nationally recognized compendia in accordance with the patient's diagnosis, age, body weight, and concomitant medical conditions; AND • For ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV, Epysqli), Ultomiris (ravulizumab), Empaveli (pegcetacoplan), and PiaSky (crovalimab-akkz) ○ Documentation patient complies with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria ~~○~~ • For Soliris or BKEMV, patient must have a documented trial and failure or intolerance to Epysqli or a medical reason why Epysqli cannot be used **For Generalized Myasthenia Gravis (gMG):** • Refer to the "Myasthenia Gravis Agents" policy **For Neuromyelitis Optica Spectrum Disorders (NMOSD):** • Refer to the: **"Neuromyelitis Optica Spectrum Disorder (NMOSD) Agents"** policy

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	For paroxysmal nocturnal hemoglobinuria (PNH): • Documentation of diagnosis by high sensitivity flow cytometry • For Empaveli (pegcetacoplan): Hemoglobin (Hgb) < 10.5 g/dL • If the request is for Empaveli (pegcetacoplan), documented trial and failure of, contraindication to, or medical reason for not using ~~Soliris (~~eculizumab~~)~~ (Soliris, BKEMV, Epysqli) or Ultomiris (ravulizumab) **Atypical Hemolytic Uremic Syndrome (aHUS)/Complement-Mediated HUS)** • Documentation of confirmed diagnosis as evidenced by complement genotyping and complement antibodies; **OR** • Provider attestation treatment is being used empirically and delay in therapy will lead to unacceptable risk to the patient **Geographic Atrophy (GA):** • If the request is for Syfovre (pegcetacoplan injection), member must be ≥ 60 years of age • If the request is for Izervay (avacincaptad pegol injection), member must be ≥ 50 years of age • Diagnosis of GA secondary to age-related macular degeneration (AMD) • Absence of choroidal neovascularization (CNV) in treated eye • Best-corrected visual acuity (BCVA) 24 letters (approximately 20/320) or better using Early Treatment Diabetic Retinopathy Study (ETDRS) • GA lesion size ≥2.5 and ≤17.5 mm2 with at least 1 lesion ≥1.25 mm2 **Re-Authorization:** • Re-authorization may be considered for all agents included in these criteria with the exception of Izervay (avacincaptad pegol injection), which is only indicated for a 12 month duration • Provider has submitted documentation of clinical response to therapy (e.g., reduction in disease severity, improvement in quality of life scores, increased Hgb, reduced need for blood transfusions, slowing of growth rate of GA lesions, etc.); **AND** • The request is for a dose that is FDA approved or in nationally recognized compendia in accordance with the patient's diagnosis, age, and concomitant medical condition • **If the request is for atypical hemolytic uremic syndrome (aHUS)/ complement-mediated HUS:** o Documentation of confirmed diagnosis as evidenced by: ▪ Complement genotyping ▪ Complement antibodies If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~12/2024~~6/2025

Recommendation:

- Add newly launched biosimilars for Soliris--BKEMV and Epysqli to policy
- Add age restriction exception for Soliris, since it received an approval in pediatric patients 6 years of age and above
- Add requirements for pediatric patients for Soliris based on pediatric study protocol
- Add trial and failure of Epysqli before Soliris or BKEMV for cost containment

Myasthenia Gravis Agents	
Medications	Vyvgart (efgartigimod) Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase) Rystiggo (rozanolixizumab) Soliris (eculizumab) Ultomiris (ravulizumab) BKEMV (eculizumab-aeeb) Epysqli (eculizumab-aagh)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age Drugs listed in Myasthenia Gravis Agents criteria ≥ 18 years (Except for Soliris ≥ 6 years)
Prescriber Restrictions	Prescribed by a neurologist or rheumatologist
Coverage Duration	If all of the criteria are met, the initial request will be approved for 6 months. For continuation of therapy, the request will be approved for 12 months.

Other Criteria	**Initial Authorization:**
	• Diagnosis of generalized myasthenia gravis (gMG)
	• Patient has a positive serological test for one of the following:
	  ○ Anti-AChR antibodies
	  ○ Anti-muscle-specific tyrosine kinase (MuSK) antibodies (Rystiggo only)
	• Patient has a Myasthenia Gravis Foundation of America (MGFA) clinical classification of class II, III or IV
	• For adults: Ppatient has tried and failed, or has contraindication, to one of the following:
	  ○ Two (2) or more conventional therapies (i.e. acetylcholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressive therapies)
	  ○ Failed at least 1 conventional therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin
	• For Soliris in patients 6-17 years: one of the following:
	  ○ Trial and failure of at least 1 conventional therapy (i.e. acetylcholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressive therapies)
	  ○ Patient requires maintenance plasma exchange or intravenous immunoglobulin to control symptoms
	• For Soliris or BKEMV, patient must have a documented trial and failure or intolerance to Epysqli or a medical reason why Epysqli cannot be used (does not apply to pediatric patients)
	• Medication is prescribed at an FDA approved dose
	• Patient is not using agents covered by this policy concurrently (i.e. no concurrent use of Vyvgart, Vyvgart Hytrulo, Rystiggo, Soliris, BKEMV, Epysqli or Ultomiris)
	• Requests for Soliris (eculizumab), BKEMV, Epysqli and Ultomiris (ravulizumab) will

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	also require the following: ○ Documentation that patient complies with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against meningococcal infections in patients receiving a complement inhibitor **Re-Authorization:** • Provider has submitted documentation of clinical response to therapy (e.g., reduction in disease severity, improvement in quality-of-life scores, MG-ADL scores, etc). • Medication is prescribed at an FDA approved dose. If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last P&T Review Date	~~12/2024~~6/2025

Recommendation: Add new bleeding disorder products to policy: Alhemo, Hympavzi, and Qfitlia

Bleeding Disorder Products	
Therapeutic Classes (AHFS)	Hemostatics
Medications	Advate, Adynovate, Afstyla, Alhemo, Alphanate, Alphanine SD, Alprolix, Altuviiio, Benefix, Eloctate, Esperoct, Hemlibra, Hemofil M, Humate-P, Hympavzi Idelvion, Ixinity, Jivi, Koate, Koate-DVI, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Profilnine, Qfitlia, Rebinyn, Recombinate, Rixubis, Wilate, Xyntha, Xyntha Solofuse, Obizur, Vonvendi, Coagadex, Corifact, Feiba, NovoSeven RT, Tretten, Sevenfact, Fibryga RiaStap, and any newly marketed blood product indicated for a bleeding disorder
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age Patient must be age appropriate per package insert
Prescriber Restrictions	Prescriber must be a hematologist
Coverage Duration	If all of the criteria are met, the request will be approved for 1 month. If the provider states that the requested medication is for a chronic or long-term condition for which the medication may be necessary for the life of the patient, the request will be approved for 12 months.
Other Criteria	• Patient has a diagnosis of a bleeding disorder and the type of deficiency has been provided • Product is being used for an FDA-approved indication at an FDA approved dose or the indication/dose are otherwise supported by treatment guidelines or compendia If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last P&T Review Date	~~12/2024~~6/2025

New Product Review

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Prevymis	Letermovir oral packet 120mg, 20mg	Merck Sharp & Dohme LLC	• Prophylaxis of cytomegalovirus (CMV) infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) • Prophylaxis of CMV disease in adult and pediatric patients 12 years of age and older and weighing at least 40 kg who are kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])	$342 – $2,058 per box (dosing is body weight and indication specific in pediatric patients)	Ganciclovir, Foscavir, Valcyte	Non-formulary
Jivi	antihemophilic factor (recombinant), PEGylated-aucl intravenous solution reconstituted 4000 unit	Bayer	• On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes	$3 per vial	Advate, Adynovate, Eloctate, Hemlibra, Novoeight, Recombinate, etc.	Non-formulary
Fenopron	Fenoprofen oral capsule 300mg	Galt Pharmaceuticals, LLC	• Relief of mild to moderate pain in adults • Relief of the signs and symptoms of rheumatoid arthritis • Relief of the signs and symptoms of osteoarthritis	$22 per capsule (dose varies from 200mg – 600mg every 4 to 6 hours as needed)	Nalfon, ibuprofen, ketoprofen, diclofenac, etodolac, etc.	Non-formulary
Alhemo	concizumab-mtci pen-injector 60mg/1.5ml, 150 mg/1.5ml	Novo Nordisk Inc.	For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors	$51,600 per month (cost of two 150mg pens per month) (maintenance dose varies based on concentration post loading dose)	Hympavzi	Non-formulary (see updated MRG policy)

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Steqeyma	ustekinumab-stba subcutaneous solution prefilled syringe 45 mg/0.5ml, 90mg/ml	Celltrion USA, Inc.	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)	$4,176 every 12 weeks (for 90mg dose)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana & other Stelara biosimilars (once they launch)	Non-formulary (see updated MRG policy)
Datroway	Datopotamab deruxtecan-dlnk intravenous solution reconstituted 100 mg	Daiichi Sankyo, Inc.	For the treatment of adult patients with unresectable or metastatic, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received prior endocrine-based therapy and chemotherapy for unresectable or metastatic disease.	$19,564 every 3 weeks (dose is weight specific)	Trodelvy	Non-formulary
Adalimumab-adaz	Adalimumab-adaz Subcutaneous Solution Prefilled Syringe 20 MG/0.2ML	Sandoz	• Rheumatoid Arthritis • Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Ankylosing Spondylitis • Crohn's Disease • Ulcerative Colitis • Plaque Psoriasis • Hidradenitis Suppurativa • Uveitis *Note: Adalimumab-adaz has many approved indications. See full prescribing information for details of each indication.*	$657 per syringe	Humira, Amjevita, Idacio, Cyltezo, Hyrimoz, Yusimry, Yuflyma, Hadlima and other biosimilars	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Esperoct	Antihemophilic Factor (recombinant) glycopegylated-exei 4,000 unit	Novo Nordisk	For use in adults and children with hemophilia A for: • On-demand treatment and control of bleeding episodes • Perioperative management of bleeding • Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of use: Esperoct is not indicated for the treatment of von Willebrand disease.	$3 per vial	Advate, Jivi, Adynovate, Eloctate, Hemlibra, Novoeight, Recombinate, etc	Non-formulary
Simlandi	adalimumab-ryvk subcutaneous prefilled syringe kit 20 mg/0.2ml, 80mg/0.8ml	Teva Pharmaceuticals	• Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$519 per dose (20mg syringe) $1,038 per dose (80mg syringe)	Humira, Amjevita, Idacio, Cyltezo, Hyrimoz, Yusimry, Yuflyma, Hadlima and other biosimilars	F-QL (already added via CRF) (QL: 80mg/0.8mL: 2 syringes/28 days, LD: 4 syringes; 20mg/0.2mL: 4 syringes/28 days, LD: use 40mg strength)
Fulvicin P/G	Griseofulvin oral tablet 165mg	Solubiomix LLC	• Fungal infections (see PI for full details)	$5,184 per month (for twice daily dosing, dose is weight and indication specific)	Terbinafine, itraconazole, fluconazole, etc.	Non-formulary
Steqeyma	ustekinumab-stba intravenous solution 130 mg/26ml	Celltrion USA, Inc.	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)	$911 single infusion for UC or CD (for patients weighing 55 kg to 85 kg)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Yesintek, &other Stelara biosimilars (once they launch)	Non-formulary (see updated MRG policy)

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Yesintek	Ustekinumab-kfce subcutaneous solution/ prefilled syringe 45 MG/0.5ML, 90 MG/ML	Biocon Biologics	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy active psoriatic arthritis (PsA)	$3,000 every 12 weeks (for 90mg dose)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Steqeyma, & other Stelara biosimilars (once they launch)	Add to F-PA (see updated MRG policy)
Niktimvo	Axatilimab-csfr intravenous solution 9mg/0.18ml, 22mg/0.44ml	Incyte	• For the treatment of chronic graft-versus-host disease (cGVHD) after failure of at least two prior lines of systemic therapy in adult and pediatric patients weighing at least 40 kg	$23,100 per month (for 70kg patient)	Rezuorck, Imbruvica	Non-formulary (see new PAD policy)
Metformin#	Metformin HCl oral tablet 750mg	Lifsa Drugs	• As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus	$33 per tablet (based on WAC, NADAC and MAC pricing not available)	DPP4 inhibitors, GLP1 agonists, sulfonylureas, thiazolidinediones, etc.	Non-formulary
Frindovyx	Cyclophosphamide intravenous solution 500mg/ml, 1g/2ml, 2g/4ml	Avyxa Pharma	• For treatment of adults and pediatric patients with malignant diseases: malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma	$875 per ml (dose depends on regimen and body weight)	Bendamustine, ifosfamide (and other antineoplastic alkylating agents)	Non-formulary
Griseofulvin	Griseofulvin ultramicrosize oral tablet 165 mg	Ayurax	• Fungal infections (see PI for full details)	$33 per tablet (based on WAC, NADAC and MAC pricing not available)	Terbinafine, itraconazole, fluconazole, etc.	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Halcinonide	Halcinonide External Solution 0.1%	Ina Pharmaceuticals	• For the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	$624 per bottle	High potency steroids – fluocinonide, betamethasone dipropionate, clobetasol propionate, etc.	Non-formulary
Ustekinumab-ttwe	Ustekinumab-ttwe subcutaneous solution prefilled syringe 45 mg/0.5ml, 90mg/ml Ustekinumab-ttwe intravenous solution 130 mg/26ml	Quallent Pharmaceuticals	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy active psoriatic arthritis (PsA)	$15,742 every 12 weeks (for 90mg dose)	Yesintek, Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Steqeyma, & other Stelara biosimilars (once they launch)	Non-formulary (see updated MRG policy)
Journavx	Suzetrigine 50mg oral tablet	Vertex Pharmaceuticals	• For the treatment of moderate to severe acute pain in adults	$434 for 14 days of treatment	Opioids	Non-formulary
Feirza 1.5/30	ethinyl estradiol and norethindrone oral tablet 1.5-30 mg-mcg	Xiromed	• For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception	$8 per pack	Loestrin, Microgestin, Larin, Junel, etc.	Add to F
Valtya 1/50	ethynodiol diacetate and ethinyl estradiol oral tablet 1-50 mg-mcg	Xiromed	• For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception	$24 per pack	Kelnor 1/50	Add to F
Rybelsus	Semaglutide oral tablet 1.5mg, 4mg, 9mg	Novo Nordisk	• An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	$997 (max dose of 9mg/day)	Ozempic, Trulicity, etc.	F-ST-QL (Already added via CRF) ST: Requires a previous trial with a metformin-containing product. QL: 30 tabs/30 days

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Palforzia	Peanut allergen powder • initial dose 1-3yrs oral capsule sprinkle therapy pack 0.5 & 1 & 1.5 & 3 mg • initial dose 4-17yrs oral capsule sprinkle therapy pack 0.5 & 1 & 1.5 & 3 & 6 mg • oral capsule sprinkle therapy pack 1 x 1 mg	Greer Laboratories	• For the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up-Dosing and Maintenance may be continued in patients 4 years of age and older. Palforiza is to be used in conjunction with a peanut-avoidant diet. Limitation of Use: Not indicated for the emergency treatment of allergic reactions, including anaphylaxis.	$960 per pack	Xolair	Non-formulary
Evrysdi	Risdiplam 5mg oral tablet	Genentech	• For the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients	$33,660	Spinraza, Zolgensma	Non-formulary
Selarsdi	Ustekinumab-aekn subcutaneous solution prefilled syringe 45 mg/0.5ml, 90mg/ml	Teva Pharmaceuticals	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy active psoriatic arthritis (PsA)	$4,176 every 12 weeks (for 90mg dose)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Yesintek, Steqeyma, & other Stelara biosimilars (once they launch)	Non-formulary (see updated MRG policy)

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Gomekli	Mirdametinib oral capsule 1mg, 2mg Mirdametinib oral tablet soluble 1mg	Springwork Therapeutics	• For the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection	$34,650 (for average adult BSA)	Koselugo	Non-formulary (see new MRG policy)
Grafapex	Treosulfan IV solution reconstituted 1gm, 5m	Medexus Pharma	• Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation (alloHSCT) in adult and pediatric patients 1 year of age and older with acute myeloid leukemia (AML) • Use in combination with fludarabine as a preparative regimen for allogeneic hematopoietic stem cell transplantation in adult and pediatric patients 1 year of age and older with myelodysplastic syndrome (MDS)	$610 per gram	Melphalan, busulfan	Non-formulary
Zepbound	Tirzepatide subcutaneous solution 7.5mg/0.5ml, 10mg/0.5ml	Eli Lilly	Indicated in combination with a reduced-calorie diet and increased physical activity: • to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition • to treat moderate to severe obstructive sleep apnea (OSA) in adults with obesity Limitations of use: Coadministration with other tirzepatide-containing products or with any GLP-1 receptor agonist is not recommended	$838 (per month for 10mg dose)	Wegovy, Saxenda	Non-formulary
Omvoh (300mg dose)	Mirikizumab-mrkz (300 mg dose) subcutaneous solution auto-injector and prefilled syringe 100 mg/ml & 200 mg/2ml	Eli Lilly	• Treatment of moderately to severely active ulcerative colitis in adults • Treatment of moderately to severely active Crohn's disease in adults	$10,878	Humira, Infliximab, Rinvoq, Stelara, Entyvio	Non-formulary

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New Product Review

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Onapgo	Apomorphine hydrochloride subcutaneous solution cartridge 98 mg/20ml	Supernus Pharmaceuticals	• For the treatment of motor fluctuations in adults with advanced Parkinson's disease	$8,628	Vyalev, Apokyn	Non-formulary
Ivra	Melphalan intravenous solution 90 mg/ml	Apotex	• For palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate	$5,500 per vial	Bendamustine, cyclophosphamide (both off label)	Non-formulary
Xromi	Hydroxyurea oral solution 100 mg/ml	Rare Disease Therapeutics	• To reduce the frequency of painful crises and reduce the need for blood transfusions in pediatric patients 6 months of age and older with sickle cell anemia with recurrent moderate to severe painful crises	$760 per bottle	Droxia, Siklos	Non-formulary
Metaxalone	Metaxalone oral tablet 640 mg	Ina Pharmaceuticals	• Muscle relaxant indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions in adult and pediatric patients 13 years of age and older	$ 4,510 (per month for max dose)	Flexeril, Zanaflex, NSAIDs	Non-formulary
Zunveyl	Benzgalantamine oral tablet delayed release 5 mg, 15mg	Alpha Cognition Inc.	• For the treatment of mild to moderate dementia of the Alzheimer's type in adults	$749 (per month for max dose)	Adlarity, Aricept, galantamine, Namzaric, Exelon	Non-formulary (see updated MRG policy)
Feirza 1/20	ethinyl estradiol and norethindrone oral tablet 1-20 mg-mcg	Xiromed	• For the prevention of pregnancy in women who elect to use oral contraceptives as a method of contraception	$8 per pack	Loestrin, Microgestin, Larin, Junel, etc.	Add to F
Promethazine	Promethazine hcl oral solution 12.5 mg/10ml	Chartwell Rx	Antihistamine with multiple approved indications such as seasonal allergic rhinitis, motion sickness, and nausea/vomiting. See full PI for details.	$100.5 per unit dose cup (10mL)	Zyrtec, Claritin, Benadryl, etc.	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Valtoco	Diazepam 15 mg dose nasal liquid therapy pack 2 x 7.5 mg/0.1ml Diazepam 20 mg dose nasal liquid therapy pack 2 x 10 mg/0.1ml	Neurelis	• For the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older	$1,830 per box	Nayzilam	Non-formulary
Pyzchiva	Ustekinumab-ttwe subcutaneous solution prefilled syringe 45mg/0.5ml and 90 mg/ml Ustekinumab-ttwe Intravenous Solution 130 MG/26ML	Sandoz	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy active psoriatic arthritis (PsA)	$5,830 every 12 weeks (for 90mg dose)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Yesintek, Steqeyma, & other Stelara biosimilars (once they launch)	Non-formulary (see updated MRG policy)
Alhemo	Concizumab-mtci subcutaneous solution pen-injector 300 mg/3ml	Novo Nordisk	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors	$51,600 per month (for one 300mg pen per month)	Hympavzi	Non-formulary (see updated MRG policy)
Raldesy	Trazodone oral solution 10 mg/ml	Validus Pharmaceuticals	• For the treatment of major depressive disorder (MDD) in adults	$1,944 per month (for a dose of 400mg per day)	Vilazodone, Vortioxetine, SSRIs, atypical agents, SNRIs, tricyclic/tetracyclic antidepressants, MAOis	Non-formulary
Vimkunya	Chikungunya vaccine, recombinant intramuscular suspension prefilled syringe 40 mcg/0.8ml	Bavarian Nordic	• For the prevention of disease caused by chikungunya virus (CHIKV) in individuals 12 years of age and older	$275 per dose	Ixchiq	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
BKEMV	Eculizumab-aeeb intravenous solution 300 mg/30ml	Amgen	• Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis • Treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complement-mediated thrombotic microangiopathy Limitation of Use: BKEMV is not indicated for the treatment of patients with Shiga toxin E. coli related hemolytic uremic syndrome (STEC-HUS)	$5,870/300 mg vial	Soliris, Epysqli, & other Soliris biosimilars (once they launch)	Non-formulary (see updated MRG and PAD policies)
Otulfi	Ustekinumab-aauz subcutaneous solution prefilled syringe 45 mg/0.5ml Ustekinumab-aauz subcutaneous solution prefilled syringe 90 mg/ml Ustekinumab-aauz intravenous solution 130 mg/26ml	Fresenius Kabi	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA)	$3,619 every 12 weeks (for 90 mg dose)	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Yesintek, Steqeyma, & other Stelara biosimilars (once they launch)	Add to F-PA (see updated MRG policy)
Romvimza	Vimseltinib oral capsule 14, 20, 30 mg	Deciphera Pharmaceuticals	• For the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity	$26,128 per month	Turalio	Non-formulary
Zunveyl	Benzgalantamine oral tablet delayed release 10 mg	Alpha Cognition USA	• For the treatment of mild to moderate dementia of the Alzheimer's type in adults	$749 per month (for max dose of 15mg twice daily)	Adlarity, Aricept, galantamine, Namzaric, Exelon	Non-formulary (see updated MRG policy)
Lidocaine HCl	Lidocaine HCl urethral/mucosal external gel 2 %	Armas Pharmaceuticals	• For prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)	$247 for max dose of 30 ml in a 12 hour period	Xylocaine, Jelcaine Sterile	Non-formulary

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New Product Review

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Epysqli	Eculizumab-aagh intravenous solution 300 mg/30ml	Teva Pharmaceuticals	• The treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce hemolysis. • The treatment of patients with atypical hemolytic uremic syndrome (aHUS) to inhibit complementmediated thrombotic microangiopathy.	$4,566 per 300mg vial	Soliris, BKEMV	Non-formulary (see updated MRG and PAD policies)
Purified Cortrophin Gel	Corticotropin subcutaneous prefilled syringe 40 unit/0.5ml, 80 unit/ml	ANI Pharmaceuticals	• Rheumatic disorders, Collagen diseases, Dermatologic diseases, Allergic states, Ophthalmic diseases, Symptomatic sarcoidosis, Nephrotic syndrome and Multiple Sclerosis	$7,421 per 1ml syringe	Cortrophin, Acthar	F-PA (Already added via CRF)
Inzirqo	hydrochlorothiazide oral suspension 10mg/ml	ANI Pharmaceuticals	• The treatment of hypertension in adult and pediatric patients alone or in combination with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction. • The treatment of edema associated with congestive heart failure, hepatic cirrhosis and renal disease including the nephrotic syndrome in adult and pediatric patients.	$702 per month (for dose of 50mg daily)	Thiazide diruetics	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Xpovio (40 MG Once Weekly)	Selinexor (40 mg once weekly) oral tablet therapy pack 10 mg	Karyopharm Therapeutics	• In combination with bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy, • In combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody • For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least 2 lines of systemic therapy. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).	$8,196 per week	Velcade, Kyprolis, Ninlaro, Revlimid	Non-formulary
Ryoncil	remestemcel-L various intravenous kit sizes	Mesoblast	• Indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older	$194k per infusion	Rezurock, Imbruvica, Niktimvo	Non-formulary (see new PAD policy)
Abirtega	Abiraterone acetate oral tablet 250mg	Civicascript	Indicated in combination with prednisone for the treatment of patients with: • metastatic castration-resistant prostate cancer (CRPC) • metastatic high-risk castration-sensitive prostate cancer	$120 per pack of 120 tablets	Zytiga, Yonsa	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Emend BiPack	Aprepitant oral capsule 80mg	Merck Sharp & Dohme	In combination with other antiemetic agents, in patients 12 years of age and older for prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin • nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)	$438 per pack (pack of 2)	Aponvie, Cinvanti, Zofran, Focinvez	Non-formulary
BAC (Butalbital-Acetamin-Caff)	Butalbital-acetaminophen-caff oral tablet 50-325-40mg	Mikart	• For the relief of the symptom complex of tension (or muscle contraction) headache	$367 per month (for max dose of 6 per day)	Esgic, Fioricet	Non-formulary

cefazolin sodium-dextrose	cefazolin sodium-dextrose intravenous solution reconstituted 3-2 gm-% (50ml)	B. Braun Medical	• Treatment of the following infections caused by susceptible isolates of the designated microorganisms in adult and pediatric patients for whom appropriate dosing with this formulation can be achieved:
			  ○ Respiratory tract infections
			  ○ Urinary tract infections
			  ○ Skin and skin structure infections
			  ○ Biliary tract infections
			  ○ Bone and joint infections
			  ○ Genital infections
			  ○ Septicemia
			  ○ Endocarditis
			• Perioperative prophylaxis in adults and pediatric patients aged 10 to 17 years old for whom appropriate dosing with this formulation can be achieved
				$15 per bag	Other cephalosporins and antibacterials	Non-formulary

Simlandi	Adalimumab-ryvk (1 pen) subcutaneous auto-injector kit 80 mg/0.8ml	Teva Pharmaceuticals	• Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$1,038 per kit	Humira, Amjevita, Idacio, Cyltezo, Hyrimoz, Yusimry, Yuflyma, Hadlima and other biosimilars	F-QL (Already added via CRF) (QL: 2 pens/28 days; LD: 4 pens)

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Sevenfact	coagulation factor viia-jncw intravenous solution reconstituted 2 mg	Hema Biologics	• For the treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with hemophilia A or B with inhibitors Limitation of Use: Sevenfact is not indicated for treatment of congenital factor VII deficiency	$2.66 per vial	NovoSeven RT, Advate, Recombinate, etc.	Non-formulary
Ivermectin	ivermectin oral tablet 6 mg	Advagen Pharma	• Strongyloidiasis of the intestinal tract • Onchocerciasis	$11 per tablet	Moxidectin	Non-formulary
Revuforj	Revumenib oral tablet 25 mg	Syndax Pharmaceuticals	• For the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older	$333 per tablet (25mg tablets used for BSA dosing in patients weighing less than 40kg)	Venflexta	Non-formulary
Rapiblyk	Landiolol intravenous solution reconstituted 280 mg	AOP Orphan Pharmaceuticals	• For the short-term reduction of ventricular rate in adults with supraventricular tachycardia including atrial fibrillation and atrial flutter	$850 per vial	Adenosine, amiodarone, metoprolol, etc.	Non-formulary
Ctexli	Chenodiol 250 mg tablets	Mirum Pharmaceuticals	• For treatment of cerebrotendinous xanthomatosis (CTX) in adults	$53,730	None	Non-formulary
Baclofen Refill Kit-SynchroMed	Baclofen intrathecal kit 40 mg/20ml	Nexus	• For use in the management of severe spasticity	$640 per kit	Zanaflex, Botox, Dysport	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Selarsdi	Ustekinumab-aekn intravenous solution 130 mg/26ml	Teva Pharmaceuticals	Treatment of adult patients with: • moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy • active psoriatic arthritis (PsA) • moderately to severely active Crohn's disease (CD) • moderately to severely active ulcerative colitis Treatment of pediatric patients 6 years and older with: • moderate to severe plaque psoriasis, who are candidates for phototherapy or systemic therapy active psoriatic arthritis (PsA)	$1,530 per vial	Stelara, Skyrizi, Tremfya, Ilumya, Wezlana, Yesintek, Steqeyma, & other Stelara biosimilars	Non-formulary (see updated MRG policy)
Encelto	revakinagene taroretcel-lwey intravitreal implant 200000 cells	Neurotech Pharmaceuticals	• For the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel)	$250,000 per implant	None	Non-formulary
Acyclovir	Acyclovir Oral Suspension 800 MG/20ML	Chartwell Rx	• Herpes zoster infections • Genital herpes • Chickenpox	$96 per cup	Valtrex	Non-formulary
Tremfya	Guselkumab crohns induction subcutaneous solution auto-injector 200 mg/2ml	Janssen BioTech, Inc.	• Moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • Active psoriatic arthritis • Moderately to severely active ulcerative colitis • Moderately to severely active Crohn’s disease	$14,566 (per month for maintenance dosing)	Stelara, Skyrizi, Humira, Cosentyx, Taltz, etc.	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Octreotide	SandoSTATIN LAR depot intramuscular kit 10 mg	Teva Pharmaceuticals	• Treatment in patients who have responded to and tolerated octreotide acetate injection subcutaneous injection for: ○ Acromegaly ○ Severe diarrhea/flushing episodes associated with metastatic carcinoid tumors ○ Profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIP) secreting tumors	$3,044 per kit	Signifor, Somatuline Depot	Non-formulary
Qfitlia	Fitusiran subcutaneous solution 20 mg/0.2ml, subcutaneous solution auto-injector 50 mg/0.5ml	Genzyme Corporation	• For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients aged 12 years and older with hemophilia A or B with or without factor VIII or IX inhibitors.	$64,560 (per month for dose of 20mg a month) (note prices varies by antithrombin activity levels)	Hemlibra, Hympavzi, Alhemo	Non-formulary (see updated MRG policy)
Combogesic	Ibuprofen-acetaminophen oral tablet 325-97.5mg	AFT Pharmaceuticals	• For the short term management of mild to moderate acute pain	$936 (for max dose)	NSAIDs, Tylenol, opioids etc.	Non-formulary
Tremfya Pen	Guselkumab pen subcutaneous solution auto-injector 100 mg/ml	Janssen BioTech, Inc.	• Moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • Active psoriatic arthritis • Moderately to severely active ulcerative colitis • Moderately to severely active Crohn's disease	$14,566 every 8 weeks (maintenance dosing)	Stelara, Skyrizi, Humira, Cosentyx, Taltz, etc.	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Vyloy	Zolbetuximab-clzb intravenous solution reconstituted 300 mg	Astellas Pharma	• Indicated in combination with fluoropyrimidine and platinum-containing chemotherapy for the first-line treatment of adults with locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-negative gastric or gastroesophageal junction adenocarcinoma whose tumors are claudin (CLDN) 18.2 positive as determined by an FDA-approved test	$19,200 every 3 weeks (BSA of 2)	Keytruda, Opdivo	Non-formulary
Tezruly	Terazosin oral solution 1 mg/ml	ANI Pharmaceuticals	• The treatment of signs and symptoms of benign prostatic hyperplasia (BPH) • The treatment of hypertension alone or with other antihypertensive agents, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarction	$474 per bottle	Doxazosin, prazosin	Non-formulary
Lutrate Depot	Leuprolide acetate intramuscular injectable 22.5 mg	Avyxa Pharma, LLC	• Treatment of advanced prostate cancer	$2,000 every 3 months	Lupron, Eligard, Camcevi	Non-formulary
Xelria Fe	Norethin-eth estradiol-fe oral tablet chewable 0.4-35 mg-mcg	Xiromed	• Indicated for use by females of reproductive potential to prevent pregnancy	$25 per pack	Finzala, Mibelas 24 Fe, Wymzya Fe, etc.	Add to F
Lamivudine	Lamivudine oral solution 300 mg/30ml	Chartwell Rx	• Indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection. Limitations of Use: The dosage of this product is for HIV-1 and not for HBV	$2,970	Epivir, Ziagen, Emtriva, stavudine, etc.	Non-formulary

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New Product Review

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Albuterol	Albuterol sulfate oral syrup 8 mg/20ml	Chartwell Rx	• For the relief of bronchospasm in adults and children 2 years of age and older with reversible obstructive airway disease	$0.8 per cup (based on MAC)	Levalbuterol, formoterol, budesonide, etc.	Non-formulary
Paxlovid	Nirmatrelvir & ritonavir oral tablet therapy pack 6 x 150 mg & 5 x 100mg	Pfizer	• For the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death	$1,496 per pack	Lagevrio, Veklury	F-QL-AL (Already added via CRF) (QL: 11 tabs/180 days, AL: 12 years and older)
Sunlenca	Lenacapavir 300mg oral tablet	Gilead Sciences	• For the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 whose current antiretroviral regimen is failing due to resistance, intolerance, or safety considerations	$813 per tablet (dosing depends on initiation schedule)		F (Already added via CRF)
Zevtera	Ceftobiprole medocaril intravenous solution reconstituted 500 mg	LA Jolla Pharmaceuticals	• Treatment of adult patients with Staphylococcus aureus bloodstream infections (bacteremia) (SAB), including those with right-sided infective endocarditis • Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) • Treatment of adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP)	$235 per vial	vancomycin and other antibiotics with activity against MRSA	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Vyvgart Hytrulo	Efgartigimod alfa-Hyalur-qvfc subcutaneous solution prefilled syringe 1000-10000 mg-unt/5ml	Argenx US	Adult patients with: • generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AChR) antibody positive • chronic inflammatory demyelinating polyneuropathy (CIDP)	$66,920 every 4 weeks	Soliris, Ultomiris, Rystiggo, Vyvgart, Zilbrysq	Non-formulary
Neffy	Epinephrine nasal solution 1 mg/0.1ml	ARS Pharmaceutical Operations	• For emergency treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients 4 years of age and older who weigh 15 kg or greater	$355 per dose	EpiPen	Non-formulary
Amnesteem	Isotretinoin oral capsule 30 mg	Mylan	• Severe recalcitrant nodular acne	$414 per month (initial dosing for 60kg patient)	Accutane, Claravis, Zenatane	F-PA (Already added via CRF)
Morphine sulfate	Morphine sulfate intravenous solution 2 mg/ml	Hikma Pharmaceuticals USA	• For adult and pediatric patients for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, reserve Morphine Sulfate Injection for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]: • Have not been tolerated, or are not expected to be tolerated • Have not provided adequate analgesia, or are not expected to provide adequate analgesia	$2.58 per syringe	Opioids	Non-formulary

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BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Adrenalin	Epinephrine in sodium chloride intravenous solution 5-0.9 mg/250ml-%	Endo USA	• Used to increase mean arterial blood pressure in adult patients with hypotension associated with septic shock	$50 per bag	Vasopressors	Non-formulary
Marcaine	Bupivacaine hydrochloride preservative free injection solution 0.75 %	Hospira	• For the production of local or regional anesthesia or analgesia for surgery, dental and oral surgery procedures, diagnostic and therapeutic procedures, and for obstetrical procedures	$8 per 30ml vial	Local anesthetics (lidocaine, mepivacaine, etc.)	Non-formulary
Adalimumab-aaty	Adalimumab-aaty CD/UC/HS Start Subcutaneous auto-injector kit 80 mg/0.8ml	Celltrion USA	• Rheumatoid Arthritis • Juvenile Idiopathic Arthritis • Psoriatic Arthritis • Ankylosing Spondylitis • Crohn's Disease • Ulcerative Colitis • Plaque Psoriasis • Hidradenitis Suppurativa • Uveitis *Note: Adalimumab-aaty has many approved indications. See full prescribing information for details of each indication.*	$519 per kit	Humira, Amjevita, Idacio, Cyltezo, Hyrimoz, Yusimry, Hadlima and other biosimilars	F-QL (Already added via CRF) (QL: 2 pens/28 days, LD: 4 pens)

*	Pricing reflects Wholesale Acquisition Cost (WAC) per month unless otherwise noted.
^	The recommendation may be affected by state specific requirements including carve out lists and individual state mandates.
†	Pricing based on standard twice-monthly dosing for most indications.
‡	Pricing is per each kit on items listed as a kit.
#	Re-activation of previously discontinued product (i.e., other available NDCs now inactive)

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