PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, September 24th, 2024
5:00pm – 7:00pm

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

Location: Microsoft Teams
Meeting ID: 283 830 804 049
Password: jyp46b

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: +1 510-210-0967,112676987#. 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 VOTE	DESCRIPTION	TIME	
I)	**Call to order** *Donna Carey, MD, Interim Chief Medical Officer – Alameda Alliance* • Agenda Overview	2 min	-
II)	**Informational Updates** *Donna Carey, MD, Chief Medical Officer – Alameda Alliance* *TBD, PharmD, Senior Pharmacy Director – Alameda Alliance* • DHCS Audit • Search for Permanent/Interim Director • DSNP Readiness	15 min	-
III)	**Pharmacy Utilization Reports (Quarter 2, 2024)** *Rahel Negash, PharmD, Pharmacy Supervisor – 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: 9/24/2024*** *(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

Rahel Negash, PharmD, Pharmacy Supervisor – 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 closedsession.)

Monographs/Class Reviews	Changes
Chelating Agents Class Review	• No changes
Continuous Glucose Monitors (CGMs) Class Review	• No changes
Pancreatic Enzymes Class Review	• No changes
Medication Request Guidelines	**Changes**
Physician Administered Medication (PAD)/ Medical Benefit Guidelines	• No changes
Off-label uses	• No changes
Safety Edit Exception	• No changes
Quantity Limit Exception	• No changes
Antibiotic Eye Medications	• No changes
Antiemetics	• Remove Zuplenz as it has been discontinued
Nuedexta (dextromethorphan/quinidine)	• No changes
Cartilaginous Repair Agents	• No changes
Memantine ER (Namenda XR)	• No changes
Ophthalmic Anti-inflammatory Immunomodulators	• No changes
Penicillamine (Depen, Cuprimine), Trientine HCl (Syprine) for Wilson's disease	• No changes
Iron-chelating Agents	• No changes
Vancomycin	• No changes
Dronabinol	• No changes
Multaq (dronedarone)	• No changes
Erythropoiesis-Stimulating Agents	• No changes

10 min EV

Drugs for Gender Dysphoria For Less Than 21 Years Old	• No changes
Drugs for Gender Dysphoria For At Least 21 Years Old	• No changes, add 10mg available dosage form for medroxyprogesterone
Mesalamine	• Remove Mesalamine DR (Asacol HD) tablet as it has been discontinued
Corticosteroids for Ulcerative Colitis and Crohn's disease	• Add Ortikos to coverage duration section
Atovaquone-proguanil (Malarone)	• No changes
Intranasal Steroids	• Remove Rhinocort Allergy brand product as it was discontinued
Scabicides and Pediculicides	• Remove Lindane product as it was discontinued
Rifamycin Antibiotics	• No changes
Topical Acne Agents	• No changes
Injectable/Infusible Bone-Modifying Agents for Oncology Indications	• Remove Aredia and Zometa brands as they were discontinued
Alosetron (Lotronex)	• No changes
Viberzi (eluxadoline)	• No changes
Rifabutin (Mycobutin)	• No changes
Medications for the treatment of Multi-Drug Resistant Tuberculosis	• No changes
Tranexamic acid (Lysteda)	• No changes
Moxifloxacin Oral Tablet	• No changes
Spravato (esketamine) Intranasal	• No changes
Santyl Ointment	• No changes
Topical Antibiotics	• No changes
Fertility Agents	• No changes
Erectile Dysfunction Medications	• Remove IFE PG20 as it has been discontinued
Vowst	• No changes
Physician Administered Drug (PAD) Guidelines	**Changes**
Adakveo	• No changes
Exondys 51	• No changes, minor grammatical correction
Erythropoiesis-Stimulating Agents	• No changes
Iron-containing Products	• No changes
Tepezza	• No clinical changes, minor formatting change

Fecal microbiota	• No changes
Omisirge	• No changes, addition of medical necessity review statement
Qalsody (tofersen)	• No changes, addition of medical necessity review statement
Lamzede	• No changes, addition of medical necessity review statement
Enzyme Replacement Therapies for Fabry Disease	• No changes, addition of medical necessity review statement
Roctavian	• No changes, addition of medical necessity review statement
Enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD)	• No changes, addition of medical necessity review statement
Interim Formulary Updates	
• See p. 150 in packet	
Interim Physician Administered Drug (PAD) Updates	
• See p. 151 in packet	
Pharmacy Policy & Procedure Updates	
• RX-002 Pharmacy Benefit Prior Authorization Review Process	• Add G&A submission for appeal language
• RX-005 P&T Committee Roles and Scope	• Language to include DMHC psychiatric specialist requirement
ED Oversight	
• None	
90 Day Maintenance List updates	
• Formatting change with dates	
P&T Meeting Minutes	
• P&T Meeting Minutes Q2 June 11, 2024	

V) New Business

Iryna Makukh, PharmD, Pharmacist – PerformRx

New MRG

- Xolremdi

New PAD

- Rytelo

VI) Class Reviews, Monographs, and Recommendations

Iryna Makukh, PharmD, Pharmacist – PerformRx

1. Duvyzat Monograph
   a. New MRG: Duvyzat
2. Glaucoma Agents Class Review
   a. New MRG: Rho Kinase Inhibitors
3. Hepatitis B Class Review

45 min V

VII)	**Medication Request Guidelines** *Rahel Negash, PharmD, Pharmacy Supervisor – Alameda Alliance* 1. Specialty Biologic Agents 2. White Blood Cell Stimulators 3. Constipation agents 4. Vaginal Progesterone 5. Injectable/Infusible Agents for Osteoporosis and Paget's Disease 6. Fabhalta 7. Vasodilators for Pulmonary Arterial Hypertension (PAH) 8. Palforzia		
VIII)	**Physician Administered Drug (PAD) Policies** *Iryna Makukh, PharmD, Pharmacist – PerformRx* 1. Injectable/Infusible Agents for Osteoporosis and Paget's Disease 2. White Blood Cell Stimulators 3. Gene Therapy for Hemophilia 4. Elevidys 5. B-Cell Maturation Antigen (BCMA) Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy	10 min	V
IX)	**Informational Updates on New Developments in Pharmacy** *Iryna Makukh, PharmD, Pharmacist – PerformRx* • New Product Review	2 min	-
X)	**Old Business** *Iryna Makukh, PharmD, Pharmacist – PerformRx* • Tadalafil (Cialis) for BPH MRG • Febuxostat (Uloric) MRG	2 min	-
	RECONVENE IN OPEN SESSION		
XI)	**Public Comment**		
XII)	**Adjournment**		

PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, September 24th, 2024
5:00pm – 7:00pm

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

FUTURE P&T MEETINGS	
NEXT MEETING	**2025 P&T MEETINGS**
December 17, 2024	March 18, 2025 June 17, 2025 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 2nd Quarter 2024

- The top 50 drugs accounted for **1,095 claims** for **588 members** and cost **$1,442,371,** which is an increase of $85,169 in spend from the previous quarter.
- Biktarvy remains at number one, claims have gone up by 1, and there are two additional members since the previous quarter.
- Zejula remains at number 2 with 3 claims for 1 member. This medication is managed via the Oral and Injectable Oncology Medications MRG.
- Ozempic is at numbers 3, 5 and 7, with 209 total claims for 103 members. There was an increase of 28 claims and of 14 members from the previous quarter.
- Vemlidy is down to number 4 with 51 claims for 21 members. 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 4 claims for one 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	31	12	$119,274.22
2	223302	Zejula Oral Tablet 100 MG	3	1	$106,178.85
3	221271	Ozempic (0.25 or 0.5 MG/DOSE) Subcutaneous Solution Pen-injector 2 MG/3ML	87	46	$80,474.64
4	195609	Vemlidy Oral Tablet 25 MG	51	21	$75,925.28
5	209911	Ozempic (1 MG/DOSE) Subcutaneous Solution Pen-injector 4 MG/3ML	65	32	$60,537.93
6	199757	Verzenio Oral Tablet 50 MG	4	1	$59,098.00
7	218338	Ozempic (2 MG/DOSE) Subcutaneous Solution Pen-injector 8 MG/3ML	57	25	$53,204.32
8	215662	Rezurock Oral Tablet 200 MG	3	1	$52,724.52
9	120505	Sprycel Oral Tablet 20 MG	3	1	$44,782.98
10	214809	Skyrizi Pen Subcutaneous Solution Auto-injector 150 MG/ML	2	2	$41,332.16
11	219135	Skyrizi Subcutaneous Solution Cartridge 360 MG/2.4ML	2	1	$41,332.16

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
12	219459	Paxlovid (300/100) Oral Tablet Therapy Pack 20 x 150 MG & 10 x 100MG	28	28	$38,051.72
13	122702	Januvia Oral Tablet 100 MG	64	27	$35,910.58
14	207961	Rybelsus Oral Tablet 7 MG	38	17	$35,414.94
15	170343	Jakafi Oral Tablet 5 MG	2	1	$33,309.60
16	217445	Tarpeyo Oral Capsule Delayed Release 4 MG	2	1	$31,936.26
17	197146	Cosentyx Sensoready (300 MG) Subcutaneous Solution Auto-injector 150 MG/ML	4	2	$29,101.68
18	223809	Cosentyx UnoReady Subcutaneous Solution Auto-injector 300 MG/2ML	1	1	$28,791.03
19	202548	Humira (2 Syringe) Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	2	1	$26,885.14
20	177191	Eliquis Oral Tablet 5 MG	46	24	$25,675.33
21	212379	Cabenuva Intramuscular Suspension Extended Release 600 & 900 MG/3ML	4	2	$25,665.14
22	185810	Trulicity Subcutaneous Solution Pen-injector 0.75 MG/0.5ML	21	10	$19,774.38
23	201117	Steglatro Oral Tablet 15 MG	56	28	$19,369.62
24	193034	Ocaliva Oral Tablet 5 MG	2	1	$18,889.02
25	184849	Jardiance Oral Tablet 25 MG	31	15	$18,064.05
26	207962	Rybelsus Oral Tablet 14 MG	19	7	$17,773.60
27	201116	Steglatro Oral Tablet 5 MG	43	22	$17,452.40
28	185813	Trulicity Subcutaneous Solution Pen-injector 1.5 MG/0.5ML	18	10	$16,950.01
29	215135	Wegovy Subcutaneous Solution Auto-injector 0.25 MG/0.5ML	13	9	$16,849.40
30	190947	Tagrisso Oral Tablet 80 MG	1	1	$16,138.38

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
31	182488	Glatiramer Acetate Subcutaneous Solution Prefilled Syringe 40 MG/ML	3	1	$16,013.49
32	204204	Shingrix Intramuscular Suspension Reconstituted 50 MCG/0.5ML	74	67	$15,705.52
33	190802	Genvoya Oral Tablet 150-150-200-10 MG	4	2	$15,686.76
34	182336	Farxiga Oral Tablet 10 MG	27	11	$14,926.48
35	139308	Promacta Oral Tablet 25 MG	2	1	$14,318.36
36	183204	Otezla Oral Tablet 30 MG	3	1	$14,200.71
37	199152	Mavyret Oral Tablet 100-40 MG	1	1	$12,688.68
38	170142	Xarelto Oral Tablet 20 MG	21	8	$12,324.13
39	184848	Jardiance Oral Tablet 10 MG	20	12	$11,654.96
40	217440	Apretude Intramuscular Suspension Extended Release 600 MG/3ML	3	2	$11,393.25
41	197463	Dupixent Subcutaneous Solution Prefilled Syringe 300 MG/2ML	3	1	$11,318.97
42	207960	Rybelsus Oral Tablet 3 MG	12	10	$11,177.26
43	192096	Odefsey Oral Tablet 200-25-25 MG	3	1	$10,666.74
44	127437	FreeStyle Lite Test In Vitro Strip	136	81	$10,379.56
45	212084	Trulicity Subcutaneous Solution Pen-injector 3 MG/0.5ML	10	4	$9,428.82
46	122700	Januvia Oral Tablet 50 MG	19	9	$9,249.29
47	215134	Wegovy Subcutaneous Solution Auto-injector 0.5 MG/0.5ML	7	6	$9,062.65
48	192525	Descovy Oral Tablet 200-25 MG	4	2	$8,588.69
49	93533	Entecavir Oral Tablet 0.5 MG	32	15	$8,510.19
50	218796	Mounjaro Subcutaneous Solution Pen-injector 10 MG/0.5ML	8	3	$8,209.56
TOTAL			**1095**	**588**	**$1,442,371.41**

Medi-Cal Top 50 Drugs by Cost for 2nd Quarter 2024

- The top 50 drugs accounted for **37,622 claims** for **32,013 members** and cost **$53,049,668.03,** which is an increase of $4,633,273.16 in spend from the previous quarter.
- Biktarvy remains at the number 1 spot with 884 claims for 656 members. An increase of 34 claims from last quarter.
- Ozempic also remains at the number 2 spot, with 2,115 claims for 1,704 members. This is an increase of 238 claims from last quarter.
- Skyrizi has risen from the number 6 from the number 4 spot with 99 claims for 87 members. This is an increase of 10 claims since last quarter.
- Jardiance 25mg has risen from the number 5 to the number 3 spot with 1,677 claims for 1,570 claims, while Jardiance 10mg has fallen from the number 4 to the number 5 spot with 1,755 claims for 1,577 members. Both Jardiance 25mg and Jardiance 10mg had an increase of 141 and 108 claims, respectively, since last quarter.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	44426	BIKTARVY 50-200-25 MG TABLET	884	656	$5,681,249.06
2	53536	OZEMPIC 0.25-0.5 MG/DOSE PEN	2115	1704	$2,973,720.08
3	36723	JARDIANCE 25 MG TABLET	1677	1570	$2,311,014.43
4	49591	SKYRIZI 150 MG/ML PEN	99	87	$2,267,750.95
5	36716	JARDIANCE 10 MG TABLET	1755	1577	$2,264,727.87
6	43506	HUMIRA(CF) PEN 40 MG/0.4 ML	127	99	$2,060,950.40
7	48208	OZEMPIC 1 MG/DOSE (4 MG/3 ML)	1148	970	$1,989,674.21
8	48277	DUPIXENT 300 MG/2 ML PEN	195	151	$1,594,544.35
9	28159	STELARA 90 MG/ML SYRINGE	41	33	$1,590,844.94
10	42624	VEMLIDY 25 MG TABLET	439	358	$1,334,008.61
11	52125	OZEMPIC 2 MG/DOSE (8 MG/3 ML)	684	561	$1,291,985.44
12	97400	JANUVIA 100 MG TABLET	912	834	$1,278,495.43
13	49748	WEGOVY 0.25 MG/0.5 ML PEN	810	732	$1,161,502.34

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
14	33935	ELIQUIS 5 MG TABLET	1055	815	$1,114,269.70
15	27418	INVEGA SUSTENNA 234 MG/1.5 ML	171	136	$1,093,367.69
16	49099	CABENUVA ER 600 MG-900 MG SUSP	143	125	$1,062,600.14
17	46965	RYBELSUS 7 MG TABLET	437	405	$911,553.22
18	40953	DESCOVY 200-25 MG TABLET	261	192	$910,316.54
19	34394	FARXIGA 10 MG TABLET	645	562	$874,908.84
20	25200	FREESTYLE LITE TEST STRIP	4667	4372	$867,768.84
21	40133	TAGRISSO 80 MG TABLET	30	21	$859,823.05
22	97724	ENBREL 50 MG/ML SURECLICK	85	65	$851,014.83
23	49754	WEGOVY 2.4 MG/0.75 ML PEN	385	286	$839,186.00
24	46966	RYBELSUS 14 MG TABLET	368	336	$827,989.24
25	98637	BASAGLAR 100 UNIT/ML KWIKPEN	1629	1352	$801,436.62
26	43968	SYMTUZA 800-150-200-10 MG TAB	104	77	$744,301.81
27	47136	TRIKAFTA 100-50-75 MG/150 MG	15	11	$735,056.58
28	49749	WEGOVY 0.5 MG/0.5 ML PEN	511	461	$700,105.69
29	40092	GENVOYA TABLET	104	73	$698,281.15
30	38702	INVEGA TRINZA 819 MG/2.63 ML	64	59	$682,899.13
31	37682	ABILIFY MAINTENA ER 400 MG SYR	126	91	$666,747.79
32	37169	TRULICITY 0.75 MG/0.5 ML PEN	382	323	$629,729.47
33	97005	HUMIRA PEN 40 MG/0.8 ML	39	36	$626,745.55
34	22913	ALBUTEROL HFA 90 MCG INHALER	13338	10992	$623,775.56

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
35	44014	HUMIRA(CF) PEN 80 MG/0.8 ML	15	13	$623,594.47
36	37789	COSENTYX SNRDY 300MG DOSE-2PEN	40	30	$560,967.59
37	44106	HEMLIBRA 105 MG/0.7 ML VIAL	7	5	$549,918.93
38	49752	WEGOVY 1 MG/0.5 ML PEN	377	343	$545,789.05
39	49487	APRETUDE ER 600 MG/3 ML VIAL	109	91	$527,496.51
40	37171	TRULICITY 1.5 MG/0.5 ML PEN	316	262	$523,844.06
41	43699	MAVYRET 100-40 MG TABLET	31	30	$520,723.20
42	51742	PAXLOVID 300-100 MG DOSE PACK	385	380	$514,825.50
43	47426	VYONDYS-53 100 MG/2 ML VIAL	2	2	$512,092.40
44	30819	XARELTO 20 MG TABLET	440	373	$489,089.46
45	54456	FERRIPROX 1,000 MG TAB(2X/DAY)	8	8	$486,127.00
46	49753	WEGOVY 1.7 MG/0.75 ML PEN	279	226	$485,132.75
47	43222	DUPIXENT 300 MG/2 ML SYRINGE	62	51	$457,238.67
48	43148	ILARIS 150 MG/ML VIAL	8	7	$450,352.68
49	37788	COSENTYX 300 MG DOSE-2 SYRINGE	21	16	$440,770.83
50	37633	ODEFSEY TABLET	77	54	$439,359.38
TOTAL			**37,622**	**32,013**	**$53,049,668.03**

636 IHSS Top 50 Prior Authorization Requests by Volume for 2nd Quarter 2024

- Top 50 PA requests = 175. There were 256 total PA requests for quarter 2.
  - 73 requests (42%) were approved. This approval rate is higher, by 7%, than what was observed last quarter.
  - 102 requests (58%) were denied or partially approved.
- Wegovy is up at numbers 1 and 6 with 36 total requests and 5 approvals (13%).
  - 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.
- Jardiance is at numbers 2 & 8 with 19 total requests and 12 approvals (63%).
  - 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.
- Ozempic and Vemlidy are at numbers 3 and 4 with 10 requests for each drug. There were 6 approvals (60%) for Ozempic and 7 approvals (70%) for Vemlidy.
  - Ozempic requires a trial and failure of metformin.
  - Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets.
- Zepbound is at numbers 5 and 19 with 12 total requests and 4 approvals (33%).
  - Zepbound 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.

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
1	Wegovy Subcutaneous Solution Auto-injector 0.25 MG/0.5ML	30	4	13.33%	24	80.0%	2	6.67%
2	Jardiance Oral Tablet 10 MG	14	9	64.29%	3	21.43%	2	14.29%
3	Ozempic (0.25 or 0.5 MG/DOSE) Subcutaneous Solution Pen-injector 2 MG/3ML	10	6	60.0%	4	40.0%	0	0.0%

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
4	Vemlidy Oral Tablet 25 MG	10	7	70.0%	3	30.0%	0	0.0%
5	Zepbound Subcutaneous Solution Auto-injector 2.5 MG/0.5ML	9	2	22.22%	6	66.67%	1	11.11%
6	Wegovy Subcutaneous Solution Auto-injector 0.5 MG/0.5ML	6	1	16.67%	4	66.67%	1	16.67%
7	Entecavir Oral Tablet 0.5 MG	5	3	60.0%	1	20.0%	1	20.0%
8	Jardiance Oral Tablet 25 MG	5	3	60.0%	2	40.0%	0	0.0%
9	Lidocaine External Patch 5 %	5	0	0.0%	5	100.0%	0	0.0%
10	Ezetimibe Oral Tablet 10 MG	4	3	75.0%	1	25.0%	0	0.0%
11	Cequa Ophthalmic Solution 0.09 %	3	0	0.0%	3	100.0%	0	0.0%
12	Contrave Oral Tablet Extended Release 12 Hour 8-90 MG	3	1	33.33%	2	66.67%	0	0.0%
13	Emgality Subcutaneous Solution Auto-injector 120 MG/ML	3	1	33.33%	1	33.33%	1	33.33%
14	Phentermine HCl Oral Tablet 37.5 MG	3	3	100.0%	0	0.0%	0	0.0%
15	Rybelsus Oral Tablet 3 MG	3	0	0.0%	3	100.0%	0	0.0%
16	Tacrolimus External Ointment 0.1 %	3	2	66.67%	0	0.0%	1	33.33%
17	Xifaxan Oral Tablet 550 MG	3	3	100.0%	0	0.0%	0	0.0%
18	Xiidra Ophthalmic Solution 5 %	3	1	33.33%	2	66.67%	0	0.0%
19	Zepbound Subcutaneous Solution Auto-injector 5 MG/0.5ML	3	2	66.67%	1	33.33%	0	0.0%
20	ZTlido External Patch 1.8 %	3	1	33.33%	2	66.67%	0	0.0%
21	Bicillin L-A Intramuscular Suspension Prefilled Syringe 2400000 UNIT/4ML	2	1	50.0%	0	0.0%	1	50.0%
22	cefTRIAXone Sodium Injection Solution Reconstituted 2 GM	2	1	50.0%	0	0.0%	1	50.0%
23	Colchicine Oral Tablet 0.6 MG	2	2	100.0%	0	0.0%	0	0.0%
24	Cosentyx UnoReady Subcutaneous Solution Auto-injector 300 MG/2ML	2	1	50.0%	0	0.0%	1	50.0%
25	Dupixent Subcutaneous Solution Prefilled Syringe 300 MG/2ML	2	0	0.0%	1	50.0%	1	50.0%
26	Hyalgan Intra-articular Solution Prefilled Syringe 20 MG/2ML	2	1	50.0%	0	0.0%	1	50.0%
27	Lubiprostone Oral Capsule 24 MCG	2	1	50.0%	1	50.0%	0	0.0%
28	Methadone HCl Oral Tablet 10 MG	2	2	100.0%	0	0.0%	0	0.0%
29	Myrbetriq Oral Tablet Extended Release 24 Hour 50 MG	2	1	50.0%	0	0.0%	1	50.0%
30	Pirfenidone Oral Capsule 267 MG	2	1	50.0%	1	50.0%	0	0.0%

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
31	Qsymia Oral Capsule Extended Release 24 Hour 3.75-23 MG	2	0	0.0%	2	100.0%	0	0.0%
32	Qulipta Oral Tablet 60 MG	2	0	0.0%	2	100.0%	0	0.0%
33	Repatha SureClick Subcutaneous Solution Auto-injector 140 MG/ML	2	1	50.0%	1	50.0%	0	0.0%
34	Trelegy Ellipta Inhalation Aerosol Powder Breath Activated 100-62.5-25 MCG/ACT	2	0	0.0%	2	100.0%	0	0.0%
35	Tretinoin External Cream 0.025 %	2	1	50.0%	1	50.0%	0	0.0%
36	Tretinoin External Cream 0.05 %	2	1	50.0%	1	50.0%	0	0.0%
37	Xphozah Oral Tablet 20 MG	2	1	50.0%	1	50.0%	0	0.0%
38	Ajovy Subcutaneous Solution Auto-injector 225 MG/1.5ML	1	0	0.0%	1	100.0%	0	0.0%
39	Ajovy Subcutaneous Solution Prefilled Syringe 225 MG/1.5ML	1	1	100.0%	0	0.0%	0	0.0%
40	ALPRAZolam Oral Tablet 1 MG	1	0	0.0%	1	100.0%	0	0.0%
41	Amitiza Oral Capsule 24 MCG	1	0	0.0%	1	100.0%	0	0.0%
42	Anucort-HC Rectal Suppository 25 MG	1	1	100.0%	0	0.0%	0	0.0%
43	Aspirin EC Low Dose Oral Tablet Delayed Release 81 MG	1	0	0.0%	1	100.0%	0	0.0%
44	Aspirin Low Dose Oral Tablet Delayed Release 81 MG	1	0	0.0%	1	100.0%	0	0.0%
45	Atorvastatin Calcium Oral Tablet 20 MG	1	1	100.0%	0	0.0%	0	0.0%
46	Breztri Aerosphere Inhalation Aerosol 160-9-4.8 MCG/ACT	1	0	0.0%	1	100.0%	0	0.0%
47	Brilinta Oral Tablet 90 MG	1	0	0.0%	1	100.0%	0	0.0%
48	Bumetanide Oral Tablet 1 MG	1	1	100.0%	0	0.0%	0	0.0%
49	Buprenorphine HCl-Naloxone HCl Sublingual Film 8-2 MG	1	1	100.0%	0	0.0%	0	0.0%
50	Butrans Transdermal Patch Weekly 10 MCG/HR	1	1	100.0%	0	0.0%	0	0.0%
TOTAL		**175**	**73**	**42%**	**87**	**50%**	**15**	**9%**

Medi-Cal Top 50 Claims by Volume for 2nd Quarter 2024

- The top 50 drugs accounted for **214,548 claims** for **192,167 members** and cost **$4,709,064.19.** This is an increase of 6,017 claims from last quarter.
- Albuterol remains at the number 1 spot with 13,338 claims for 10,992 members. Note: there was a decrease of 892 claims from last quarter.
- Fluticasone has risen from the number 4 to the number 2 spot with 10,933 claims for 10,232 members. There was an increase of 2,297 claims from last quarter.
- Ibuprofen has fallen to the number 3 spot with 9,391 claims for 8,464 members. This is a decrease of 115 claims from last quarter.
- Aspirin has fallen from the number 3 to the number 4 spot with 9189 claims for 8,436 members. This is a decrease of only 45 claims from last quarter.
- Loratadine remains at the number 5 with 8,189 claims for 7,374 members.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	22913	ALBUTEROL HFA 90 MCG INHALER	13338	10992	$623,775.56
2	62263	FLUTICASONE PROP 50 MCG SPRAY	10933	10232	$232,402.29
3	35742	IBUPROFEN 600 MG TABLET	9391	8464	$134,057.01
4	00161	ASPIRIN EC 81 MG TABLET	9189	8436	$101,849.05
5	60563	LORATADINE 10 MG TABLET	8189	7374	$129,172.45
6	49291	CETIRIZINE HCL 10 MG TABLET	8069	7460	$130,973.12
7	45680	DICLOFENAC SODIUM 1% GEL	7038	6127	$219,443.78
8	16965	ACETAMINOPHEN 500 MG CAPLET	6998	6307	$94,234.32
9	43722	ATORVASTATIN 40 MG TABLET	5600	5123	$91,395.74
10	02683	AMLODIPINE BESYLATE 5 MG TAB	5470	4925	$76,403.00
11	02682	AMLODIPINE BESYLATE 10 MG TAB	5094	4603	$72,963.23
12	10857	METFORMIN HCL 1,000 MG TABLET	4848	4465	$78,420.98
13	25200	FREESTYLE LITE TEST STRIP	4667	4372	$867,768.84
14	10810	METFORMIN HCL 500 MG TABLET	4365	3855	$67,972.92

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
15	43721	ATORVASTATIN 20 MG TABLET	4364	4057	$66,714.88
16	86212	POLYETHYLENE GLYCOL 3350 POWD	4309	3975	$109,563.46
17	04348	OMEPRAZOLE DR 20 MG CAPSULE	4238	3652	$66,157.40
18	46430	FAMOTIDINE 20 MG TABLET	4238	3720	$63,171.94
19	00781	GABAPENTIN 300 MG CAPSULE	4217	3431	$75,640.82
20	94444	MONTELUKAST SOD 10 MG TABLET	4060	3744	$63,732.60
21	94422	VITAMIN D2 1.25MG(50,000 UNIT)	3876	3607	$59,198.73
22	20045	ONDANSETRON ODT 4 MG TABLET	3688	3366	$54,630.62
23	00223	VITAMIN D3 25 MCG TABLET	3661	3439	$45,761.12
24	43720	ATORVASTATIN 10 MG TABLET	3586	3328	$55,042.39
25	99882	VITAMIN D3 50 MCG SOFTGEL	3570	3416	$44,825.70
26	40120	PANTOPRAZOLE SOD DR 40 MG TAB	3513	2998	$56,147.16
27	09101	DOCUSATE SODIUM 100 MG SOFTGEL	3438	3055	$46,722.55
28	16965	ACETAMINOPHEN 500 MG TABLET	3329	3008	$34,103.61
29	39661	AMOXICILLIN 500 MG CAPSULE	3203	3020	$44,192.68
30	97503	FERROUS GLUCONATE 324 MG TAB	3030	2752	$43,127.61
31	35793	NAPROXEN 500 MG TABLET	2959	2594	$47,547.40
32	94781	FOLIC ACID 1 MG TABLET	2902	2470	$47,967.18
33	14851	LOSARTAN POTASSIUM 50 MG TAB	2849	2600	$43,645.13
34	48191	TAMSULOSIN HCL 0.4 MG CAPSULE	2740	2377	$46,979.78

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
35	94200	FREESTYLE 28G LANCETS	2714	2607	$51,211.11
36	39802	CEPHALEXIN 500 MG CAPSULE	2645	2513	$39,276.99
37	29840	BENZONATATE 100 MG CAPSULE	2635	2435	$37,382.96
38	35744	IBUPROFEN 800 MG TABLET	2623	2278	$41,719.36
39	16391	TRAZODONE 50 MG TABLET	2560	2000	$41,745.48
40	70330	HYDROCODONE-ACETAMIN 10-325 MG	2488	1063	$48,902.78
41	13943	HYDROXYZINE HCL 25 MG TABLET	2486	2008	$40,028.51
42	16964	ACETAMINOPHEN 325 MG TABLET	2482	2333	$26,248.32
43	14850	LOSARTAN POTASSIUM 25 MG TAB	2470	2229	$33,712.58
44	31242	TRIAMCINOLONE 0.1% OINTMENT	2459	2290	$48,770.30
45	34824	HYDROCHLOROTHIAZIDE 25 MG TAB	2438	2187	$34,718.84
46	35741	IBUPROFEN 400 MG TABLET	2358	2266	$32,796.26
47	35930	CHILDREN IBUPROFEN 100 MG/5 ML	2350	2209	$45,844.37
48	29189	SYSTANE BALANCE 0.6% EYE DROP	2320	2212	$78,292.14
49	14853	LOSARTAN POTASSIUM 100 MG TAB	2300	2100	$36,851.92
50	30370	CLOTRIMAZOLE 1% TOPICAL CREAM	2261	2093	$35,857.22
TOTAL			**214,548**	**192,167**	**$4,709,064.19**

Chelators

Executive Summary

CLASS OVERVIEW

Chelating agents are medications that form chelates within the body to help remove excess metals including copper (Cu), iron (Fe), and lead (Pb). A chelate is a chemical compound formed between a metal ion and the chelating agent. Chelators can form several bonds to a single metal ion. The resulting chelates can be excreted from the body, making these medications useful in treating Wilson disease, iron overload, and lead poisoning. Wilson disease is a rare genetic disorder that prevents the liver from properly eliminating copper resulting in its accumulation in the liver, brain and eyes. Although liver transplantation is the only curative measure for this disease, chelating medications such as trientine (Syprine®, Cuvrior™), penicillamine (Depen®, Cuprimine®), and Galzin® (zinc acetate) are mainstays of therapy to reduce copper levels and improve patient quality of life. Deferasirox (Exjade®, Jadenu®), Ferriprox™ (deferiprone), and deferoxamine (Desferal®) all have FDA indications for the treatment of iron overload. Iron overload is caused by increased iron intake (e.g., from blood transfusions) or increased iron absorption (e.g., hereditary hemochromatosis [HH], ineffective erythropoiesis that occurs in certain inherited anemias, and liver disease). Excessive iron stores must be treated to prevent end organ damage. Important in the treatment of severe, symptomatic lead toxicity are Chemet® (succimer) and Calcium Disodium Versenate (edetate calcium disodium). Asymptomatic cases of lead toxicity are treated with remediation and removal of the source of lead exposure. The scope of this class review will only be on chelating agents for the treatment of Wilson disease, thalassemia, HH, and lead poisoning.

UTILIZATION FINDINGS

There were no claims and one prior authorization request with 0 approvals.

RECOMMENDATIONS

- No changes

CLINICAL SUMMARY

Chelating agents are medications that form chelates within the body to help remove excess metals including copper (Cu), iron (Fe), and lead (Pb). A chelate is a chemical compound formed between a metal ion and the chelating agent. Chelators can form several bonds to a single metal ion. The resulting chelates can be excreted from the body, making these medications useful in treating Wilson disease, iron overload, and lead poisoning.

Wilson disease is an inherited autosomal recessive disorder occurring in 1 in 30,000 live births and leads to impaired function of the intracellular copper transporter, ATP7B. Copper build-up occurs primarily in the liver, brain, and cornea and over time, the liver becomes cirrhotic. Neurologic manifestations may also occur including dysarthria, gait abnormalities, dystonia, drooling, and tremor. Some patients may also experience psychiatric manifestations including depression, personality changes, impulsiveness, and in severe cases, psychosis. Although liver transplantation is the only curative measure for this disease, chelating medications such as trientine (Syprine®), penicillamine (Depen®, Cuprimine®), and Galzin® (zinc acetate) are mainstays of therapy to reduce copper levels and improve patient quality of life. Penicillamine or trientine should be used as initial treatment for acute, symptomatic patients with Wilson disease. Presymptomatic patients should be treated with zinc acetate, penicillamine, or trientine. Cuvrior™ (trientine tetrahydrochloride), an alternative salt version comparable to the existing hydrochloride salt version, was approved in April 2022 for the treatment of adult patients with stable Wilson's disease who are de-coppered and tolerant to penicillamine. It was marketed in the first half of 2023.

Iron overload is caused by increased iron intake (e.g., from blood transfusions) or increased iron absorption (e.g., HH, ineffective erythropoiesis that occurs in certain inherited anemias, and liver disease). Excessive iron stores must be treated to prevent end organ damage. Chelation therapy is recommended in iron-overloaded, transfusion-dependent patients (e.g., beta thalassemia major [TM], severe beta thalassemia intermedia, sickle cell anemia, myelodysplasia, aplastic anemia, Diamond-Blackfan anemia) and patients with hemochromatosis and unstable hemodynamic status because phlebotomy cannot be used in these patient populations. In patients with hemochromatosis eligible for phlebotomy, this is preferred due to high efficacy, avoidance of side effects, and paucity of clinical data for chelators in this setting. Chelation therapy is also recommended in non-transfusion dependent thalassemia (NTDT) as well as other iron-overloaded conditions. Deferasirox (Exjade®, Jadenu®), Ferriprox™ (deferiprone), and deferoxamine (Desferal®) all have FDA indications for the treatment of iron overload. Deferoxamine must be given by continuous infusion, either subcutaneously (SQ) or intravenously (IV), while deferiprone and deferasirox are orally active. Each has its own benefits, toxicities, and requirements for monitoring of side effects.

Acute lead poisoning can occur due to occupational or environmental exposure. Chemet® (succimer) is labeled for use in pediatric patients with lead poisoning and retains an off-label use for adults. Dimercaprol and calcium disodium versenate are indicated to treat lead poisoning in pediatric patients as well as adults. Lead chelation therapy is only ever used for symptomatic patients or those with severely high blood lead levels. Rather, asymptomatic lead-exposed patients with low to moderate blood lead levels are treated by removing the source of lead exposure.

There are currently no drugs in phase III or later development for the treatment of Wilson disease. iron overload, or lead poisoning. No existing agents are under investigation for a label expansion and no new agents are up for approval within the upcoming year.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Copper Chelators		
Trientine hydrochloride (Syprine®) 250 mg oral capsule	Wilson disease in patients who are intolerant of penicillamine	• Adult: 750 mg to 1250 mg/day orally given in divided doses 2 to 4 times daily (max: 2g/day) • Pediatric: 20 mg/kg/day orally in 2 to 3 divided doses (max: 1500 mg/day)
Cuvrior™ (trientine tetrahydrochloride) 300 mg oral tablet	Wilson disease in patients who are de-coppered and tolerant to penicillamine	300 to 3000 mg/day orally in 2 equally divided doses based on penicillamine total daily dose
Penicillamine (Cuprimine®) 250 mg oral capsule Penicillamine (Depen® Titratabs) 250 mg oral tablet	Cystinuria	• Adult: 1 to 4 g/day orally in 4 divided doses • Pediatric: 20 to 40 mg/kg/day orally in 4 divided doses (max: 40 mg/kg/day)
	Wilson disease	• Adult: 750 mg to 1500 mg/day orally in divided doses (max: 2g/day) • Pediatric: 20 mg/kg/day orally in 2 to 3 divided doses (max: 1500 mg/day)
Galzin® (zinc acetate) 25 mg, 50 mg oral capsule	Wilson disease, maintenance treatment following chelation therapy	• Adult: 50 mg orally 3 times daily • Pediatric (≥ 10 years): 25 mg to 50 mg orally 3 times daily
Iron Chelators		
Deferoxamine (Desferal®) 500 mg, 2 g solution for injection	Acute iron toxicity	1g, either IM or IV, may be followed by 500 mg every 4 hours for 2 doses (max: 6 g/day)
	Chronic iron overload	• IM: 500 mg to 1 g/day (max: 1 g/day) • IV: 40 to 50 mg/kg/day (max: 60 mg/kg/day) over 8 to 12 hours for 5 to 7 days per week • SQ: 1 g to 2 g/day or 20 to 40 mg/kg/day (max: 60 mg/kg/day) over 8 to 12 hours for 5 to 7 days per week
Deferasirox (Exjade®) 125 mg, 250 mg, 500 mg oral dispersible tablet	• Chronic iron overload due to transfusions • Chronic iron overload in non-transfusion-dependent thalassemia syndromes	• Chronic iron overload due to transfusions: 20 to 40 mg/kg orally once daily • Chronic iron overload in non-transfusion-dependent thalassemia syndromes: 10 to 20 mg/kg orally once daily
Deferasirox (Jadenu®) 90 mg oral tablet Deferasirox (Jadenu® Sprinkle) 90 mg oral granules in packet		• Chronic iron overload due to transfusions: 14 to 28 mg/kg once daily • Chronic iron overload in non-transfusion-dependent thalassemia syndromes: 7 to 14 mg/kg orally once daily
Deferiprone (Ferriprox™) 500, 1,000 mg tablet Ferriprox™ (deferiprone) 100 mg/mL oral solution	Transfusional iron overload	75 mg/kg/day orally in 2 divided doses (using 1000 mg twice-a-day tablet formulation only) or 3 divided doses (using oral solution, 500 mg tablet, or 1,000 mg 3-times-a-day tablet formulation) (max: 99 mg/kg/day)
Lead (and Other) Chelators		
Chemet® (succimer) 100 mg oral capsule	Arsenic poisoning (off-label) Lead poisoning (off-label) Mercury poisoning (off-label)	10 mg/kg orally 3 times daily for 5 days followed by 10 mg/kg orally twice daily for 14 days

Medication	Indications	Dosing/Administration
Calcium Disodium Versenate 200 mg/mL injection solution	Lead poisoning (acute and chronic), lead encephalopathy, lead nephropathy	• Symptomatic patients, patients with lead encephalopathy, or patients whose blood lead level (BLL) is > 100 mcg/dL: ○ 1500 mg/m^2/day or 50 to 75 mg/kg/day IM or IV for 5 days in conjunction with dimercaprol • Lead nephropathy: ○ SCr 2 to 3 mg/dL: 500 mg/m^2 IM or IV every 24 hours for 5 days ○ SCr 3 to 4 mg/dL: 500 mg/m^2 IM or IV every 48 hours for 3 doses ○ SCr >4 mg/dL: 500 mg/m^2 IM or IV once weekly

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Copper Chelators		
Trientine (Syprine®, Cuvrior™)	None	Hypersensitivity
Penicillamine (Cuprimine®, Depen® Titratabs)	• **Experienced physician**: Should be administered under close supervision of a physician familiar with dosage and toxicity considerations • **Toxicity symptoms**: Warn patients to promptly report any symptoms suggesting toxicity (fever, sore throat, chills, bruising, bleeding)	• Renal insufficiency (in rheumatoid arthritis [RA] patients) • Breast-feeding • Pregnancy (in RA patients) • Previous penicillamine-related aplastic anemia or agranulocytosis
Galzin® (zinc acetate)	None	Hypersensitivity
Iron Chelators		
Deferoxamine (Desferal®)	None	• Hypersensitivity • Severe renal disease • Anuria
Deferasirox (Exjade®, Jadenu®)	• **Gastrointestinal (GI) hemorrhage**: GI hemorrhages, which may be fatal, can occur and more likely in elderly patients with advanced hematologic malignancies or low platelet counts • **Hepatic failure**: Hepatic injury and failure may occur. Avoid use in patients with severe hepatic impairment and reduce dose with moderate hepatic impairment • **Renal failure**: Acute renal failure and death can occur, particularly in patients with comorbidities and those who are in the advanced stages of their hematologic disorders. Consider dose reductions or interruptions in therapy if increases occur or in patients with preexisting renal disease	• CrCl <40 mL/min • Poor performance status • High-risk myelodysplastic syndromes • Advanced malignancies • Platelet counts less than 50,000/mm^3 • Hypersensitivity
Deferiprone (Ferriprox™)	**Agranulocytosis/Neutropenia**: Can cause agranulocytosis that can lead to serious infections and death. Monitor absolute neutrophil count (ANC) prior to treatment and weekly during therapy. Interrupt treatment if neutropenia or infection develops	Hypersensitivity
Lead (and Other) Chelators		
Chemet® (succimer)	None	Hypersensitivity
Calcium Disodium Versenate	**Fatal Toxicity/Cerebral edema**: Capable of producing toxic effects that can be fatal. Patients with lead encephalopathy and cerebral edema may experience a lethal increase in intracranial pressure following IV infusion; the IM route is preferred for these patients	• Anuria • Active renal disease • Hepatitis

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Copper Chelators	
Trientine (Syprine®, Cuvrior™)	• **Concerns related to adverse effects:** Anemia, copper deficiency, neurologic worsening, hypersensitivity
Penicillamine (Cuprimine®, Depen®, Titratabs)	• **Concerns related to adverse effects:** Allergic reactions, anti-glomerular basement membrane (GBM) disease (Goodpasture syndrome) bronchiolitis obliterans, dermatologic concerns, drug fever, taste alteration, agranulocytosis, aplastic anemia, thrombocytopenia, hepatotoxicity, lupus-like syndrome, proteinuria, pemphigus, hematuria, myasthenic syndrome, penicillin cross-sensitivity, toxicity symptoms • **Disease-related concerns:** Cystinuria, lead poisoning, Wilson disease • **Concurrent drug therapy issues:** Hematopoietic-depressant drugs • **Special populations:** Elderly patients may be more susceptible to skin rash and/or taste alterations • **Other:** Should be administered under the close supervision of a physician familiar with the toxicity and dosage considerations
Galzin® (zinc acetate)	• **Concerns related to adverse effects:** Neurological deterioration, gastric irritation/upset • **Other**: Not recommended in symptomatic patients
Iron Chelators	
Deferoxamine (Desferal®)	• **Concerns related to adverse effects:** Acute respiratory distress syndrome (ARDS), auditory effects, growth retardation, infection, infusion reactions, mucormycosis, ocular effects, renal effects, urine discoloration • **Disease-related concerns:** Aluminum toxicity, hemochromatosis, myasthenia gravis • **Concurrent drug therapy issues:** Combination treatment with ascorbic acid (>500 mg/day in adults) may impair cardiac function
Deferasirox (Exjade®, Jadenu®)	• **Concerns related to adverse effects:** Auditory disturbances, bone marrow suppression, dermatologic toxicity, GI reactions, hepatic failure, hypersensitivity, ocular disturbances, renal failure • **Special population:** Elderly patients have higher risk of toxicity and fatal events; associated with serious and fatal adverse events in pediatric population, usually associated with volume depletion or continued doses of 20 to 40 mg/kg/day (Exjade®) or 14 to 28 mg/kg/day (Jadenu®) • **Dosage form specific issues**: Some formulations may contain lactose • **Other:** Overchelation of iron may increase development of renal toxicity with doses >25 mg/kg/day (Exjade®) or >17.5 mg/kg/day (Jadenu®) while serum ferritin values <1,000 mcg/L; may cause variable decreases in the serum concentration of zinc and copper
Deferiprone (Ferriprox™)	• **Concerns related to adverse effects:** Agranulocytosis/neutropenia, hepatotoxicity, hypersensitivity, zinc deficiency • **Dosage form specific issues:** Available in 2 different 1000 mg oral tablet formulations (twice-a-day and 3-times-a-day formulation)
Lead (and Other) Chelators	
Chemet® (succimer)	• **Concerns related to adverse effects:** Mild to moderate neutropenia, hepatic effects, hypersensitivity reactions • **Disease-related concerns:** Encephalopathy, lead poisoning, renal impairment • **Other**: Adequate hydration should be maintained during therapy
Calcium Disodium Versenate	• **Concerns related to adverse effects**: Arrhythmia, ECG changes during IV therapy, nephrotoxicity • **Disease related concerns**: Investigate, identify, and remove sources of lead exposure; consultation with a clinical toxicologist or an expert in the treatment of heavy metal poisoning is highly recommended before use; caution in renal impairment • **Other**: Name confusion with edetate disodium (not commercially available in the U.S.) which should never be used to treat lead poisoning

PRACTICE GUIDELINES

Wilson Disease

Schilsky ML, Roberts EA, Bronstein JM, et al. A Multidisciplinary Approach to the Diagnosis and Management of Wilson Disease: 2022 Practice Guidance on Wilson Disease from the American Association for the Study of Liver Diseases (AASLD). Hepatology. Published online December 7, 2022.

- All patients with a newly established diagnosis of Wilson disease should be initiated on lifelong medical therapy for Wilson disease. Timing of treatment in children who are less than 3 years-old should be individualized to the degree of organ damage.
- Initial treatment for symptomatic patients with Wilson disease should include a chelating agent (D-penicillamine or trientine). Trientine may be better tolerated.
- Treatment of asymptomatic patients with Wilson disease can be a chelating agent (D-penicillamine or trientine at a lower dose than for initial therapy) or zinc.
- The suitability for transition to maintenance therapy for Wilson disease includes time on therapy (generally more than 1 year) and favorable clinical and biochemical response to therapy. Maintenance therapy may be a lower dose of chelating agent (D-penicillamine or trientine) or full-dose zinc.

Socha P, Janczyk W, Dhawan A, et al. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Feb;66(2):334-344. doi: 10.1097/MPG.0000000000001787.

- Given its safety profile, zinc salts, preferably zinc acetate, could be used in presymptomatic children identified through family screening, or as maintenance therapy after de-coppering with chelators as long as serum transaminase levels remain normal. Grade 2C
- Children with signs of significant liver disease, such as cirrhosis or abnormal INR, should be preferably treated with copper chelating agents. Grade 2B
- Children with decompensated liver cirrhosis should be treated with a chelating agent or a combination of zinc salts and a chelating agent that may preclude the need for a liver transplantation. The King's Wilson index should be monitored for prognostic assessment and timely decision for LT. Grade 2B
- Because liver transplantation corrects the enzymatic defect, chelating agents or zinc treatment is no longer required after transplantation. Grade 1A
- Evidence for non-adherence to zinc can be assessed by measuring serum zinc levels and/or urinary zinc/copper 24-hour excretion. Grade 2B
- If increased transaminases remain or relapse despite treatment, poor compliance should be suspected. Grade 2B
- The occurrence of penicillamine-related adverse events should prompt discontinuation and switching to trientine or zinc salts according to the severity of liver disease. Grade 2B

Recommendation Definitions

Strength of Recommendation	Description
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption

Quality of Evidence	Description
High (A)	Further research is unlikely to change confidence in the estimate of the effect
Moderate (B)	Further research is likely to have impact on confidence in the estimate of effect and may change the estimate
Low (C)	Any estimate of effect is very uncertain

Hereditary Hemochromatosis

Kowdley KV, Brown KE, Ahn J, Sundaram V. American College of Gastroenterology Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019 Aug;114(8):1202-1218.

- We recommend that phlebotomy be used as the first-line treatment in patients diagnosed with HH as determined by C282Y homozygosity or C282Y/H63D compound heterozygosity (Strong recommendation, moderate quality of evidence).
- We recommend against chelation as the first-line therapy for HH, given the effectiveness of phlebotomy, the associated side effects of chelation including hepatic and renal toxicity, and the relatively small sample size of clinical trials supporting chelation (Strong recommendation, low quality of evidence).
- We recommend the use of iron chelation for the treatment of HH in the patient who is intolerant or refractory to phlebotomy or when phlebotomy has the potential for harm such as in patients with severe anemia or congestive heart failure (Strong recommendation, low quality of evidence).
- We recommend against the routine use of proton pump inhibitors (PPIs) as the primary treatment of HH (Strong recommendation, low quality of evidence).

Recommendation Definitions

Strength of Recommendation	Description
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption.

Quality of Evidence	Description
High	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate	Further research may change confidence in the estimate of the clinical effect.
Low	Further research is very likely to affect the confidence on the estimate of clinical effect.
Very low	Any estimate of the effect is very certain.

Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Jul; 54(1): 328-43

- Patients with hemochromatosis and iron overload should undergo therapeutic phlebotomy weekly (as tolerated). (1A) Target levels of phlebotomy should be a ferritin level of 50-100 µg/L. (1B)
- In the absence of indicators suggestive of significant liver disease (ALT, AST elevation), C282Y homozygotes who have an elevated ferritin (but <1000 µg/L) should proceed to phlebotomy without a liver biopsy (1B)
- Patients with end-organ damage due to iron overload should undergo regular phlebotomy to the same endpoints as indicated above (1A)
- We recommend treatment by phlebotomy of patients with non-*HFE* iron overload who have an elevated hepatic iron concentration (HIC). (1B)
- Iron chelation with either deferoxamine mesylate or deferasirox is recommended in iron overloaded patients with dyserythropoietic syndromes or chronic hemolytic anemia. (1A)

Recommendation Definitions

Strength of Recommendation	Description
Strong (1)	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost.
Weak (2)	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, or higher cost or resource consumption.

Quality of Evidence	Description
High (A)	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate (B)	Further research may change confidence in the estimate of the clinical effect.
Low (C)	Further research is very likely to impact confidence on the estimate of clinical effect.

Thalassemia

Cappellini M, Cohen A, Porter J, Taher A, Vprakasit V, eds. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th edition. Thalassaemia International Federation; 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf

Iron Overload and Chelation

- Chelation therapy is an effective treatment modality in improving survival, decreasing the risk of heart failure and decreasing morbidities from transfusion-induced iron overload (A).
- Chelation therapy at the correct doses and frequency can balance iron excretion with iron accumulation from transfusion (A).
- Absolute change in total body iron in response to chelation can be calculated from change in LIC (B).
- Direction of change in body iron in response to transfusion and chelation can usually but not always be estimated from the trend in serum ferritin (B).
- Prevention of iron accumulation using chelation therapy is preferable to rescue treatment because iron-mediated damage is often irreversible, and removal of storage iron by chelation is slow - particularly after it has escaped the liver (B).
- Response to chelation is dependent on the dose applied and the duration of exposure (A).
- Response to chelation is affected by the rate of blood transfusion (B).
- Chelation can reverse iron-mediated cardiac dysfunction rapidly (within weeks) by rapid chelation of labile iron, if 24 h chelation cover is achieved (A).
- Chelation therapy removes myocardial storage iron slowly (months or years) (A).
- Over-chelation increases side effects from chelation therapy, and doses should therefore be decreased as serum ferritin or liver iron levels fall (demonstrated most clearly with DFO) (B).
- The optimal chelation regime must be tailored for the individual and will vary with their current clinical situation. (*not a graded recommendation*)
- Chelation therapy will not be effective if it is not taken regularly – a key aspect of chelation management is to work with patients to optimize adherence (B).

Cardiac Complications in Thalassemia Major

- Combined therapy with deferoxamine and deferiprone represent the best available intensive chelation for thalassaemia major patients with severe cardiac iron overload, with or without overt cardiac dysfunction or heart failure (B).

Liver Disease

- Deferoxamine, deferiprone and deferasirox are effective in decreasing total body iron burden as well as LIC (A).

Infections

- As a measure, temporary discontinuation of deferoxamine during a febrile illness until establishing whether the episode is caused by a pathogen that can use deferoxamine as siderophore or taken under control is strongly advised (B).
- Deferasirox or deferiprone can be continued during febrile episodes (C).

Endocrine Disease

- Short Stature and Retarded Growth
  - Prevention and Treatment of growth abnormalities in patients with TM should include:
    - Use of new iron-chelators with lower toxicity on the skeleton and with better patient compliance. (*not a graded recommendation*)
- Hypothyroidism
  - If subclinical hypothyroidism is detected, chelation should be intensified and the patient carefully monitored

- Impaired Glucose Tolerance (IGT) and Diabetes Mellitus (DM)
- Intensive chelation therapy is effective to normalize β-cell function and may improve insulin secretion and glucose tolerance and reduce liver iron deposition (*not a graded recommendation*).
- Summary
  - Endocrine complications, growth and pubertal delay are common manifestations of iron overloading in TM and carry significant morbidity. As such, patients with TM need regular monitoring for signs and symptoms of endocrine complications. Prevention remains the priority, and there are limited data to support a role for chelation therapy in this. Once endocrine complications have developed, management should focus on halting the progression of such complications and treating associated symptoms. (*not a graded recommendation*)
  - Normalization of total body iron load with very intensive combined chelation (deferoxamine plus deferiprone) reverses cardiac and endocrine complications of TM (B).

Osteoporosis

- Adequate iron chelation may prevent iron toxicity in the bone and sufficient blood transfusions may help prevent and treat early bone loss (*not a graded recommendation*).

Psychological Support

- Patient-reported health outcome shows that oral chelation therapy has a beneficial impact, relative to parenteral chelation (B).
- Benefits of psychological support have been suggested using a variety of approaches (C) which include:
  - targeting changes in institutional organization practices
  - patient group sessions
  - family therapy
  - patient chelation camps

Quality of Evidence	Description
A	Data derived from multiple randomized clinical trials or meta-analyses.
B	Data derived from a single randomized clinical trial or large non-randomized studies.
C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

Taher A, Musallam K, Domenica Cappellini M, eds. Guidelines for the Management of Non Transfusion Dependent Thalassemia (NTDT) [Internet]. 2nd edition. Nicosia (CY): Thalassaemia International Federation; 2018. Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf.

Iron Overload and Chelation Therapy

Phlebotomy is not an option in NTDT considering that the disease is already complicated with anemia. Some simple measures may be of benefit, like tea consumption, which decreases iron absorption and has antioxidant properties. However, iron chelation therapy is an inevitable option in iron overloaded patients with NTDT. As iron overload has been an 'overlook' condition in NTDT in the past, only few, mostly small, studies determined the efficacy and safety of iron chelation therapy in NTDT patients.

- Iron chelation therapy with deferasirox should be initiated in NTDT patients ≥ 10 years of age if:
  - Liver iron concentration ≥ 5 mg Fe/g dry weight
  - Serum ferritin level ≥ 800 ng/mL
  - Serum ferritin level > 300 to < 800 ng/mL (if liver iron concentration measurement is not possible) and other clinical or laboratory measures indicative of iron overload
- Deferasirox therapy should be discontinued when patients reach a liver iron concentration value of 3 mg Fe/g dry weight or serum ferritin level 300 ng/mL and patients should continue to be monitored for iron overload as indicated earlier
- The use of other iron chelators cannot be recommended until larger, randomized studies are available

Thrombotic Disease

- There is no sufficient evidence to recommend iron chelation or hydroxyurea therapy for the primary or secondary prevention of thrombotic or cerebrovascular disease, although when used for different indications a beneficial effect may be observed

Leg Ulcers

- There is no sufficient evidence to recommend blood transfusion, iron chelation or hydroxyurea therapy for the prevention of leg ulcers in NTDT patients, although when used for different indications a beneficial effect may be observed

Lead poisoning

WHO Guideline for Clinical Management of Exposure to Lead. World Health Organization; 2021. Available at: https://www.who.int/publications/i/item/9789240037045.

Chelation therapy in individuals exposed to lead

- Children ≤ 10 years of age
  - For a child (≤ 10 years) with a blood lead concentration ≥ 45 µg/dL, oral or parenteral chelation therapy is recommended (Strong recommendation, very low-certainty evidence).
  - For a child (≤ 10 years) with a blood lead concentration of 40 to 44 µg/dL, when there is doubt about the accuracy of the measurement, a persistently elevated blood lead concentration in spite of measures to stop exposure or significant clinical features of lead poisoning, oral chelation therapy should be considered (Conditional recommendation, very low-certainty evidence).
  - For a child (≤ 10 years) with lead encephalopathy, urgent hospital admission and parenteral chelation therapy are recommended (Strong recommendation, very low-certainty evidence).
- Non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentration 45 to 70 µg/dL
  - For a non-pregnant adolescent girl or woman of child-bearing age who has a blood lead concentration of 45 to 70 µg/dL but who does not show clinical features of lead poisoning, oral chelation therapy should be considered (Conditional recommendation, very low-certainty evidence).
  - For a male patient aged ≥ 11 years or a woman who is no longer of child-bearing age who has a blood lead concentration of 45 to 70 µg/dL but who does not show clinical features of lead poisoning, chelation therapy is not indicated. The patient should, however, be re-evaluated within 2–4 weeks to ensure that the blood lead concentration is decreasing and the patient remains well (Conditional recommendation, very low-certainty evidence).
  - For a non-pregnant adolescent or adult with a blood lead concentration of 45 to 70 µg/dL and who has mild–moderate clinical features of lead poisoning (such as abdominal pain, constipation, arthralgia, headache, lethargy), chelation therapy is suggested (Conditional recommendation, very low-certainty evidence).
- Non-pregnant adolescents (11–18 years) and adults (≥ 19 years) with blood lead concentrations of >70 to 100 µg/dL
  - For a non-pregnant adolescent or an adult with a blood lead concentration >70 to 100 µg/dL but who does not show significant neurological features of toxicity, chelation therapy is suggested (Conditional recommendation, very low-certainty evidence).
  - For a non-pregnant adolescent or adult with a blood lead concentration >70 to 100 µg/dL and with significant neurological features of lead toxicity (e.g., irritability, drowsiness, ataxia, convulsions, coma) or lead encephalopathy, urgent parenteral chelation therapy is recommended (Strong recommendation, very low-certainty evidence).
- Pregnant women
  - For a pregnant woman with lead encephalopathy, regardless of trimester, urgent chelation therapy is recommended. The preferred chelating agent depends on the stage of the pregnancy and available data on safety of use in pregnancy (Strong recommendation, very low-certainty evidence).
  - For a pregnant woman with a blood lead concentration ≥ 45 µg/dL, with or without clinical features of lead poisoning, but without lead encephalopathy:

- In the first trimester: the guideline development group could not make a recommendation because of an uncertain balance of risks and benefits (No recommendation).
- In the second or third trimester: chelation therapy is recommended (Strong recommendation, very low-certainty evidence).

Recommendation Definitions

Strength of Recommendation	Description
Strong	The group is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects.
Weak	The group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects but is not confident of this interpretation.

Certainty of Evidence	Description
High	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate	Further research may change confidence in the estimate of the clinical effect.
Low	Further research is very likely to affect the confidence on the estimate of clinical effect.
Very low	Any estimate of the effect is very certain.

Medical Management Guidelines for Lead. Agency for Toxic Substances and Disease Registry. Last reviewed October 2014. Available at: https://wwwn.cdc.gov/TSP/MMG/MMGDetails.aspx?mmgid=1203&toxid=22.

- Chelation therapy should be considered for treatment of severe symptoms or markedly elevated blood lead levels. Chelation therapy is controversial in cases of asymptomatic and mildly symptomatic intoxication and should never be given prophylactically or during ongoing lead exposure. Once initiated, chelation therapy should be continued until symptoms improve and acceptable blood lead levels are achieved (Dart et al. 2004).
- Adults: In the presence of severe encephalopathy or when blood lead levels exceed 100 µg/dL, chelation should start with dimercaprol (BAL) followed in 4 hours by another dose of BAL and either succimer (if oral administration is tolerated) or CaNa2-EDTA (if intravenous infusion is required). BAL treatment is phased out while treatment with one of the other chelating agents is continued (typically for 5 days), followed by decreased or interrupted dosing because continued chelator usage is associated with decreasing amounts of urinary lead excretion (Dart et al. 2004).
- Children: Use of chelators is not recommended for blood lead levels less than 25 µg/dL. At blood lead levels between 25 and 45 µg/dL, oral chelators may be of benefit if elevated blood levels persist following environmental intervention. Children with blood lead levels between 45 and 70 µg/dL should undergo chelation, usually with oral succimer; those with encephalopathy or with blood lead levels in excess of 70 µg/dL should be admitted to the hospital for parenteral therapy with BAL and EDTA. Therapy begins with BAL intramuscularly every 4 hours, establishment of adequate urinary output (hydration as needed), followed by CaNa2-EDTA continuous infusion. CaNa2-EDTA may be administered intramuscularly in divided doses every 4 hours. This combined therapy is continued for 5 days while liver and renal functions and blood lead levels are monitored. If blood lead levels rebound after 2 days without chelation therapy, a second course of therapy may be necessary (Dart et al. 2004).

Medical Management Guidelines for Lead-exposed Adults. Association of Occupational and Environmental Clinics. April 24, 2007.

- Chelation therapy is recommended for adults with BLLs 100 µg/dL (4.83 µmol/L) or greater, can be strongly considered for BLLs 80 to 99 µg/dL (3.86-4.78 µmol/L), and possibly considered for BLLs between 50 and 79 µg/dL (2.41-3.81 µmol/L) in the presence of lead-related symptoms.

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Schilsky ML, Czlonkowska A, Zuin M, et al. Trientine tetrahydrochloride versus penicillamine for maintenance therapy in Wilson disease (Chelate): a randomized, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2022;7(12):1092-1102.	Randomized, open-label, non-inferiority, phase 3 trial comparing penicillamine with trientine tetrahydrochloride for maintenance therapy in patients with Wilson disease. N=53 Arms: Patients were randomly assigned (1:1) to continue receiving oral penicillamine or switched to oral trientine tetrahydrochloride Inclusion criteria: Patients aged 18-75 years with stable Wilson disease who were treated for at least 1 year with penicillamine Exclusion criteria: None listed	**Primary:** Serum non-caeruloplasmin-bound copper (NCC) levels at 24 weeks **Secondary:** Urinary copper excretion at 24 weeks, side effects
Results: After 24 weeks, the mean difference in serum NCC between the penicillamine group and trientine tetrahydrochloride group was -9.1 µg/L (95% confidence interval [CI], -24.2 to 6.1), with the lower limit of the 95% CI within the defined non-inferiority margin. At 24 weeks, urinary copper excretion was lower with trientine tetrahydrochloride than with penicillamine (mean difference, 238 µg/24 h [99% CI, 116 to 360]). At 48 weeks, trientine tetrahydrochloride remained non-inferior to penicillamine in terms of NCC (mean difference NCC, -15.5 µg/L [95% CI, -34.5 to 3.6]). Urinary copper excretion at 48 weeks remained in the expected range for well treated patients in both study groups, and the mean difference (125 µg/24 h [99% CI, -37.6 to 287]) was not significantly different. The most common treatment-emergent adverse events were headache for penicillamine (19% vs. 8%) and abdominal pain for trientine tetrahydrochloride (4% vs. 15%); all treatment-emergent adverse events resolved and were mild to moderate. **Conclusion**: The efficacy of trientine tetrahydrochloride as oral maintenance therapy was non-inferior to penicillamine and well tolerated in adults with Wilson disease.		
Citation	**Design**	**Endpoints**
Bollig C, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev. 2017 Aug 15;8:CD007476.	Systematic review and meta-analysis of randomized controlled trials (RCTs) of trials through August 2016 of deferasirox versus no therapy, placebo or another iron-chelating treatment in patients with transfusion-dependent thalassemia or NTDT. N=16 studies; 1,807 participants	**Primary:** Overall mortality measured at any point in time **Secondary:** Reduced end-organ damage, measures of iron overload, measures of iron excretion **Safety:** Any adverse events (i.e., increased SCr, kidney failure, rash, GI disturbance)
Results: Deferasirox was effective at removing iron in patients with transfusion-dependent thalassaemia when compared to placebo. Nine studies compared deferasirox with standard treatment of deferoxamine – similar effectiveness for overall mortality, reduced end-organ damage, measures of iron overload, and measures of iron excretion was considered achievable depending on the doses of the two drugs being compared. Although rates of discontinuation were similar for both drugs, patients had a higher satisfaction rate with deferasirox over deferoxamine due to fewer adverse events. **Conclusion**: Although deferasirox does not seem to be superior to deferoxamine, similar efficacy is likely achievable. Deferasirox could be offered as a reasonable, first-line option to individuals with thalassaemia and secondary iron overload who show a strong preference to deferasirox.		
Citation	**Design**	**Endpoints**
Appenenzeller-Herzog C, Mathes T, Heeres MLS, Heinz Weiss K, Houwen RHJ, Ewald H.	Systematic review and meta-analysis of prospective and retrospective, randomized and non-randomized, controlled studies and comparative observational trials through	**Primary:** Mortality and asymptomatic/improved

Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies. Liver Int. 2019 Nov;39(11):2136-2152.	January 2019 of patients with Wilson disease (any age or stage) mostly comparing D-penicillamine to no treatment, zinc, trientine or succimer. N=23 studies; 2,055 participants	**Secondary:** Side effects, early neurological deterioration, treatment discontinuation and orthotopic liver transplantation (OLT).

Results:

D-penicillamine vs. no treatment

- Mortality – Odds ratio (OR), 0.013 (95% CI, 0.0010 to 0.17; I^2 = 31%)
- Remaining or becoming asymptomatic – OR, 22.3 (95% CI, 0.40 to 1.2 x 10^3; I^2 = 86%)
- Other outcomes were not reported for this comparison

D-penicillamine vs. zinc salts

- Mortality – OR, 0.73 (95% CI, 0.16 to 3.40; I^2 = 37%)
- Asymptomatic/improved – OR, 0.84 (95% CI, 0.48 to 1.48; I^2 = 0%)
- Side effects – OR, 3.28 (95% CI, 0.542 to 19.9; I^2 = 24%)
- Neurological deterioration – OR, 3.71 (95% CI, 0.42 to 32.7; I^2 = 10%)
- Treatment discontinuation – OR, 2.96 (95% CI, 1.14 to 7.66; I^2 = 48%)
- OLT – OR, 1.74 (95% CI, 0.066 to 46.0; I^2 = 37%)

Other comparisons

- Not enough studies comparing other drug combinations to perform meta-analysis.

Conclusion: There are some indications that zinc is safer than D-penicillamine therapy while being similarly effective in preventing or reducing hepatic or neurological Wilson Disease symptoms. Study quality was low warranting cautious interpretation of our findings.

Citation	Design	Endpoints
Cao Y, Chen A, Bottai M, Caldwell KL, Rogan WJ. The impact of succimer chelation on blood cadmium in children with background exposures: a randomized trial. J Pediatr. 2013 Aug; 163(2):598-600.	Randomized, double-blind, placebo-controlled trial utilizing cadmium, a toxic metal with known detrimental effects including renal toxicity, hypertension, and skeletal disorders, to investigate the use of the drug in lead poisoning. N=780 Arms: Children received up to three 26-day courses of succimer or placebo Inclusion criteria: Children between 12 and 33 months of age, who had a confirmed blood lead concentration between 20 and 44 µg/dL, and who lived in a residence suitable for lead dust reduction Exclusion criteria: None listed	**Primary:** Blood cadmium levels after 1-week of treatment

Results: There was almost no difference in blood cadmium levels when measured after one week. The 90th percentile group receiving succimer actually saw a slight increase in blood cadmium levels when measured after one week.

Between Group Difference of Blood Cadmium Level (µ/L) After Treatment

	Median		**75th Percentile**		**90th Percentile**	
	Difference (95% CI)	**P-value**	**Difference (95%CI)**	**P value**	**Difference (95%CI)**	**P value**

Adjusted	0.00 (-0.01 to 0.01)	0.98	0.00 (-0.01 to 0.01)	0.69	0.01 (-0.01 to 0.02)	0.42

Conclusion: Succimer has shown efficacy in animals diminishing GI absorption and cadmium tissue retention, however there is no evidence for therapeutic efficacy following chronic cadmium exposure. This trial specifically finds that succimer has no effect on background blood cadmium concentrations resulting from background exposure in U.S. children. Succimer may not reduce cadmium because succimer is mainly distributed in extracellular space while cadmium is mostly bound intracellularly to metallothionein. However it is approved for the treatment of pediatric lead poisoning as of 1991.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (04-01-2024 to 06-30-2024)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Copper Chelators								
trientine hydrochloride (Syprine®) 250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F-PA AL > 21 yrs	No change
Cuvrior™ (trientine tetrahydrochloride) 300 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
penicillamine (Cuprimine®) 250 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
penicillamine (Depen® Titratabs) 250 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Galzin® (zinc acetate) 25 mg, 50 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Iron Chelators								
deferoxamine (Desferal®) 500 mg, 2 g solution for injection	0	0	$0.00	$0.00	0	0 (0%)	F	No change
deferasirox (Exjade®) 125 mg, 250 mg, 500 mg dispersible tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA AL > 21 yrs	No change
deferasirox (Jadenu®) 90 mg tablet	0	0	$0.00	$0.00	1	0 (0%)	F-PA	No change
deferasirox (Jadenu® Sprinkle) 90 mg oral granules in packet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
deferiprone (Ferriprox™) 500, 1000 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Ferriprox™ (deferiprone) 100 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Lead (and Other) Chelators								
Chemet® (succimer) 100 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Calcium Disodium Versenate 200 mg/mL injection solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	0	0	$0.00	$0.00	1	0 (0%)		

PRIOR AUTHORIZATION CRITERIA

Recommendation: No changes

Iron-chelating Agents	
Therapeutic Classes (AHFS)	Heavy Metal Antagonists
Medications	Formulary, PA required Deferasirox (Jadenu) tablet -PREFERRED Deferasirox (Jadenu) granules Deferasirox (Exjade) tablet Non-Formulary Ferriprox (deferiprone) tablet Ferriprox (2 times a day) (deferiprone) 1,000 mg tablet Ferriprox (deferiprone) 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	Physician must be a hematologist.
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 CHRONIC IRON OVERLOAD DUE TO BLOOD TRANSFUSIONS FOR DEFERASIROX**
	• Patient must be ≥ 2 years old. (check AAH active CCS cases for members < 21 years of age)
	• Diagnosis of chronic iron overload due to blood transfusions
	• Patient receiving blood transfusions on a regular basis/participating in blood transfusion program
	• Serum ferritin concentration consistently greater than 1000mcg/L.
	  ○ If serum ferritin falls to <1,000 mcg/L at 2 consecutive visits, consider dose reduction (especially if dose is >17.5 mg/kg/day)
	  ○ (If the serum ferritin levels fall below 500 mcg/L on any one monitoring visit, deferasirox therapy discontinued).
	• Documented treatment failure, contraindication, or significant intolerance to deferoxamine (Desferal) treatment.
	• If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferoxamine (Desferal) AND deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Jadenu) tablet must be provided.
	• If the request is for deferasirox (Jadenu) granules, member must meet the criteria above and have tried and failed deferoxamine (Desferal) AND deferasirox (Exjade) tablet AND (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet must be provided
	REAUTHORIZATION CRITERIA FOR CHRONIC IRON OVERLOAD DUE TO BLOOD TRANSFUSIONS FOR DEFERASIROX
	• If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferoxamine (Desferal) AND deferasirox (Jadenu) tablet OR a medical

reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Jadenu) tablet must be provided.
- Serum ferritin concentration consistently greater than 1000 mcg/L.
  - If serum ferritin falls to <1,000 mcg/L at 2 consecutive visits, consider dose reduction (especially if dose is >17.5 mg/kg/day)
  - If the serum ferritin levels fall consistently below 500 mcg/L on any one monitoring visit, deferasirox therapy must be discontinued

INITIAL CRITERIA FOR CHRONIC IRON OVERLOAD IN NON-TRANSFUSION DEPENDENT THALASSEMIA SYNDROMES FOR DEFERASIROX

- Patient must be ≥ 10 years old (check AAH active CCS cases for members < 21 years of age)
- Diagnosis of thalassemia syndrome
- Liver iron content (LIC) by liver biopsy of ≥ 5 mg Fe/g dry weight
- Serum ferritin level on ≥ 2 measurements at least one month apart of >300 mcg/L
- If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Jadenu) tablet must be provided.
- If the request is for deferasirox (Jadenu) granules, member must meet the criteria above and have tried and failed deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet must be provided

REAUTHORIZATION CRITERIA FOR CHRONIC IRON OVERLOAD IN NON-TRANSFUSION DEPENDENT THALASSEMIA SYNDROMES FOR DEFERASIROX

- If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Jadenu) tablet must be provided.
- Serum ferritin consistently > 300 mcg/L.
- If serum ferritin < 300 mcg/L, LIC must be obtained. If LIC < 3 mg Fe/g, treatment should be discontinued.

INITIAL CRITERIA FOR TRANSFUSIONAL IRON OVERLOAD DUE TO THALASSEMIA SYNDROMES OR SICKLE CELL DISEASE AND OTHER ANEMIAS FOR FERRIPROX (DEFERIPRONE)

- Patient must be ≥ 3 years old for oral solution OR ≥ 8 years old for tablets (check AAH active CCS cases for members < 21 years of age)
- Diagnosis of thalassemia syndrome, or sickle cell disease, or other anemia
- Patient receiving blood transfusions on a regular basis/participating in blood transfusion program
- Serum ferritin concentration is consistently > 1000 mcg/L. If the serum ferritin levels fall consistently below 500 mcg/L, Ferriprox must be discontinued
- Documentation that the patient is unable to use deferoxamine (Desferal) parenterally
- Documented trial and failure of deferasirox (Exjade, Jadenu) or medical reason why deferasirox cannot be used
- Brand Ferriprox (2 times a day) 1000mg tablets and Ferriprox liquid will be approved with documentation of trial and failure, contraindication, or intolerance to generic deferiprone tablets

REAUTHORIZATION CRITERIA FOR TRANSFUSIONAL IRON OVERLOAD DUE TO THALASSEMIA SYNDROMES OR SICKLE CELL DISEASE AND OTHER ANEMIAS FOR FERRIPROX (DEFERIPRONE)

	• Patient continues to receive blood transfusions on a regular basis/ or participates in a blood transfusion program • Serum ferritin concentration is consistently > 1000 mcg/L. If the serum ferritin levels fall consistently below 500 mcg/L, Ferriprox must be discontinued • If the request is for brand Ferriprox (2 times a day) 1000mg tablets or Ferriprox liquid, documentation of trial and failure, contraindication, or intolerance to generic deferiprone tablets
Criteria Statement	For chronic iron overload due to blood transfusions deferasirox (Jadenu) tablet is reserved for members who have used (or cannot/should not use) deferoxamine. Deferasirox (Exjade) tablet is reserved for members who have used (or cannot/should not use) deferoxamine AND (Jadenu) tablet. Deferasirox (Jadenu) granules are reserved for members who have used (or cannot/should not use) deferoxamine AND deferasirox (Jadenu) tablet AND deferasirox (Exjade) tablet. For chronic iron overload in non-transfusion dependent thalassemia syndromes deferasirox (Exjade) tablet is reserved for members who have used (or cannot/should not use) deferasirox (Jadenu) tablet. Deferasirox (Jadenu) granules are reserved for members who have used (or cannot/should not use) deferasirox (Jadenu) tablet AND deferasirox (Exjade) tablet. For transfusional iron overload due to thalassemia syndromes or sickle cell disease and other anemias, deferiprone (Ferriprox) tablet is reserved for members who are receiving blood transfusions who have used (or cannot/should not use) deferoxamine (Desferal) and deferasirox (Exjade, Jadenu). Brand Ferriprox (2 times a day) 1000mg tablets and Ferriprox liquid are reserved for members who have used (or cannot/should not use) generic deferiprone tablets.
Last P&T Review Date	~~9/2023~~9/2024

Recommendation: No changes

Penicillamine (Depen, Cuprimine), Trientine HCl (Syprine) for Wilson's disease	
Therapeutic Classes (AHFS)	Heavy Metal Antagonists
Medications	Formulary, PA required Penicillamine (Depen Titratabs) tablet Trientine (Syprine) Penicillamine (Cuprimine) capsule Non-Formulary Cuvrior (trientine tetrahydrochloride)
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** **Reauthorization**	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. 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 initial approval: • Documented confirmed diagnosis of Wilson's disease • For penicillamine (Depen, Cuprimine), documented adequate trial (at least 3 months) and failure of, or intolerance to, due to significant side effects/toxicity, or a contraindication to therapy with trientine (Syprine) • For Cuvrior (trientine tetrahydrochloride), documented adequate trial (at least 3 months) and failure of, or intolerance to, due to significant side effects/toxicity, or a contraindication to therapy with BOTH trientine (Syprine) and penicillamine Criteria for re-authorization: • Documentation of positive clinical response.	
Criteria Statement	Penicillamine (Depen, Cuprimine) are reserved for members who have used (or cannot/should not use) trientine (Syprine). Cuvrior (trientine tetrahydrochloride) is reserved for members who have used (or cannot/should not use) both trientine (Syprine) and penicillamine.	
Last P&T Review Date	~~9/2023~~9/2024	

REFERENCES

1. Lexicomp Online, Lexi-Drugs, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on June 4, 2024.
2. Facts & Comparisons, Facts & Comparisons eAnswers, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on June 4, 2024.
3. Drugs@FDA: FDA-Approved Drugs. U.S. Food and Drug Administration. www.fda.gov. Accessed on June 4, 2024.
4. Biomedtracker. Informa. Available at: www.biomedtracker.com. Accessed on June 4, 2024.
5. Bacon BR, Kwiatkowski JL. Approach to the Patient with Iron Overload. Mentzer WC, Mahoney DH, Tirnauer JS, Kunins L, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on June 4, 2024.
6. Bacon BR. Iron chelators: Choice of agent, dosing, and adverse effects. Mentzer WC, Tirnauer JS, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on June 4, 2024.
7. Aaseth J, Skaug MA, Cao Y, Anderson O. Chelation in metal intoxication—Principles and paradigms. J Trace Elem Med Biol. 2015; 31:260-6.
8. Schilsky ML, Roberts EA, Bronstein JM, et al. A Multidisciplinary Approach to the Diagnosis and Management of Wilson Disease: 2022 Practice Guidance on Wilson Disease from the American Association for the Study of Liver Diseases. Hepatology. Published online December 7, 2022.
9. Socha P, Janczyk W, Dhawan A, et al. Wilson's Disease in Children: A Position Paper by the Hepatology Committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Feb;66(2):334-344. doi: 10.1097/MPG.0000000000001787.
10. Kowdley KV, Brown KE, Ahn J, Sundaram V. American College of Gastroenterology Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019 Aug;114(8):1202-1218. doi: 10.14309/ajg.0000000000000315.
11. Bacon BR, Adams PC, Kowdley KV, Powell LW, Tavill AS; American Association for the Study of Liver Diseases. Diagnosis and management of hemochromatosis: 2011 practice guideline by the American Association for the Study of Liver Diseases. Hepatology. 2011 Jul; 54(1): 328-43.
12. Cappellini M, Cohen A, Porter J, Taher A, Vprakasit V, eds. Guidelines for the Management of Transfusion Dependent Thalassaemia (TDT) [Internet]. 4th edition. Thalassaemia International Federation; 2021. Available at: https://www.thalassemia.org/boduw/wp-content/uploads/2021/06/TIF-2021-Guidelines-for-Mgmt-of-TDT.pdf.
13. Taher A, Musallam K, Domenica Cappellini M, eds. Guidelines for the Management of Non Transfusion Dependent Thalassemia (NTDT) [Internet]. 2nd edition. Nicosia (CY): Thalassaemia International Federation; 2018. Available at: https://thalassaemia.org.cy/wp-content/uploads/2017/10/NTDT-final-combined-1.pdf.
14. WHO Guideline for Clinical Management of Exposure to Lead. World Health Organization; 2021. Available at: https://www.who.int/publications/i/item/9789240037045.
15. Medical Management Guidelines for Lead. Agency for Toxic Substances and Disease Registry. Last reviewed October 2014. Available at: https://wwwn.cdc.gov/TSP/MMG/MMGDetails.aspx?mmgid=1203&toxid=22.
16. Medical Management Guidelines for Lead-exposed Adults. Association of Occupational and Environmental Clinics. April 24, 2007. Available at: http://www.aoec.org/documents/positions/MMG_FINAL.pdf.
17. Schilsky ML, Czlonkowska A, Zuin M, et al. Trientine tetrahydrochloride versus penicillamine for maintenance therapy in Wilson disease (Chelate): a randomized, open-label, non-inferiority, phase 3 trial. Lancet Gastroenterol Hepatol. 2022;7(12):1092-1102.
18. Bollig C, et al. Deferasirox for managing iron overload in people with thalassaemia. Cochrane Database Syst Rev. 2017 Aug 15;8:CD007476.
19. Appenenzeller-Herzog C, Mathes T, Heeres MLS, Heinz Weiss K, Houwen RHJ, Ewald H. Comparative effectiveness of common therapies for Wilson disease: A systematic review and meta-analysis of controlled studies. Liver Int. 2019 Nov;39(11):2136-2152.
20. Cao Y, Chen A, Bottai M, Caldwell KL, Rogan WJ. The impact of succimer chelation on blood cadmium in children with background exposures: a randomized trial. J Pediatr. 2013 Aug; 163(2):598-600.

Continuous Glucose Monitoring Devices

Product Name	Manufacturer
FreeStyle Libre	Abbott
FreeStyle Libre 2	Abbott
FreeStyle Libre 3	Abbott
Dexcom G6	Dexcom
Dexcom G7	Dexcom
Eversense E3	Senseonics
Guardian Connect	Medtronic

Class Overview

Continuous glucose meters (CGMs) are devices intended to measure blood glucose (BG), typically in patients with type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM), more frequently, more conveniently and less invasively compared to traditional fingerstick BG monitoring. Some persons without diabetes utilize CGM to monitor their BG for general health purposes. CGM has historically been restricted to concurrent use with insulin pumps and only the frailest patients with diabetes. However, technology advances are making CGM available to a wider population. Studies have demonstrated that they are useful for certain patient populations to improve diabetes management.

Both CGMs intended to replace standard BG monitoring with fingersticks and those that are indicated as a supplement to standard BG monitoring have been included in this review. Fingersticks to calibrate and, in some cases, confirm readings are still, at times, required with these devices. The types of CGMs included in this review can be sub-classified as stand-alone CGMs or *integrated* CGMs (iCGMs).

iCGMs are components of a system of compatible medical devices which may include insulin dosing systems, insulin pumps, BG meters or other electronic devices for diabetes management. FreeStyle Libre and Eversense are standalone CGMs. FreeStyle Libre 2, FreeStyle Libre 3, Dexcom G6, Dexcom G7, and Medtronic Guardian Connect are iCGMs. An iCGM together with an insulin pump and an algorithm (software) that calculates insulin doses, comprises an automated insulin delivery (AID) system. Currently, insulin delivery systems are not truly, fully automated, relying on announced meals/snacks and appropriate bolus insulin doses. This is termed a “hybrid closed-loop” insulin delivery system.

The majority of CGMs are real-time CGMs, which measure and transmit glucose values every 5 minutes. Most real-time CGM devices alert for hypoglycemia or hyperglycemia. The immediate feedback of glucose results allows timely intervention for rising or low/decreasing glucose levels to aid management and avert serious hypoglycemic events. All of the CGMs in this review are real-time CGMs, with the exception of FreeStyle Libre, which is an intermittently scanned CGM. Intermittently scanning CGMs (also called flash CGM) measure glucose every minute and record measurements every 15 minutes.

Price, motivation for treatment, availability, and lifestyle should all be taken into account when choosing a CGM. New products and improvements to current products are in the near-term future pipeline. Interoperability will also be a driving force in product selection. Select products, particularly software, are likely to be operable with contracted devices.

UTILIZATION FINDINGS

There were no claims and no prior authorization requests.

RECOMMENDATIONS

- No changes

Device Description

FreeStyle Libre 14 day

Two primary components: Sensor (disposable) and Reader (reusable)

Sensor

- Measures interstitial glucose levels every 1 minute.
- Can be worn for 14 days.
- Once applied, the Sensor must be activated and can be used to check BG after 1 hour.
- The Sensor must be scanned to activate.
- The Sensor must be scanned to provide a reading.
- Fingersticks may be necessary at times to confirm the reading. The Reader will show a  symbol if the reading may not be accurate.
- Trend arrows indicate the direction and magnitude of glucose change (↑↑,↑,↗,→,↘,↓,↓↓)
- The sensor does not need to be calibrated.

Reader

- Contains a built in meter for use with FreeStyle Precision Neo test strips and MediSense Glucose and Ketone control solution (Note: the meter does not have a ketone testing functionality).

FreeStyle Libre 2

Two primary components: Sensor (disposable) and Reader (reusable)

Sensor

- Can be used with other "compatible" devices including pumps, pens, etc. Not for use with AID systems.
- Measures interstitial glucose levels every 1 minute.
- Can be worn for 14 days.
- Once applied, the Sensor must be activated and can be used to check BG after 1 hour.
- The Sensor must be scanned to activate.
- The Sensor automatically streams results to the reader.
- Optional, customizable, real-time BG alarms for high and low BG readings.
- Fingersticks may be necessary during the first 12 hours of sensor wear, to confirm the reading. The Reader will show a  symbol.
- Trend arrows indicate the direction and magnitude of glucose change (↑↑,↑,↗,→,↘,↓,↓↓)
- The sensor does not need to be calibrated.

Reader

- Contains a built in meter for use with FreeStyle Precision Neo test strips and MediSense Glucose and Ketone control solution (Note: the meter does not have a ketone testing functionality).

FreeStyle Libre 3

Two primary components: Sensor (disposable) and Reader (reusable)

Sensor

- Can be used with other "compatible" devices including pumps, pens, etc. **Not for use with AID systems.**
- Sensor is smaller than FreeStyle Libre 2
- Measures interstitial glucose levels every 1 minute.
- Can be worn for 14 days.
- Once applied, the Sensor must be activated and can be used to check BG after 1 hour.
- The Sensor must be scanned to activate.
- The Sensor automatically streams results to the reader.
- Optional, customizable, real-time BG alarms for high and low BG readings.

- Fingersticks may be necessary during the first 12 hours of sensor wear, to confirm the reading. The Reader will show a  symbol.
- Trend arrows indicate the direction and magnitude of glucose change (↑↑,↑,↗,→,↘,↓,↓↓)
- The sensor does not need to be calibrated.

Reader

- Contains a built in meter for use with FreeStyle Precision Neo test strips and MediSense Glucose and Ketone control solution (Note: the meter does not have a ketone testing functionality).

Dexcom G6

Three primary components: Sensor (disposable), Transmitter (reusable), Mobile app/or receiver (reusable)

Sensor

- Measures BG levels every 5 minutes.
- Can be worn for 10 days.
- Must input sensor code into mobile app/or receiver before application
- Once applied, must attach transmitter and pair to mobile app/or receiver device (more information in transmitter and receiver section)
- Sensor must be warmed up for 2 hours to activate
- Sensor must be within 20 feet of mobile app/or receiver device
- No fingersticks are needed for calibration

Transmitter

- Relays information from sensor to mobile app/or receiver device every 5 minutes
- Transmitter must be connected to app/or receiver before application via SN number found on the back of transmitter box
- Transmitter can be used up to 3 months

Mobile App or Receiver

- The mobile app and receiver require individual setups
- Receives information from sensor every 5 minutes and displays readings
- Must enter a sensor code found on the sensor applicator
- Mobile app/or receiver must be connected to the transmitter before application via SN number found on the back of transmitter box
- Trend arrows and colors indicate the direction and speed of glucose change
- Alarms alert for very low, low, and high glucose readings

Dexcom G7

Two primary components: Sensor (disposable), Mobile app/or receiver (reusable)

Sensor

- Includes pre-attached transmitter
- Measures BG levels every 5 minutes.
- Can be worn for 10 days.
- Must input sensor code into mobile app/or receiver before application
- Once applied, must attach transmitter and pair to mobile app/or receiver device (more information in transmitter and receiver section)
- Sensor must be warmed up for 30 minutes to activate
- Sensor must finish warm up completed to provide a reading.
- No fingersticks are needed for calibration
- Relays information from sensor to mobile app/or receiver device every 5 minutes

Mobile App or Receiver

- The mobile app and receiver require individual setups
- Receives information from sensor every 5 minutes and displays readings
- Must enter a sensor code found on the sensor applicator
- Trend arrows and colors indicate the direction and speed of glucose change
- Alarms alert for very low, low, and high glucose readings

Guardian Connect

Three primary components: Sensor (disposable), Transmitter (reusable), Mobile app

Sensor

- Measures BG levels every 5 minutes
- Can be worn for 7 days.
- Sensor must be warmed up for 2 hours to activate
- Fingersticks for calibration for first week

Transmitter

- Can be removed and reapplied
- Water-resistant
- On-body vibratory hypo-/hyper-glycemia alerts
- Must be within Bluetooth range of mobile device (mobile app)
- Stores readings and relays to mobile app
- Rechargeable (a charge lasts approximately 36 hours, the transmitter recharges in about 15 minutes)

Mobile App

- Receives information and displays readings
- Must be paired with transmitter
- Trend arrows indicate the direction of glucose change
- Colors indicate range (below, within, above
- Various alert settings available

Eversense E3

Three primary components: Sensor (disposable), Transmitter (reusable), Mobile app

Sensor

- Measures BG levels every 5 minutes
- Inserted by a healthcare provider every 180 days
- Day 1 warm-up period after placement
- Fingersticks for calibration required twice daily (BID), when symptoms do not match readings, and when taking tetracyclines (TCNs).

Transmitter

- Attached to sensor
- Must be within Bluetooth range of mobile device (mobile app)
- Stores readings and relays to mobile app
- Rechargeable

Mobile App

- Receives information and displays readings
- Must be paired with transmitter
- Trend arrows indicate the direction of glucose change
- Colors indicate range (below, within, above)
- Various alert settings available
- Displays sensor glucose data, and also provides a user interface for sensor calibration, entering data such as exercise and meals, and uploading information

Device Comparison

	FreeStyle Libre	FreeStyle Libre 2	FreeStyle Libre 3	Dexcom G6	Dexcom G7	Guardian Connect	Eversense E3
Replace or Supplement Standard BG Testing	Replace	Replace	Replace	Replace	Replace	Supplement	Replace
Ages Indicated	≥ 18 years	≥ 4 years	≥ 4 years	≥ 2 years	≥ 2 years	14 to 75 years	≥ 18 years
Insertion Site	Arm	Arm	Arm	Abdomen	Abdomen or arm	Abdomen or arm	Arm
Duration of Sensor	14 days	14 days	14 days	10 days	10 days	7 days	180 days
Calibration Required?	No	No	No	No	No	No	Yes, every 12 hours for the first 21 days of use, then once daily
Warm-up Time	1 hour	1 hour	1 hour	2 hours	30 minutes	2 hours	24 hours
Method of Insertion	Self-insertion	Self-insertion	Self-insertion	Self-insertion	Self-insertion	Self-insertion	Requires office-based procedure
Optional or Customized Alarms for Glucose Values	Low and high	Low and high	Low and high	Predictive low and high, rate of change, low and high	Predictive low and high, rate of change, low and high	Predictive low and high, rate of change, low and high	Predictive low and high, rate of change, low and high
Programmed/mandatory Alarms for Glucose Values	None	None	Urgent low	Urgent low	Urgent low	Urgent low	Urgent low
Insulin pump integration?	No	No	No	Yes	No (in development)	Yes	No
Share feature for health care providers	LibreView	LibreView	LibreView	Clarity	Clarity	CareLink	Eversense Data Management System (DMS) Pro
Intermittent scanning ("flash") or real-time?	Intermittent scanning	Real-time	Real-time	Real-time	Real-time	Real-time	Real-time

Price

	FreeStyle Libre	FreeStyle Libre 2	FreeStyle Libre 3	DexcomG6	Dexcom G7	Guardian Connect	Eversense E3
Formulary Status	NF	NF	NF	NF	NF	NF	NF
Price^							
Reader	$70 once	$70 once	$70 once				
Receiver				$365 once	$299 once		
Sensor	$136/28 days	$136/28 days	$136/28 days	$366/30 days	$366/30 days	$501/28 days	$2,327/6 months
Transmitter	N/A	N/A	N/A	$238/3 months	N/A	$878/once *	$650/once*

^Based on wholesale acquisition cost (WAC) for 1 month supply unless otherwise noted.

*Warranty expires at the end of 1 year after which patients can continue to use the transmitter if it's working, but if it breaks a new device must be purchased

Practice Guidelines

American Diabetes Association Professional Practice Committee. 7. Diabetes Technology: Standards of Medical Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S126-S144.

- Initiation of CGM **should** be offered to people with type 1 diabetes early in the disease, even at time of diagnosis. **(A)**
- People who have been using CGM, continuous subcutaneous insulin infusion, and/or automated insulin delivery for diabetes management **should** have continued access across third-party payers. **(E)**
- Real-time CGM **(A)** or intermittently scanned CGM **(B) should** be offered for diabetes management in adults with diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using devices safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs.
- Real-time CGM **(A)** or intermittently scanned CGM **(B) should** be offered for diabetes management in adults with diabetes on basal insulin who are capable of using devices safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs.
- Real-time CGM **(A)** or intermittently scanned CGM **(E) should** be offered for diabetes management in youth with type 1 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using the device safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs.
- Real-time CGM or intermittently scanned CGM **should** be offered for diabetes management in youth with type 2 diabetes on multiple daily injections or continuous subcutaneous insulin infusion who are capable of using devices safely (either by themselves or with a caregiver). The choice of device should be made based on patient circumstances, desires, and needs. **(E)**
- In people with diabetes on multiple daily injections or continuous subcutaneous insulin infusion, real-time CGM devices **should** be used as close to daily as possible for maximal benefit. **(A)** Intermittently scanned CGM devices **should** be scanned frequently, at a minimum once every 8 hours to avoid gaps in data. **(A)** People with diabetes **should** have uninterrupted access to their supplies to minimize gaps in CGM. **(A)**
- When used as an adjunct to preprandial and postprandial blood glucose monitoring, CGM can help to achieve A1C targets in diabetes and pregnancy. **(B)**
- Periodic use of real-time CGM or intermittently scanned CGM or use of professional CGM can be helpful for diabetes management in circumstances where consistent use of CGM is not desired or available. **(C)**

Recommendation Definitions

Level of Evidence	Definition
A	Clear evidence from well-conducted, generalizable randomized controlled trials (RCTs) that are adequately powered, including: • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis
	Supportive evidence from well-conducted RCTs that are adequately powered, including: • Evidence from a well-conducted trial at one or more institutions • Evidence from a meta-analysis that incorporated quality ratings in the analysis
B	Supportive evidence from well-conducted cohort studies • Evidence from a well-conducted prospective cohort study or registry • Evidence from a well-conducted meta-analysis of cohort studies
	Supportive evidence from a well-conducted case-control study
C	Supportive evidence from poorly controlled or uncontrolled studies • Evidence from randomized clinical trials with one or more major or three or more minor methodological flaws that could invalidate the results • Evidence from observational studies with high potential for bias (such as case series with comparison with historical controls) • Evidence from case series or case reports
	Conflicting evidence with the weight of evidence supporting the recommendation
E	Expert consensus or clinical experience

Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocr Pract. 2021;27(6):505-537. doi:10.1016/j.eprac.2021.04.008.

- CGM **is strongly recommended** for all persons with diabetes treated with intensive insulin therapy, defined as 3 or more injections of insulin per day or the use of an insulin pump. Grade **A**; High Strength of Evidence; Best evidence level (BEL) 1
- CGM **is recommended** for all individuals with problematic hypoglycemia (frequent/severe hypoglycemia, nocturnal hypoglycemia, hypoglycemia unawareness). Grade **A**; Intermediate-High Strength of Evidence; BEL 1
- CGM **is recommended** for children/adolescents with T1D. Grade **A**; Intermediate-High Strength of Evidence; BEL 1
- CGM **is recommended** for pregnant women with T1D and T2D treated with intensive insulin therapy. Grade **A**; Intermediate-High Strength of Evidence; BEL 1
- CGM **is recommended** for women with gestational diabetes mellitus (GDM) on insulin therapy. Grade **A**; Intermediate Strength of Evidence; BEL 1
- CGM **may** be recommended for women with GDM who are not on insulin therapy. Grade **B**; Intermediate Strength of Evidence; BEL 1
- CGM **may** be recommended for individuals with T2D who are treated with less intensive insulin therapy. Grade **B**; Intermediate Strength of Evidence; BEL 1
- Initiation and use of diabetes technology **should** be implemented by health care professionals who are trained, committed, and experienced to prescribe and direct the use of these tools. Clinicians should have the infrastructure to support the needs of persons with diabetes using the technology. Grade **B**; Intermediate Strength of Evidence/Expert Opinion of Task Force; BEL 1

Recommendation Definitions

Grade	Definition
A	Strong
B	Intermediate
C	Weak
D	No conclusive evidence and/or expert opinion

Evidence Level	Definition
1	Meta-analysis of RCTs
1	RCTs
2	Meta-analysis of nonrandomized prospective or case-controlled trials
2	Nonrandomized controlled trial
2	Prospective cohort study
2	Retrospective case-control study
3	Cross-sectional study
3	Surveillance study (registries, surveys, epidemiologic study, retrospective chart review, mathematical modeling of database)
3	Consecutive case series
3	Single case reports
4	No evidence (theory, opinion, consensus, review, or preclinical study)

Clinical Studies

FreeStyle Libre/2/3

Title	Use of Flash Continuous Glucose Monitoring Is Associated With A1C Reduction in People With Type 2 Diabetes Treated With Basal Insulin or Noninsulin Therapy NCT N/A PMID 34149259
Design	Retrospective study of observational data from the IBM Explorys database
Population	N=1034 Most patients were >50 years of age, had a baseline A1C of ≥8.0 to <10.0%, and were treated with noninsulin therapy. The majority of patients had hypertension and dyslipidemia, and more than half had a BMI >30 kg/m2.
Endpoint(s)	Primary: change from baseline A1C levels after prescription of the flash CGM system
Inclusion Criteria	Diagnosis of type 2 diabetes, age <65 years, naive to any CGM, a baseline A1C ≥8.0%, prescription of a flash CGM system (10- or 14-day) between October 2017 and February 2020, no record of short- or rapid-acting insulin use, presence of baseline A1C test within the 180 days before or including the flash CGM prescription date, and presence of a post-observation A1C value between 60 and 300 days after the CGM prescription date.
Exclusion Criteria	Diabetes type 1, gestational DM in the 6 months before flash CGM prescription, patients with evidence of prior CGM prescription, A1C < 8.0%
Results	Primary: at study end point (mean follow-up 159 days), a significant A1C reduction of 1.5 ± 2.2 percentage points was observed within the full cohort. Baseline A1C was 10.1% and A1C at 159 days was 8.6%.
Conclusion	The authors concluded that “Prescription of the flash CGM system was associated with significant reductions in A1C in patients with type 2 diabetes treated with basal insulin or noninsulin therapy.”
Interpretation	The study appears to provide solid evidence for using flash CGM in the type 2 diabetes population, irrespective of insulin use.

Title	The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: a Meta-analysis of Clinical Trials and Real-world Observational Studies. NCT N/A PMID 31673972
Design	Meta-analysis
Population	N=25 studies, 1723 participants
Endpoint(s)	Primary: mean change in laboratory HbA1c
Inclusion Criteria	Studies reporting longitudinal HbA1c data in participants with T1D or T2D using the FreeStyle Libre flash glucose monitoring (FGM) system that reported longitudinal HbA1c data over 1–12 months.
Exclusion Criteria	Studies in which no initial mean HbA1c was reported; no outcome timings were reported for mean change in HbA1c; 12-month outcomes in children only were reported as the study end point
Results	Primary: mean change in laboratory HbA1c at 2–4 months was − 0.55% (95% CI − 0.70, − 0.39). In the adult group, the mean change in HbA1c was − 0.56% (95% CI − 0.76, − 0.36); for the pediatric group, mean change in HbA1c was − 0.54% (95% CI − 0.84, − 0.23). No significant differences were detected between type 1 and type 2 diabetes groups.
Conclusion	The authors concluded that “starting the FreeStyle Libre system as part of diabetes care results in a significant and sustained reduction in HbA1c for adults and children with T1D and for adults with T2D.”
Interpretation	Real world evidence appears to confirm findings from RCTs that isCGM with Freestyle Libre FGM reduces HbA1c. Although a surrogate marker, HbA1c is reliable and well correlated with final outcomes. The results of this meta-analysis are reassuring that isCGM is a useful tool for managing diabetes, at least in some populations.

Title	The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. NCT 02073058 PMID 26171659
Design	Allocation: N/A Intervention Model: No treatment Masking: Sensor readings were masked to the participants. Primary Purpose: Accuracy evaluation of the device

Population	N=75 18 years and older Type 1 or type 2 diabetes for ≥ 2 years prior to enrollment and requiring multiple (≥ 3) daily insulin injections (MDI) or continuous subcutaneous insulin infusion for ≥ 6 months prior to enrollment
Arms	Single, observational arm A sensor was inserted on the back of each upper arm for up to 14 days. Three factory-only calibrated sensor lots were used in the study. Sensor glucose measurements were compared with capillary BG results (approximately eight per day) obtained using the BG meter built into the reader (BG reference) and with the YSI analyzer (Yellow Springs Instrument, Yellow Springs, OH) reference tests at three clinic visits (32 samples per visit).
Endpoint(s)	Primary: Clinical point accuracy as assessed by the Consensus Error Grid.
Inclusion Criteria	Other than those listed in the "Population," inclusion criteria were standard (willing and able to participate and provide informed consent, etc.)
Exclusion Criteria	• Allergy to medical grade adhesive or topically applied isopropyl alcohol • Pregnancy, attempt to conceive or unwilling/unable to practice birth control during study period • Skin lesions, scarring, redness, infection or edema that could interfere with device placement or accuracy • Donated blood within 112 days • History of HIV, Hepatitis B or C • X-ray, MRI or CT appointment scheduled during study period which cannot be rescheduled
Results	The accuracy of the results was demonstrated against capillary BG reference values, with 86.7% of sensor results within Consensus Error Grid Zone A. The percentage of readings within Consensus Error Grid Zone A on Days 2, 7, and 14 was 88.4%, 89.2%, and 85.2%, respectively. The overall mean absolute relative difference was 11.4%. The mean lag time between sensor and YSI reference values was 4.5±4.8 min. Sensor accuracy was not affected by factors such as body mass index, age, type of diabetes, clinical site, insulin administration, or hemoglobin A1c.
Conclusion	Interstitial glucose measurements with the FreeStyle Libre system were found to be accurate compared with capillary BG reference values, with accuracy remaining stable over 14 days of wear and unaffected by patient characteristics.
Interpretation	According to FDA guidance for industry and staff on the topic of BG monitoring device applications, ≥ 95% of sample results should fall within Zone A, although other distributions are permissible. Zone A is result differences are considered harmless; Zone C result differences are considered to be associated with serious harm; and Zone B result differences are considered not discrepant enough to cause serious harm. Less than 95% of results in this study fell within Zone A. However, the FDA reference guidance was published in 1988 and does not address interstitial BG monitoring, as used by FreeStyle Libre, only venous and capillary.

Title	Novel glucose-sensing technology and hypoglycemia in type 1 diabetes: a multicenter, non-masked, randomized controlled trial (IMPACT) NCT 02232698 PMID 27634581
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (open-label) Primary Purpose: Evaluation of the impact on hypoglycemia in Type 1 DM
Population	N=328 18 years and older Type 1 diabetes for ≥ 5 years and on current insulin regimen for ≥ 3 months prior to enrollment
Arms	Experimental: Sensor-based glucose monitoring system unmasked for 6 months. All subjects wore the same monitoring system masked (glucose measurements not visible) for 14 days prior to randomization. Active Comparator: Standard BG monitoring device for 6 months. All subjects wore the sensor-based monitoring system masked (glucose measurements not visible) for 14 days prior to randomization and at 3 and 6 months.
Endpoint(s)	Primary: Difference in time <70 mg/dL between intervention and control group assessed in days 194 to 208 adjusting for baseline (days 1 to 15).
Inclusion Criteria	• Screening HbA1c result ≤ 7.5% • Reports self-testing of BG levels on a regular basis ≥ 3 times daily for ≥ 2 months prior to study entry
Exclusion Criteria	• Allergy to medical grade adhesives.

	• Pregnancy, attempt to conceive or breast feeding during study period. • Hypoglycemia unawareness, diabetic ketoacidosis (DKA) within prior 6 months. • Currently using animal insulin or oral steroid therapy or is likely to require oral steroid therapy. • Currently or planning on using a CGM device or has used one within the previous 4 months. • Currently using Sensor augmented pump therapy. • Currently receiving dialysis treatment or planning to receive dialysis during the study • Has a pacemaker. • Acute myocardial infarction within previous 6 months. • Concomitant disease or condition that may compromise safety including but not limited to: unstable coronary heart disease, cystic fibrosis, serious psychiatric disorder.
Results	Mean time in hypoglycemia changed from 3.38 h/day at baseline to 2.03 h/day at 6 months (baseline adjusted mean change −1.39) in the intervention group, and from 3.44 h/day to 3.27 h/day in the control group (−0.14); with the between-group difference of −1.24 (SE 0.239; p<0.0001), equating to a 38% reduction in time in hypoglycemia in the intervention group. No device-related hypoglycemia or safety issues were reported. Thirteen adverse events were reported by ten participants related to the sensor—four of allergy events (one severe, three moderate); one itching (mild); one rash (mild); four insertion-site symptom (severe); two erythema (one severe, one mild); and one edema (moderate). There were ten serious adverse events (five in each group) reported by nine participants; none were related to the device.
Conclusion	Novel flash glucose testing reduced the time adults with well controlled type 1 diabetes spent in hypoglycemia.
Interpretation	Interpretive commentary is unavailable due to restricted access to the full article.

Title	Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. (REPLACE) NCT 02082184 PMID 28000140
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: None (open-label) Primary Purpose: Evaluation of the effect of novel glucose sensing technology on HbA1c in Type 2 diabetes
Population	N=302 18 years and older Type 2 diabetes on insulin therapy for ≥ 6 months and on their current regimen for ≥3 months
Arms	Experimental: Sensor-based glucose monitoring system unmasked for 6 months. All subjects wore the same monitoring system masked (glucose measurements not visible) for 14 days prior to randomization. Active Comparator: Standard BG monitoring device for 6 months. All subjects wore the sensor-based monitoring system masked (glucose measurements not visible) for 14 days prior to randomization and at 6 months.
Endpoint(s)	Primary: Difference in HbA1c between intervention and control group at day 194 adjusting for baseline HbA1c at day 1 using ANCOVA.

Inclusion Criteria	• Screening HbA1c result ≥ 7.5% ≤ 12%.
	• Reports self-testing of BG levels on a regular basis ≥ 10 times per week for ≥ 2 months prior to study entry.
	• Insulin management must be one of the following;
	  ○ an injection regimen of prandial insulin at least once daily,
	  ○ or, prandial insulin at least once daily plus basal insulin at least once daily,
	  ○ or, continuous subcutaneous insulin infusion (CSII) with no plans to change during the study.

Exclusion Criteria	• Allergy to medical grade adhesives. • Pregnancy, attempt to conceive or breast feeding during study period. • Episode of severe hypoglycemia (requiring 3rd party assistance and/or hospital admission), DKA or hyperosmolar hyperglycemic state (HHS) within prior 6 months. • Currently using animal insulin; insulin regimen consists entirely of basal or includes bi-phasic insulin; total daily dose of insulin > 1.75 IU/kg at study entry. • Currently using steroid therapy or is likely to require steroid therapy. • Currently or planning on using a CGM device or has used one within the previous 4 months. • Currently receiving dialysis treatment or planning to receive dialysis during the study • Has a pacemaker or any other neuro stimulators. • Acute myocardial infarction within previous 6 months.

	• Concomitant disease or condition that may compromise safety including but not limited to: unstable coronary heart disease, cystic fibrosis, serious psychiatric disorder.
Results	At 6 months, there was no difference in the change in HbA1c between intervention and controls: -3.1 ± 0.75 mmol/mol, [-0.29 ± 0.07% (mean ± SE)] and -3.4 ± 1.04 mmol/mol (-0.31 ± 0.09%) respectively; p = 0.8222. A difference was detected in participants aged <65 years [-5.7 ± 0.96 mmol/mol (-0.53 ± 0.09%) and -2.2 ± 1.31 mmol/mol (-0.20 ± 0.12%), respectively; p = 0.0301]. Time in hypoglycemia <3.9 mmol/L (70 mg/dL) reduced by 0.47 ± 0.13 h/day [mean ± SE (p = 0.0006)], and <3.1 mmol/L (55 mg/dL) reduced by 0.22 ± 0.07 h/day (p = 0.0014) for intervention participants compared with controls; reductions of 43% and 53%, respectively. SMBG frequency, similar at baseline, decreased in intervention participants from 3.8 ± 1.4 tests/day (mean ± SD) to 0.3 ± 0.7, remaining unchanged in controls. Treatment satisfaction was higher in intervention compared with controls (DTSQ 13.1 ± 0.50 (mean ± SE) and 9.0 ± 0.72, respectively; p < 0.0001). No serious adverse events or severe hypoglycemic events were reported related to sensor data use. Forty-two serious events [16 (10.7%) intervention participants, 12 (16.0%) controls] were not device-related. Six intervention participants reported nine adverse events for sensor-wear reactions (two severe, six moderate, one mild).
Conclusion	Flash glucose-sensing technology use in type 2 diabetes with intensive insulin therapy results in no difference in HbA1c change and reduced hypoglycemia, thus offering a safe, effective replacement for SMBG.
Interpretation	The sensor-based device appears to be a safe and effective alternative to traditional capillary self-monitoring BG. Although HbA1c was not improved in this study, hypoglycemia was, and hypoglycemia is a source of morbidity and mortality as well as being associated with high costs to treat, especially in the emergency setting. Average sensor-scanning frequency was double the frequency of BG testing; however, this did not correlate with reduced time in hypoglycemia. This raises the question of the mechanism behind the reduced hypoglycemic events and calls into question whether this outcome was attributable to the sensor-based glucose monitor or if it was attributable to other factors.

Dexcom G6/G7

Title	Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial NCT 03772600 PMID 34089660
Design	Allocation: Randomized 1:1 Intervention Model: Parallel Assignment Masking: None (open-label)
Population	N= 269 The rtCGM and isCGM groups had similar baseline characteristics. Average age of participants was 42.9 years (SD 14.1; range 18–76 years). 239 (94%) were White and most were highly educated. 205 (81%) were using multiple daily injections with insulin analogues, had long experience with isCGM and were scanning frequently (median 11 scans per day). Mean HbA1c was 7.4% (SD 0.9; range 5.3–9.9%) with a mean time in range (TIR) of 51.9% (SD 15.1).
Arms	Experimental: Dexcom G6 for 36 months Active Comparator: FreeStyle Libre FGM for 6 months (during which patients wear a blinded Dexcom G6 for 28 days); cross over to Dexcom G6 for 30 months
Endpoint(s)	Primary endpoint: Difference in TIR (70-180 mg/dL) between the control and experimental group measured by Dexcom G6.
Inclusion Criteria	• Patients with type 1 diabetes for at least 6 • Using FreeStyle Libre FGM system ≥6 months • Intensified insulin therapy/insulin pump therapy • HbA1c ≤10% • Willing to wear the glucose monitoring device >80% of the time • Willing to download glucose monitoring data at regular intervals
Exclusion Criteria	• Non-type 1 diabetes participants or diagnosis <6 months • Participant with type 1 diabetes not on insulin, or on non-intensified insulin therapy • Pregnancy or planning pregnancy within next 6 months • Severe cognitive dysfunction or other disease which makes sensor use difficult • Current treatment with drugs known to have significant interference with glucose metabolism, such as systemic corticosteroids • Abnormal skin at the anticipated glucose sensor insertion sites (excessive hair, burn, inflammation, infection, rash, and/or tattoo)

	• Presence of concomitant pathology that might cause edema at the insertion sites (such as heart failure, liver failure, kidney failure defined as eGFR <30 mL/min [stage ≥4]) • Beta-cell transplantation and c-peptide positive and/or under immunosuppressive therapy
Results	Primary endpoint: TIR did not change in the isCGM group during the study (51.3% [95% CI 48.7–54.0] at baseline vs 51.9% [49.1–54.7] at month 6). Starting from a similar baseline TIR of 52.5% (49.8–55.1) in the rtCGM group, TIR increased to 59.6% (56.8–62.4) at 6 months. Correcting for baseline TIR, this resulted in a mean difference of 6.85 percentage points (4.36–9.34; p<0.0001) at 6 months, which corresponds to being on average 1 h 39 min per day more in range when using rtCGM. Of note, baseline TIR was similar in isCGM and rtCGM at every time of day and night. At month 6, higher TIR was observed in the rtCGM group over 24 hours.
Conclusion	The authors concluded that "In an unselected adult type 1 diabetes population, switching from isCGM to rtCGM significantly improved TIR after 6 months of treatment, implying that clinicians should consider rtCGM instead of isCGM to improve the health and quality of life of people with type 1 diabetes."
Interpretation	isCGM appears to be more effective at maintaining TIR in at least a subset of patients with diabetes using multiple daily doses of insulin or pump therapy. This is a surrogate endpoint and whether this translates to clinical improvement is still an outstanding question.

Title	Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycemia awareness or severe hypoglycemia treated with multiple daily insulin injections (HypoDE): a multicenter, randomized controlled trial NCT 02671968 PMID 29459019
Design	Allocation: Randomized 1:1 Intervention Model: Parallel Assignment Masking: Participants wore a masked rtCGM for 28 weeks and then randomly assigned to 26 weeks of unmasked rtCGM or SMBG Primary Purpose: Demonstrate that usage of RT-CGM (Real time CGM) reduces the frequency of low CGM-recorded glucose events (glucose values <55 mg/dL) in patients using multiple day injections that are at risk for hypoglycemic events
Population	N= 141 18 years and older Type 1 diabetes for at least 12 months on multiple daily injections
Arms	Experimental: CGM group (devices were Dexcom G5 mobile and Dexcom G4) Active Comparator: SMBG
Endpoint(s)	Primary endpoint: Change in total number of low glucose events between baseline and outcome phase of weeks 22-26 in the rtCGM group and SMBG
Inclusion Criteria	• Patients with type 1 diabetes for at least 12 months on multiple daily injections (MDI). MDI is defined as prandial insulin injections at each major meal (excludes pre-mixed insulin) with doses determined by SMBG and carbohydrate counting, and basal insulin injection(s) • HbA1c ≤ 9.0 % performed within 4 months before begin of the study • High risk for severe hypoglycemia (defined as a score of 4 or higher on the Hypoglycemia unawareness scale (HUS) or a history of at least one severe hypoglycemic event in the last 12 months (required third part assistance, not able to treat themselves)) • Willing to not use paracetamol or drugs containing it • Signed and dated Informed Consent Form
Exclusion Criteria	• Use of personal real-time-CGM 3 months prior to study entry and during the study (except study devices) • Use of a flash-glucose monitoring system 3 months prior to study and during the study • Alcoholism or drug abuse • Unable to comply with the protocol at the investigators discretion, such as known psychiatric diagnosis, cognitive / physical decline • Pregnancy or lactation period • Severe known allergies (e.g. plaster) • Mental incapacity or language barriers precluding adequate compliance with the study procedures • Limited or no legal capacity or legal guardianship • Dependency from the sponsor or the clinical investigator (e.g. co-workers of the sponsor or the clinical research center or their families)

	• Participation in another study at the same time with a non-approved drug or a non-CE-labelled medical device
Results	The mean number of hypoglycemic events per 28 days among participants in the rtCGM group was reduced from 10.8 (SD 10.0) to 3.5 (4.7); reductions among control participants were negligible (from 14.4 [SD 12.4] to 13.7 [SD 11.6]). Incidence of hypoglycemic events decreased by 72% for participants in the rtCGM group (incidence rate ratio 0.28 [95% CI 0.20-0.39] with a p<0.0001). 18 serious adverse events were reported with 7 in the control group, 10 in the rtCGM group, and 1 before randomization. No event was considered to be related to the investigational device.
Conclusion	The use of CGM in those with type 1 diabetes and multiple daily injection insulin therapy, and impaired hypoglycemia awareness or severe hypoglycemia, results a reduction of hypoglycemia events, thus offering a safe, effective tool to replace SMBG.
Interpretation	The CGM appears to be a safe and effective alternative to traditional self-monitoring BG. However, the full article is behind a paywall so limited, reliable conclusions can be drawn from the data that is publicly available. It shows a reduction in the number of hypoglycemic events overall, and shows particular use for those with hypoglycemic unawareness or severe hypoglycemia symptoms. Studies to date have not shown clinical evidence in those with high risk to hypoglycemic events and the use of CGM.

Title	Effectiveness and Safety Study of the Dexcom G4 Platinum With Modified Algorithm NCT 02087995 PMID 25370149
Design	Allocation: N/A single group Intervention Model: single group assignment Masking: none (open-label) Primary Purpose: to assess the accuracy and reliability of the new algorithm, used in a modified Dexcom G4 Platinum receiver, in comparison with frequent venous samples measured on a laboratory reference system during a clinic session and in comparison to SMBG during home use
Population	N= 51 18 years and older Type 1 or type 2 diabetes with high intensive insulin therapy
Arms	Single arm: Dexcom G4 CGM System
Endpoint(s)	Primary endpoint: The percentage of CGM system values that are within 20% of the reference value for YSI glucose levels > 80 mg/dL or within 20 mg/dL at the reference glucose levels < 80 mg/dL
Inclusion Criteria	• Diagnosis of Type 1 diabetes or Type 2 diabetes on Intensive Insulin Therapy (ITT) • Willing to participate in a clinic session
Exclusion Criteria	• Use of Acetaminophen during study period • Pregnancy • Hematocrit (HCT) <35% (females) and 38% (males) • Dialysis, history of cardiovascular disease, epilepsy, severe migraines in the past 6 months, adrenal disease, syncope, significant hypoglycemia unawareness, or a history of severe hypoglycemia within the last 6 months. • Any condition that, in the opinion of the Investigator, would interfere with their participation in the study or pose and excessive risk to study staff
Results	In comparison with the laboratory reference method (n = 2,263) the system provided a mean and median absolute relative differences (ARD) of 9.0% and 7.0%, respectively. The mean absolute difference for CGM was 6.4 mg/dL when the YSIs were within hypoglycemia ranges (≤ 70 mg/dL). The percentage in the clinically accurate Clarke error grid A zone was 92.4% and in the benign error B zone was 7.1%. Majority of the sensors (73%) had an aggregated MARD in reference to YSI ≤ 10%. The MARD of CGM-SMBG for home use was 11.3%.
Conclusion	The point and rate accuracy, clinical accuracy, reliability, and consistency over the duration of wear and across glycemic ranges were superior to current commercial real-time CGM systems. The performance of this CGM is reaching that of a self-monitoring BG meter in real use environment.
Interpretation	The study shows a marked improvement in CGM performance and should show real life benefits to its users because 92.4% of glucose monitoring points fell within Zone A, and 99.5% of points falling into zone A and B. This comes close to the FDA guidelines for industry and staff on the topic of BG monitoring, where Zone A is considered harmless and should be targeted 95%. The performance improvements in hypoglycemia and hyperglycemia detection came from the newly low glucose alert threshold of 70mg/dL and high glucose

	threshold of 200mg/dL, which 91% for hypoglycemia and 98% for hyperglycemia of the time were within 15mins of an event and was able to correctly alert 92% and 96% in a timely manner

Title	Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIaMonD) NCT 02282397 PMID 28118453
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: none (open-label) Primary Purpose: To determine the effectiveness of CGM in adults with type 1 diabetes treated with insulin injections
Population	N= 158 25 Years and older Type 1 diabetes mellitus or insulin-requiring Type 2 diabetes mellitus
Arms	Of note, in phase 1 of the study, all participants used a "blinded" CGM for 2 weeks Experimental: CGM device Dexcom G4 Platinum CGM System with an enhanced algorithm Active control: SMBG Contour Next USB meter and test strips and instructed to check glucose levels at least 4 times daily
Endpoint(s)	Primary endpoint: the difference in change in central laboratory measured HbA1c level from baseline to 24 weeks
Inclusion Criteria	• Diagnosis of Type 1 diabetes mellitus or insulin-requiring Type 2 diabetes mellitus • Followed regularly by a physician or diabetes educator • Using multiple daily injections • stable control of diabetes • willing to wear a device such as pump or continuous glucose monitor
Exclusion Criteria	• recent or planned use of non-insulin injectable hypoglycemic agents • Pregnancy or planning to become pregnant during the study • Medical conditions that make it inappropriate or unsafe to target an A1C of <7% • Renal disease with Glomerular Filtration Rate <45 • Extensive skin changes/disease that precludes wearing the sensor on normal skin • Known allergy to medical-grade adhesives • Recent hospitalization or emergency room visit in the 6 months prior to screening resulting in primary diagnosis of uncontrolled diabetes
Results	Among the 158 randomized participants (mean age, 48 years [SD, 13]; 44% women; mean baseline HbA1c level, 8.6% [SD, 0.6%]; and median diabetes duration, 19 years [interquartile range, 10-31 years]), 155 (98%) completed the study. In the CGM group, 93% used CGM 6 d/wk or more in month 6. Mean HbA1c reduction from baseline was 1.1% at 12 weeks and 1.0% at 24 weeks in the CGM group and 0.5% and 0.4%, respectively, in the control group (repeated-measures model P < .001). At 24 weeks, the adjusted treatment-group difference in mean change in HbA1c level from baseline was -0.6% (95% CI, -0.8% to -0.3%; P < .001). Median duration of hypoglycemia at less than <70 mg/dL was 43 min/d (IQR, 27-69) in the CGM group vs 80 min/d (IQR, 36-111) in the control group (P = .002). Severe hypoglycemia events occurred in 2 participants in each group.
Conclusion	Among adults with type 1 diabetes who used multiple daily insulin injections, the use of CGM compared with usual care resulted in a greater decrease in HbA1c level during 24 weeks
Interpretation	The magnitude of the benefit of the CGM group with their Hb1Ac levels was consistent in the age group from 26-73 and was comparable to other trial groups where they studied the use of CGM with insulin pumps users. This is significant since those on multiple daily injections usually have less control with their glucose levels since their flexibility only comes with their bolus dosing. The trial also had a high retention rate and high degree of participant satisfaction with the CGM. Secondary endpoints also showed increased time in normal glucose range. Therefore the use of CGM compared with usual care is an option for those with type 1 diabetes, while taking into regards age and adherence to the disease management.

Title	Randomized Study of Real-Time Continuous Glucose Monitors (RT-CGM) in the Management of Type 1 Diabetes NCT 00406133 PMID 18779236
Design	Allocation: Randomized Intervention Model: Parallel Assignment

	Masking: none (open-label) Primary Purpose: Asses the value of CGM in the management of type 1 diabetes mellitus
Population	N= 322 8 Years and older type 1 diabetes and using daily insulin therapy for at least one yea
Arms	Experimental: CGM Dexcom G4 Platinum CGM System with an enhanced algorithm Control: home monitoring with a BG meter
Endpoint(s)	Primary endpoint: Change in glycated hemoglobin (HbA1c) from baseline to 26 weeks, as determined by a central laboratory (for the cohort with baseline HbA1c >=7.0% cohort).

Inclusion Criteria	• Clinical diagnosis of type 1 diabetes and using daily insulin therapy for at least one year
	  ○ The diagnosis of type 1 diabetes is based on the investigator's judgment; C peptide level and antibody determinations are not needed.
	• Glycated hemoglobin(HbA1c) 7.0%-10.0% for the primary cohort and <7.0% for the secondary cohort
	  ○ The DCA2000 or comparable point of care device will be used to assess eligibility.
	• Insulin regimen involves either use of an insulin pump or multiple daily injections of insulin (at least 3 shots per day) and has been stable for the last two months, with no plans to switch the modality of insulin administration during the next 6 months (e.g., injection user switching to a pump, pump user switching to injections, or the addition of Lantus (Glargine) insulin)
	  ○ Subjects using premixed fixed doses of insulin at the time of enrollment will not be eligible
	• Subject (and parent/guardian for children) understands the study protocol and agrees to comply with it
	• Subjects >9 years old and primary care giver (i.e., parent or guardian if subject is a minor) comprehend written English or Spanish
	  ○ This requirement is due to the fact that the questionnaires to be used as outcome measures do not have validated versions in other languages.
	  ○ Spanish-speaking subjects will be enrolled only if a RT-CGM device that functions in Spanish and has a User Guide in Spanish is available.
	• No expectation that subject will be moving out of the area of the clinical center during the next year, unless the move will be to an area served by another study center.
	• Informed Consent Form signed by the subject (or parent/guardian if subject is a minor, with subject signing the Child Assent Form)

Exclusion Criteria	• The presence of a significant medical disorder or use of a medication such as oral/inhaled glucocorticoids that in the judgment of the investigator will affect the wearing of the sensors or the completion of any aspect of the protocol.
	• The presence of any of the following diseases:
	  ○ Asthma if treated with systemic or inhaled corticosteroids in the last 6 months
	  ○ Cystic fibrosis
	• Adequately treated thyroid disease and celiac disease do not exclude subjects from enrollment
	• Inpatient psychiatric treatment in the past 6 months (if the subject is a minor, for either the subject or the subject's primary care giver).
	• Home use of RT-CGM in past 6 months
	  ○ Use of a CGMS or GlucoWatch does not exclude subjects from enrollment
	• Participation in an intervention study (including psychological studies) in past 6 weeks.
	• Another member of the same household is participating in this study.
	• For females, pregnant or intending to become pregnant during the next year Pregnancy is exclusion because of uncertainty about the lag between interstitial fluid glucose and BG during pregnancy, which might affect the accuracy of the sensor. Subjects who become pregnant during the study will be discontinued from the study.

Results	The changes in glycated hemoglobin levels in the two study groups varied markedly according to age group (P=0.003), with a significant difference among patients 25 years of age or older that favored the continuous-monitoring group (mean difference in change, -0.53%; 95% confidence interval [CI], -0.71 to -0.35; P<0.001). The between-group difference was not significant among those who were 15 to 24 years of age (mean difference, 0.08; 95% CI, -0.17 to 0.33; P=0.52) or among those who were 8 to 14 years of age (mean difference, -0.13; 95% CI, -0.38 to 0.11; P=0.29). Secondary glycated hemoglobin outcomes were better in the continuous-monitoring group than in the control group among the oldest and youngest patients but not among those who were 15 to 24 years of age. The use of CGM averaged 6.0 or more days per week for 83% of patients 25 years of age or older, 30% of those 15 to 24 years of age, and 50% of those 8 to 14 years of age. The rate of severe

	hypoglycemia was low and did not differ between the two study groups; however, the trial was not powered to detect such a difference
Conclusion	Study indicates that CGM improves glycated hemoglobin levels and may enhance the management of type 1 diabetes in adults who have the motivation to use this technology and the capability to incorporate it into their own daily diabetes management
Interpretation	The different age groups have varying results when it came to their glycated hemoglobin levels. This study received similar results for the age group 25 years old and older as other studies, that being a reduction in their HbA1c levels. However, when other ages groups are in comparison, ages 8-14 showed a decrease rate of reduction in their HbA1c levels, and almost no benefit in ages 15-24. The differences in reduction rates could be due to adherence to diabetes treatment management. In ages 8-14, parental guidance for treatment is still evident, but there can be a lag between treatments. When moving towards patient-only management, in ages 15-24, there are already studied effects of deterioration of glycemic control. There this study serves to show that HbA1c level reduction with the use of CGM is best used in those highly motivated patients who are able to assess daily diabetes management. Further work should be done with the lack of effectiveness in children and adolescents.

Title	Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: A COMISAIR Study NCT - N/A, not registered PMID 27482825
Design	Allocation: nonrandomized Intervention Model: Multi-Parallel Assignment Masking: None (open-label) Primary Purpose: To compare different treatment modalities for patients with type 1 diabetes (T1D) based on real-time continuous glucose monitoring (RT-CGM) or self-monitoring of blood glucose (SMBG) combined with multiple daily injections (MDIs) or continuous subcutaneous insulin infusion (CSII)
Population	N= 65 18 years and older Type 1 diabetes mellitus with insulin therapy
Arms	Experimental: rtCGM with sensor augmented insulin regimen rtCGM with MDI no rtCGM with CSII Control: MDI + SMBG
Endpoint(s)	Primary endpoint: reduction of HbA1c, glycemic variability (GV), and incidence of hypoglycemia
Inclusion Criteria	• Patients with diabetes for at least 2 years with insulin analogs • HbA1c level between 7.0% and 10%
Exclusion Criteria	• Use of personal real-time-CGM 3 months prior to study entry and during the study (except study devices) • Patients with ketoacidosis within the past 3 months • Severe noncompliance • Pregnancy or lactation period • Concomitant therapy influencing glucose metabolism • Severe known allergies (e.g. plaster)
Results	After a year, the baseline mean HbA1c in the SAIR group (8.3%) decreased to 7.1% ($P < 0.0001$); both SAIR subgroups, SAP and MDIs + RT-CGM, showed comparable improvement. The CSII group also had reduced HbA1c (8.4% – 0.9% vs. 7.9% – 0.7%; $P < 0.05$). Both SAIRs were superior to MDIs ($P = 0.002$) and CSII ($P = 0.0032$). GV was also lowered, both in the SAIR ($P < 0.0001$) and CSII ($P < 0.05$) groups. Reduced incidence of hypoglycemia was observed only with SAIR (8% – 4% vs. 6% – 3%; $P < 0.01$).
Conclusion	Both sensor-augmented insulin regimens, sensor augmented pump and MDIs + RT-CGM, provided significant and comparable decrease of HbA1c with concurrent reduction of hypoglycemia. This improvement was greater than that seen with CSII. The combination of RT-CGM and MDIs can be a suitable alternative to SAP for some patients.
Interpretation	This is one of the first studies to compare four different treatment strategies based on different combinations of insulin therapy. This, along with previous studies, has shown significant glycemic control benefits when using rtCGM. The results of rtCGM MDI are the reduction of HbA1c levels along with reduced time spent in hypoglycemia which are comparable to the superiority of SAP over CSII. Of note, the reduced time in hypoglycemia is not always described in previous studies. Therefore in patients with type 1 diabetes either SAP

	or MDI with rtCGM were superior to solely MDI or CSII in reducing HbA1c, hypoglycemia time, and other endpoints. The use of rtCGM+MDI is an alternative to for those unwilling to use a pump.

Title	CGM Treatment in Patients With Type 1 Diabetes Treated With Insulin Injections NCT 02092051 PMID 28118454
Design	Allocation: Randomized Intervention Model: Crossover Assignment Masking: None (open-label) Primary Purpose: To evaluate the effects of CGM in adults with type 1 diabetes treated with multiple daily insulin injections.
Population	N= 161 18 Years and older Type 1 diabetes mellitus with insulin therapy
Arms	Experimental: Continuous glucose monitoring with Dexcom G4 platina during 6 months Control: Conventional therapy during 6 months using only SMBG for glucose monitoring
Endpoint(s)	Primary endpoint: Difference in HbA1c between week 26 and week 69 [Time Frame: Week 26, week 69]
Inclusion Criteria	• Type 1 diabetes • HbA1c greater than or equal to 58 mmol/mol (7.5% DCCT standard)
Exclusion Criteria	• Pregnancy, planned pregnancy for the study duration or pregnancy during the last six months • Severe cognitive dysfunction or other disease, which is judged by the physician to be not suitable for inclusion. • Required continuous use of paracetamol. Paracetamol must not have been used the week before the study and shall not be used during CGM-use because it disturbs the interpretation of BG levels estimated by the DexComG4. However, other pain killers can be used throughout the study duration. • Current CGM use. (within the past 4 months • History of allergic reaction to any of the CGMS materials or adhesives in contact with the skin. • History of allergic reaction to chlorhexidine or alcohol antiseptic solution. • Abnormal skin at the anticipated glucose sensor attachment sites (excessive hair, burn, inflammation, infection, rash, and/or tattoo). • Patient is uncomfortable by using the sensor during the blinded run-in period and believes it is unlikely that he/she will use the sensor more than 80% of the time during the trial. • The patient has on average performed 12 or less calibrations per week during the run-in period. • Insulin pump therapy=Continuous subcutaneous insulin infusion (CSII) • Diabetes duration < 1 year • Participation in another study. • Fasting C-peptide level of 0.3 mmol/l or higher • eGFR < 30 ml/min (estimated from creatinine, age and sex at the inclusion visit by the MDRD-formula) • Planned house move during the next 1.5 years, making it difficult to come to study visits • Other investigator-determined criteria making patients unsuitable for participation.
Results	Among 161 randomized participants, mean age was 43.7 years, 45.3% were women, and mean HbA1c was 8.6% (70 mmol/mol). A total of 142 participants had follow-up data in both treatment periods. Mean HbA1c was 7.92% (63 mmol/mol) during CGM use and 8.35% (68 mmol/mol) during conventional treatment (mean difference, -0.43% [95% CI, -0.57% to -0.29%] or -4.7 [-6.3 to -3.1 mmol/mol]; P < .001). Of 19 secondary end points comprising psychosocial and various glycemic measures, 6 met the hierarchical testing criteria of statistical significance, favoring CGM compared with conventional treatment. Five patients in the conventional treatment group and 1 patient in the CGM group had severe hypoglycemia. During washout when patients used conventional therapy, 7 patients had severe hypoglycemia.
Conclusion	Among patients with inadequately controlled type 1 diabetes treated with multiple daily insulin injections, the use of CGM compared with conventional treatment for 26 weeks resulted in lower HbA1c.
Interpretation	This trial didn't have an upper limit to their patients HbA1c levels and the baseline was 8.7%, this gives better insight to those with less glycemic control over their type 1 diabetes. Less control for their glucose levels are demonstrated via their HbA1c levels and lack of SMBG despite the availability of free glucose meters and strips in Sweden where the study was performed. The use of CGM showed a significant reduction in HbA1c after 26 weeks and of note better psychosocial benefits as well.

Eversense E3

Title	Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial NCT 02154126 PMID 27815290
Design	Allocation: Nonrandomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Diagnostic
Population	N = 71 18 Years and older Type 1 or type 2 diabetes mellitus
Arms	Experimental: Accuracy assessment of Continuous Glucose Monitoring System
Endpoint(s)	Primary endpoint: The MARD for venous reference glucose values >4.2 mmol/L (75 mg/dL), defined as the average of the absolute difference of paired CGM system and YSI reading multiplied by 100
Inclusion Criteria	• Clinically confirmed diagnosis of diabetes mellitus for a duration of 1 year and uses insulin therapy for their diabetes management (including subjects on insulin pump therapy)
Exclusion Criteria	• Past 6 month history of severe hypoglycemia (e.g. loss of consciousness or seizure) or DKA • Significantly impaired hepatic function and renal failure • Known microvascular (diabetic) complications, including active proliferative diabetic retinopathy or macular edema, active non-proliferative retinopathy, diabetic nephropathy • Hematocrit >50% or <30% • Females lactating or pregnant or intending to become pregnant • A condition requiring or likely to require MRI
Results	The MARD value against reference glucose values >4.2 mmol/L (75 mg/dL) was 11.1% (95% CI 10.5, 11.7). Clarke Error Grid Analysis showed 99.2% of samples in the clinically acceptable error zones A and B. Eighty-one percent of hypoglycemic events were detected by the CGM system within 30 min. No device-related serious adverse events occurred during the study.
Conclusion	The results indicate the safety and accuracy of this new type of implantable CGM system and support it as an alternative for transcutaneous CGM.
Interpretation	This was the first PRECISE trial investigating the accuracy, longevity and safety, along with glycemic control data and self-reported quality of life. The use of the CGM device reduced mean glucose and HbA1c levels compared with baseline in 71 participants with type 1 and type 2 diabetes. A limited reduction of CGM measurement accuracy occurred in the last month of use, which may be a result of long-term degradation of the glucose-indicating gel. While the study reports accuracy with a MARD of 11.6%, further improvements are needed for the glucose calculation algorithm used within the system.

Title	A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor: PRECISE II NCT 02647905 PMID 29381090
Design	Allocation: Nonrandomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Diagnostic
Population	N = 90 18 Years and older Type 1 or type 2 diabetes mellitus
Arms	Experimental: Accuracy assessment of Continuous Glucose Monitoring System
Endpoint(s)	Primary endpoint: The MARD between paired Eversense and YSI reference measurements through 90 days post-insertion for reference BG values from 40 to 400 mg/dL
Inclusion Criteria	• Clinically confirmed diagnosis of diabetes mellitus for a duration of 1 year or greater
Exclusion Criteria	• Past 6 month history of severe hypoglycemia (e.g. loss of consciousness or seizure) or DKA requiring emergency room visit or hospitalization • Female subjects of childbearing capacity, who are lactating or pregnant, intending to become pregnant, or not practicing birth control

	• Symptomatic coronary artery disease (CAD); unstable angina; myocardial infarction, transient ischemic attack or stroke in the past 6 months; uncontrolled hypertension; current congestive heart failure; history of cardiac arrhythmia (benign PACs and PVCs allowed). Subjects with asymptomatic CAD (e.g. CABG, stent placement or angioplasty) may participate if negative stress test within 1 year prior to screening and documented clearance from cardiologist • Hematocrit <30% or >55% • History of hepatitis B, hepatitis C, or HIV
Results	The overall MARD value against reference glucose values was 8.8% (95% confidence interval: 8.1%–9.3%), which was significantly lower than the prespecified 20% performance goal for accuracy (P < 0.0001). Ninety-three percent of CGM values were within 20/20% of reference values over the total glucose range of 40–400 mg/dL. Clarke Error Grid analysis showed 99.3% of samples in the clinically acceptable error zones A (92.8%) and B (6.5%). Ninety-one percent of sensors were functional through day 90. One related SAE (1.1%) occurred during the study for removal of a sensor.
Conclusion	The Eversense CGM system provided accurate BG readings with a favorable safety profile.
Interpretation	This was the second pivotal trial, PRECISE II that compared favorably with the original trial. The updated Eversense system relocated the dexamethasone ring closer to the optical detection zone of the sensor and updated the software algorithm. The MARD value against reference glucose values was lower in the PRECISE II study than what was observed in the PRECISE study (8.8% vs. 11.1%). The new sensor and algorithm configuration also appears to provide greater sensor longevity through 90 days (91% vs. 82%) and greater accuracy in terms of confirmed detection rates for hypoglycemic (93% vs. 81%) and hyperglycemic (96% vs. 88%) events. Due to the fact that patients would need multiple sensors placed over their lifetime, long term surveillance studies are needed to ensure patient safety.

Title	A Prospective Multicenter Evaluation of the Accuracy and Safety of an Implanted Continuous Glucose Sensor: The PRECISION Study NCT 02647905 PMID 30925083
Design	Allocation: Nonrandomized Intervention Model: Single Group Assignment Masking: None (Open Label) Primary Purpose: Diagnostic
Population	N = 35 18 Years and older Type 1 or type 2 diabetes mellitus
Arms	Experimental: Accuracy assessment of CGM System
Endpoint(s)	Primary endpoint: Percentage system agreement and MARD between Eversense and Yellow Springs Instrument reference measurements from 40 to 400 mg/dL.
Inclusion Criteria	• Clinically confirmed diagnosis of diabetes mellitus for a duration of 1 year or greater
Exclusion Criteria	• Past 6 month history of severe hypoglycemia (e.g. loss of consciousness or seizure) or DKA • Significantly impaired hepatic function and renal failure • Known microvascular (diabetic) complications, including active proliferative diabetic retinopathy or macular edema, active non-proliferative retinopathy, diabetic nephropathy • Hematocrit >50% or <30% • Females lactating or pregnant or intending to become pregnant • A condition requiring or likely to require MRI
Results	Eighty-five percent of CGM values were within 15/15% of reference and the MARD value against reference was 9.6% (95% confidence interval [CI]: 8.9–10.4). All sensors were functional through day 90. No device- or procedure-related SAEs occurred. Application of the updated algorithm to PRECISE II sensor data resulted in 87% of readings within 15/15% of reference and an MARD value against reference of 8.5% (95% CI: 8.0%–9.1%).
Conclusion	PRECISION corroborated prior accuracy and safety findings of the Eversense CGM System through the 90-day sensor life. The updated algorithm improved accuracy of measurements in PRECISE II.
Interpretation	This is the last pivotal PRECISION study. It captured additional data on safety and accuracy with an updated glucose calculation algorithm. The results compared favorably to the PRECISE II study. Additional studies are needed to determine the long term safety associated with serial insertions and removals of the implant.

Formulary Placement, Utilization and Cost Experience (04-01-2024 to 06-30-2024)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
CGMs								
FreeStyle Libre 14 Day	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
FreeStyle Libre 2	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
FreeStyle Libre 3	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
FreeStyle Libre Reader Device	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexcom G6	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexcom G7	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Eversense E3	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guardian Connect	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Enlite	0	0	$0.00	$0.00	0	0 (0%)	NF	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

References

1. FreeStyle Libre. [https://www.freestylelibre.us/]. Abbott, Abbott Park, Illinois. Accessed on July 1, 2024.
2. Dexcom [https://www.dexcom.com/]. Dexcom, San Diego, California. Accessed on July 1, 2024,
3. Guardian. Medtronic. Available at: https://www.medtronic.com/. Accessed on July 1, 2024.
4. Eversense. Senseonics. Available at: https://www.eversensediabetes.com/. Accessed on July 1, 2024.
5. Devices@FDA. U.S. Food and Drug Administration. U.S. Department of Health & Human Services. Available at: https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm. Accessed on July 1, 2024.
6. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on July 1, 2024.
7. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on July 1, 2024.
8. American Diabetes Association Professional Practice Committee. 7. Diabetes Technology: Standards of Medical Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S126-S144.
9. Grunberger G, Sherr J, Allende M, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: The Use of Advanced Technology in the Management of Persons With Diabetes Mellitus. Endocr Pract. 2021;27(6):505-537.
10. Wright EE Jr, Kerr MSD, Reyes IJ, Nabutovsky Y, Miller E. Use of Flash Continuous Glucose Monitoring Is Associated With A1C Reduction in People With Type 2 Diabetes Treated With Basal Insulin or Noninsulin Therapy. Diabetes Spectr. 2021;34(2):184-189.
11. Evans M, Welsh Z, Ells S, Seibold A. The Impact of Flash Glucose Monitoring on Glycaemic Control as Measured by HbA1c: A Meta-analysis of Clinical Trials and Real-World Observational Studies. Diabetes Ther. 2020;11(1):83-95.
12. Bailey T, Bode BW, Christiansen MP, Klaff LJ, Alva S. The Performance and Usability of a Factory-Calibrated Flash Glucose Monitoring System. Diabetes Technol Ther. 2015 Nov;17(11):787-94.
13. Klonoff DC, Lias C, Vigersky R, Clarke W, Parkes JL, Sacks DB, Kirkman MS, Kovatchev B, and the Error Grid Panel. The Surveillance Error Grid. J Diabetes Sci Technol. 2014 Jul; 8(4): 658–672. Published online 2014 Jun 13.
14. Bolinder J, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R. Novel glucose-sensing technology and hypoglycaemia in type 1 diabetes: a multicentre, non-masked, randomised controlled trial. Lancet. 2016 Nov 5;388(10057):2254-2263.
15. Hoss U, Budiman ES, Liu H, Christiansen MP. Feasibility of Factory Calibration for Subcutaneous Glucose Sensors in Subjects With Diabetes. J Diabetes Sci Technol. 2014 Jan;8(1):89-94. Epub 2014 Jan 1.
16. Haak T, Hanaire H, Ajjan R, Hermanns N, Riveline JP, Rayman G. Flash Glucose-Sensing Technology as a Replacement for Blood Glucose Monitoring for the Management of Insulin-Treated Type 2 Diabetes: a Multicenter, Open-Label Randomized Controlled Trial. Diabetes Ther. 2017 Feb;8(1):55-73.
17. Christiansen MP, Klaff LJ, Bailey TS, Brazq R, Carlson G, Tweden KS. A Prospective Multicenter Evaluation of the Accuracy and Safety of an Implanted Continuous Glucose Sensor: The PRECISION Study. Diabetes Technol Ther. 2019 May;21(5):231-237.
18. Visser MM, Charleer S, Fieuws S, et al. Comparing real-time and intermittently scanned continuous glucose monitoring in adults with type 1 diabetes (ALERTT1): a 6-month, prospective, multicentre, randomised controlled trial. Lancet. 2021;397(10291):2275-2283.
19. Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet. 2018 Apr 7;391(10128):1367-1377.
20. Bailey TS, Chang A, Christiansen M. Clinical accuracy of a continuous glucose monitoring system with an advanced algorithm. J Diabetes Sci Technol. 2015 Mar;9(2):209-14.
21. Beck RW, Riddlesworth T, Ruedy K, et al. Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA. 2017 Jan 24;317(4):371-378.
22. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. N Engl J Med. 2008 Oct 2;359(14):1464-76.
23. Šoupal J, Petruželková L, Flekač M, et al. Comparison of Different Treatment Modalities for Type 1 Diabetes, Including Sensor-Augmented Insulin Regimens, in 52 Weeks of Follow-Up: A COMISAIR Study. Diabetes Technol Ther. 2016 Sep;18(9):532-8.
24. Lind M, Polonsky W, Hirsch IB, et al. Continuous Glucose Monitoring vs Conventional Therapy for Glycemic Control in Adults With Type 1 Diabetes Treated With Multiple Daily Insulin Injections: The GOLD Randomized Clinical Trial. JAMA. 2017 Jan 24;317(4):379-387.
25. Kropff J, Choudhary P, Neupane S, et al. Accuracy and Longevity of an Implantable Continuous Glucose Sensor in the PRECISE Study: A 180-Day, Prospective, Multicenter, Pivotal Trial. Diabetes Care. 2017;40(1):63–68.
26. Christiansen MP, Klaff LJ, Brazg R, et al. A Prospective Multicenter Evaluation of the Accuracy of a Novel Implanted Continuous Glucose Sensor: PRECISE II. Diabetes Technol Ther. 2018;20(3):197–206.
27. Christiansen MP, Klaff LJ, Bailey TS, Brazg R, Carlson G, Tweden KS. A Prospective Multicenter Evaluation of the Accuracy and Safety of an Implanted Continuous Glucose Sensor: The PRECISION Study. Diabetes Technol Ther. 2019;21(5):231–237.

Pancreatic Enzymes
Executive Summary

CLASS OVERVIEW

Pancreatic enzyme replacement therapy (PERT) is the mainstay of therapy for pancreatic insufficiency. Current marketed products approved by the FDA include Creon, Zenpep, Viokace, Pancreaze and Pertzye. All products are indicated for treatment of pancreatic insufficiency secondary to "other conditions"; Creon and Viokace are the only agents indicated in patients with pancreatectomy; Viokace is the only agent without an indication for use in cystic fibrosis patients. The guidelines for management of cystic fibrosis briefly discuss the use of PERT and do not deem one product preferable over another. Each agent used for PERT consists of amylase, protease and lipase. Among these three, lipase plays the most important role, and all the products are dosed according to lipase content. Viokace is the only agent which is not formulated with an enteric coating, and therefore is subject to rapid degradation in the duodenum due to low pH. To prevent such degradation, it is recommended to be administered concomitantly with H2 receptor antagonist or proton pump inhibitor to transiently raise the pH. Viokace may have modest benefit in alleviating pain associated with chronic pancreatitis in a specific subgroup of patients based on results of a single trial. This benefit has not been observed with the enteric coated formulations. Pertzye is a coated formulation which consists of bicarbonate, which may confer a theoretical benefit of not requiring other concomitant acid suppressants. All PERT agents are recommended to be administered with meals to help with fat absorption and to primarily act in the duodenum. All these agents are not interchangeable as they differ in amount of amylase, bioequivalence and dissolution rates, as evident in in-vitro studies. No near-term products were noted to be in development in the PERT class.

UTILIZATION FINDINGS

There were 9 claims for 5 members, for a total cost of $10,717.86 and an average cost per claim of $1,190.87. The most highly utilized medication was Creon with 9 claims. There were no prior authorization requests.

RECOMMENDATIONS

- No changes

CLINICAL SUMMARY

Pancreatic exocrine insufficiency (PEI) can be found in a multitude of patient populations. It is commonly observed in patients with cystic fibrosis, post-pancreatic procedures, chronic pancreatitis due to other conditions, such as celiac disease, and pancreatic malignancy. Pancreatic steatorrhea is the most common symptom of PEI but can be absent in some patients. The most practical test, and most commonly used for diagnosis of pancreatic insufficiency is 72-hour stool test, which measures amylase concentration in the stool; however, it can be unreliable in patients with mild disease or those who have diarrhea. Non-pharmacologic recommendations include reduction in fat intake; however, this is not recommended once PERT is initiated, and in patients with cystic fibrosis, fat intake has been associated with positive pulmonary outcomes. In patients with a compelling condition which is highly associated with PEI, once common symptoms appear, PERT should be initiated, and improvement in symptoms would be confirmatory of the diagnosis. The degree of fat malabsorption is indicative of the degree of PEI, hence early initiation of PERT is beneficial. Goal of PERT is to minimize malabsorption of fat, improve quality of life and extend prognosis. Initial doses for all agents, are based on similar weight-based dosing. Doses exceeding 6000units/kg/meal should be carefully increased and may warrant a 72-hour stool test, as higher doses have been associated with colonic strictures. Currently there are not direct comparator trials demonstrating superiority of any one product over another; however, the enteric coated formulations are generally preferred for management of PEI, whereas the non-coated formulation (Viokace) is preferred for management of abdominal pain associated with chronic pancreatic insufficiency.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Creon®	Treatment of exocrine pancreatic insufficiency in adult and pediatric patients	Age based dosing for Creon, Zenpep, Pertzye & Pancreaze for pancreatic insufficiency **0 to 12 months** –Zenpep and Creon 3000U/120mL of breast milk or formula. For Pertzye, use 4,000U/120mL. For Pancreaze use 2600U /120mL) **1 to 4 years** – 1000U/kg/meal, max 2500U/meal or 10000U/day or 4000U/g of fat ingested/day **4years or older** – 500U/kg/meal, max 2500U/meal or 10000U/day or 4,000U/1g of fat ingested/day Capsules can be opened & contents sprinkled on applesauce for administration. Contents should not be mixed with breast milk or formula but should rather be given before or after their administration. For snacks, doses are generally half of what patient is using for their meals.
Zenpep®	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions.	
Pancreaze®		
Pertzye®		
Viokace®	Viokace (pancrelipase) tablets, in combination with a proton pump inhibitor, are indicated in adults for the treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy.	For adult patients with pancreatic insufficiency secondary to chronic pancreatitis or pancreatectomy - 500U/kg/meal, max 2,500U/meal or 10,000U/day or 4,000U/1g of fat ingested/day with a proton pump inhibitor or H2-receptor antagonist.

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Creon®	None	None
Zenpep®		
Pancreaze®		
Pertzye®		
Viokace®		

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Creon®	**Fibrosing Colonopathy** – A rare and very serious side effect, it typically occurs in pediatric patients consuming doses higher than 6,000u/kg/meal for a prolonged period time. Benefit of such high doses should be justified by obtaining results from a 72hour fecal test **Potential for Irritation to Oral Mucosa** – retention of pancreatic enzyme products in the oral cavity may lead to mucosal irritation and enzymatic inactivity **Potential for Risk of Hyperuricemia** – all pancreatic enzymes are derived from porcine tissue and therefore contain purines, which have potential for increasing serum uric acid concentrations. Caution should be exercised in patients with underlying gout or hyperuricemia at baseline. **Potential Viral Exposure from the Product Source** –derived from porcine tissue, and therefore carry a theoretical risk of transmission of novel or unknown viruses that are not tested for in manufacturing process **Allergic Reactions** – patients who have history of severe allergies or anaphylaxis from porcine products may have such reactions from consumption of pancreatic enzymes. **Potential for Exacerbation of Symptoms of Lactose Intolerance** (Viokace only) **–** contain lactose monohydrate, patients with lactose intolerance may not be able to tolerate Viokace.
Zenpep®	
Pancreaze®	
Pertzye®	
Viokace®	

PRACTICE GUIDELINES

American Gastroenterological Association (AGA) Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review (2023). Available at: https://gastro.org/clinical-guidance/epidemiology-evaluation-management-exocrine-pancreatic-insufficiency/

Best practice advice

1. EPI should be suspected in patients with high-risk clinical conditions, such as chronic pancreatitis, relapsing acute pancreatitis, pancreatic ductal adenocarcinoma, cystic fibrosis, and previous pancreatic surgery.
2. EPI should be considered in patients with moderate-risk clinical conditions, such as duodenal diseases, including celiac and Crohn's disease; previous intestinal surgery; longstanding diabetes mellitus; and hypersecretory states (eg, Zollinger–Ellison syndrome).
3. Clinical features of EPI include steatorrhea with or without diarrhea, weight loss, bloating, excessive flatulence, fat-soluble vitamin deficiencies, and protein-calorie malnutrition.
4. Fecal elastase test is the most appropriate initial test and must be performed on a semi-solid or solid stool specimen. A fecal elastase level <100 µg/g of stool provides good evidence of EPI, and levels of 100–200 µg/g are indeterminate for EPI.
5. Fecal elastase testing can be performed while on pancreatic enzyme replacement therapy.
6. Fecal fat testing is rarely needed and must be performed when on a high-fat diet. Quantitative testing is generally not practical for routine clinical use.
7. Response to a therapeutic trial of pancreatic enzymes is unreliable for EPI diagnosis.
8. Cross-sectional imaging methods (computed tomography scan, magnetic resonance imaging, and endoscopic ultrasound) cannot identify EPI, although they play an important role in the diagnosis of benign and malignant pancreatic disease.
9. Breath tests and direct pancreatic function tests hold promise, but are not widely available in the United States.
10. Once EPI is diagnosed, treatment with pancreatic enzyme replacement therapy (PERT) is required. If EPI is left untreated, it will result in complications related to fat malabsorption and malnutrition, having a negative impact on quality of life.
11. PERT formulations are all derived from porcine sources and are equally effective at equivalent doses. There is a need for H2 or proton pump inhibitor therapy with non–enteric-coated preparations.
12. PERT should be taken during the meal, with the initial treatment of at least 40,000 USP units of lipase during each meal in adults and one-half of that with snacks. The subsequent dosage can be adjusted based on the meal size and fat content.
13. Routine supplementation and monitoring of fat-soluble vitamin levels are appropriate. Dietary modifications include a low-moderate fat diet with frequent smaller meals and avoiding very-low-fat diets.
14. Measures of successful treatment with PERT include reduction in steatorrhea and associated gastrointestinal symptoms; a gain of weight, muscle mass, and muscle function; and improvement in fat-soluble vitamin levels.
15. EPI should be monitored and baseline measurements of nutritional status should be obtained (body mass index, quality-of-life measure, and fat-soluble vitamin levels). A baseline dual-energy x-ray absorptiometry scan should be obtained and repeated every 1–2 years.

Pancreatic Enzymes Clinical Care Guidelines. Cystic Fibrosis Foundation (2019). Available at: https://www.cff.org/pancreatic-enzymes-clinical-care-guidelines#pancreatic-enzyme-replacement-therapy-recommendations.

Recommendations	Evaluation of the Evidence
1. Pancreatic insufficient patients should consume a high-calorie diet with unrestricted fat that is appropriate to age and clinical status. Such diets have been shown superior to low-fat diets in promoting growth and lung function.	Consensus
2. A nutritional assessment should be performed regularly as a component of routine care in patients with CF. Additional assessment should occur when dosing of PERT is altered.	Consensus
3. Enzyme dosing may be done either by grams of fat ingested or by weight. Dosing by grams of fat is more likely to mimic the normal pancreatic response to a meal, although weight-based dosing may be simpler and more convenient, particularly in older children and adults.	Consensus
4. Infants generally require 450-900 lipase units/g of fat, OR 2,000–4,000 lipase units per 120 ml of formula or when breastfeeding. Infants generally ingest a higher amount of fat/kg of body weight than do adults.	Consensus
5. Older children and adults generally require 500–4,000 lipase units per gram of fat ingested (mean, 1,800 lipase units/g of fat), OR 500-2,500 lipase units/kg/meal, 250-1,250 lipase units/kg/snack, with three meals and two to three snacks per day. It is suggested that initial dosing be in the lower range and titrated up as needed to treat malabsorption.	Consensus
6. Doses of enzyme exceeding 2,500 lipase units/kg/meal, or 4,000 lipase units/g of fat warrant further investigation. Doses of enzyme >6,000 lipase units/kg/meal have been associated with fibrosing colonopathy. It is not clear if doses >2,500 lipase units/kg/meal or >4,000 lipase units/g of fat are safe. It is also unlikely that higher enzyme doses will improve clinical condition in patients with CF and poor growth or gastrointestinal symptoms, thus it is recommended not to exceed these doses and that patients on higher doses be titrated down to a lower dosing range.	Consensus
7. Patients should receive only the product brands prescribed by their CF care center. Enteric-coated microencapsulated enzymes are the most effective treatment for PI in CF. Patients should not use health food store enzymes or enzymes without an enteric coating unless directed to do so by their CF physician.	Consensus
8. Enzyme capsules may be opened and the contents mixed with a small quantity of applesauce or another non-alkaline food, but they should not be crushed or allowed to sit in food. Enzymes may be inactivated by exposure to alkaline environments or prolonged contact with a moist environment.	Consensus
9. Enzymes should be stored in a cool, dry place and checked regularly for expiration dates.	Consensus
10. Signs and symptoms of poor response to enzyme therapy include abdominal complaints (bloating, flatus, abdominal pain, and loose, frequent stools or overt diarrhea) along with symptomatic steatorrhea (bulky, oily, foul stools) and/or poor growth. These symptoms may also be seen with other conditions. Before increasing enzymes as a result of symptoms, consider dietary factors, adherence issues, intestinal hyperacidity, abnormal intestinal motility, and liver disease with low intestinal bile salt content, as well as non-CF gastrointestinal disease.	Consensus
11. Fibrosing colonopathy should be considered in patients with CF who have evidence of obstruction, bloody diarrhea, or chylous ascites, or who have a combination of abdominal pain, ongoing diarrhea, and/or poor weight gain. Fibrosing colonopathy is characterized by colonic strictures. Its cause is unclear, but it has been associated with high doses of pancreatic enzyme supplements. Patients at highest risk include children younger than 12 years, patients taking >6,000 lipase units/kg/meal for more than 6 months, history of meconium ileus in infancy or distal intestinal obstruction syndrome, and history of previous intestinal surgery. Diagnosis is generally made by imaging or histopathology. Fibrosing colonopathy may respond to reduction of enzyme dose, particularly in the early stages, but in later stages colectomy may be required.	Consensus

Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee (2021). Available at: https://naspghan.org/wp-content/uploads/2021/02/Medical_Management_of_Chronic_Pancreatitis_in.30.pdf

Nutrition and endocrine

1. Patients with CP are at risk for macro- and micronutrient deficiencies. Patients should be monitored for growth and pubertal delay, dietary intake, and fat-soluble vitamin deficiencies. Growth and intake should be reviewed at every clinic visit, a minimum of every 6 to 12 months. Fat-soluble vitamin laboratory analysis should occur every 12 to 18 months or as clinically indicated. 1B
2. A multidisciplinary approach that includes a clinical pediatric dietitian is needed to adequately monitor nutritional status, evaluate nutrient intake and provide education and recommendations to help prevent both malnutrition and obesity. 1C
3. There is a clear role for PERT in children with CP who have EPI with steatorrhea, poor growth and/or nutritional deficiencies. PERT dosing for CP-associated EPI is similar to that used in patients with CF. 1B
4. Children with CP should be screened yearly for pancreatogenic DM with a fasting glucose and HbA1c level. 1C
5. Consider OGTT if pre-diabetes is present based on abnormal fasting glucose (100–125 mg/dL) and/or HbA1c level (5.7%–6.4%). OGTT should be performed annually once a patient is considered to have pre-diabetes. 1C
6. Chronic pancreatitis patients with diabetes should be referred to a pediatric endocrinologist to optimize glucose management and determine if evaluation for other forms of DM should be considered. 1B
7. It is important to address clinical symptoms of malabsorption and PERT in children with CP and DM to improve glycemic control. 1C
8. Insufficient data exists to recommend the use of antioxidants as a treatment to prevent EPI or other disease progression in children with CP. 2C

Pain management

9. Treatment of pain in pediatric CP requires a multidisciplinary approach, ideally involving a pediatric pain physician, pediatric gastroenterologist, psychologist, nurse, and physical therapist. 1B
10. Cognitive behavioral Therapy (CBT) should be considered in management of pediatric CP pain. 1B
11. Physical therapy may be considered as an adjunct therapy for pain management in children with CP. 2B
12. There is insufficient data to recommend PERT as therapy for pain in children without EPI. 1B
13. There is insufficient data to recommend antioxidants, steroids, leukotriene antagonists, or somatostatins in the management of pain for children with CP. 2C
14. Analgesic pain management in CP should follow an ‘‘analgesic ladder’’ that incorporates the layering of non-opioid and opioid medications. Ideally this should be directed by a pain specialist working in partnership with a pancreatologist or gastroenterologist. 1B
15. Neuromodulators may be effective in treating pain in children with CP as part of a multidisciplinary approach. 1C
16. Celiac plexus block for pain has not been shown to be effective in children with CP and cannot be recommended. 1C
17. Children with CP suffering from pain refractory to standard medical management should be evaluated at a center with pediatric experience in pain management. 1C

Lifestyle modifications

18. On the basis of long-term adult data, providers should caution patients about the acute and chronic negative effects of alcohol abuse on pancreatic health. 1B
19. Health-care providers should caution patients about the dose-dependent response of tobacco smoking on the development and progression of CP among adult patients and should advise against smoking. 1A
20. Data are limited regarding the impact of weight and BMI on CP outcomes, as such, providers should counsel patients and parents about a balanced healthy diet and lifestyle. 1C
21. Administering a survey tool to assess QOL and/or functional assessment among pediatric patients to assess degree of impairment and drive targeted interventions indicated. 2C

Sequelae of disease

22. The majority of pancreatic fluid collections will resolve spontaneously with supportive care. Intervention is reserved for complications from mass-effect, infection/necrosis or if spontaneous regression of the collection is thought to be unlikely. 1B
23. Children with CP that continue to exhibit abdominal pain, bloating or other GI concerns deserve an appropriate GI workup to evaluate for other etiologies that may explain their symptoms. 1C

CP = chronic pancreatitis; DM = diabetes mellitus; EPI = exocrine pancreatic insufficiency; GI = gastrointestinal, OGTT = oral glucose tolerance test; PERT = pancreatic enzyme replacement therapy; QOL = quality of life.

GRADE level definitions

Class/Level	Definition
1	Strong recommendation
2	Weak recommendation
A	High quality of evidence
B	Moderate quality of evidence
C	Low quality of evidence
GPP	Good practice point

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Shafiq N, Rana S, Bhasin D. Pancreatic enzymes for chronic pancreatitis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006302.	Cochrane review which evaluated the efficacy of various pancreatic enzyme formulations for use in chronic pancreatitis. Main objective was to evaluate results of trial with PERT vs. placebo, comparing different types of PERT, comparison of different doses of PERT. Published and unpublished data were collected, and both randomized and non-randomized trials, as well as blinded and non-blinded trials were assessed. Ten trials were identified and evaluated	Multiple outcomes were assessed across heterogeneous trials. These included: change in frequency of abdominal pain, duration of pain episodes, intensity of pain, weight loss, steatorrhea, fecal fat content and quality of life.
Results: Due to small sample sizes and significant heterogeneity among the trials overall results were difficult to pool, and therefore were inconclusive. **Conclusion**: The authors concluded that despite inability to pool different trials for specific primary endpoint, each trial showed benefit in various endpoints and manifestations associated with chronic pancreatitis and improvement in quality of life when PERT was used.		

Citation	Design	Endpoints
Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010 Oct;105(10):2276-86.	This was a double-blind, randomized, multi-country, placebo-controlled, parallel-group trial enrolling patients ≥18 years old with confirmed exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery conducted in clinical research centers or hospitals. After a 5-day placebo run-in period (baseline), patients were randomized to pancrelipase (CREON) (72,000 lipase units per meal; 36,000 per snack) or placebo for 7 days. All patients received an individually designed diet to provide at least 100 g of fat per day. Primary efficacy endpoint was analyzed using non-parametric analysis of covariance.	• The primary efficacy measure was the change in coefficient of fat absorption (CFA) from baseline to end of the double-blind period • Secondary outcomes included: the coefficient of nitrogen absorption (CNA), clinical symptoms, and safety parameters.
Results: In total, 25 patients (median age of 54 years, 76% male) received pancrelipase (CREON) and 29 patients (median age of 50 years, 69% male) received placebo. The mean standard deviation change from baseline in coefficient of fat absorption was significantly greater with pancrelipase vs. placebo: 31.9 ± 18.6 vs. 8.7 ± 12.4 % (P <0.0001) [corrected]. Similarly, the mean standard deviation change from baseline in coefficient of nitrogen absorption was greater for pancrelipase vs. placebo: 35.2 ± 29.1 vs. 8.9 ± 28.0 % (= 0.0005) [corrected].Greater improvements from baseline in stool frequency, stool consistency, abdominal pain, and flatulence were observed with CREON vs. placebo. Treatment-emergent adverse events were reported in five patients (20.0%) in the CREON group and in six (20.7%) in the placebo group; the most common were gastrointestinal (GI) events and metabolism/nutrition disorders. There were no treatment discontinuations due to adverse events secondary to he treatment. **Conclusion**: The authors concluded that CREON 12,000-lipase unit capsules were effective in treating fat and nitrogen maldigestion with an adverse event rate similar to that of placebo in patients with EPI due to chronic pancreatitis or pancreatic surgery		

Citation	Design	Endpoints
Toskes PP, Secci A, Thieroff-Ekerdt R; ZENPEP Study Group. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011 Apr;40(3):376-82.	This was a randomized, double-blind, dose-response, crossover study with a run-in phase with placebo of 7 to 9 days and two treatment periods of 9 to 11 days, which consisted of a high dose treatment (seven capsules of 20,000 units of lipase per day) and a low-dose treatment (defined as seven capsules of 5,000units of lipase per day). Patients in each arm were monitored in hospital during baseline run in period, or one of the two cross over periods for the high or low dose, respectively. Inclusion criteria: age over 18 years old, women of childbearing potential must be using birth control throughout the duration of the study, documented diagnosis of	• Primary endpoint was comparison of coefficient of fat absorption between placebo, high dose and low dose groups. • Secondary endpoints include change from placebo baseline in coefficient of fat absorption in high dose and low dose groups during hospital treatment;

	chronic pancreatitis, mean coefficient of fat absorption is less than 20% and documented diagnosis of PEI exists and informed consent Exclusion criteria: unable to give informed consent, participation in another clinical trial within 30 days of enrollment, diagnosis of cystic fibrosis, excessive alcohol consumption, known drug abuse, uncontrolled diabetes mellitus, pregnancy or lactation, evidence of gastric or duodenal ulcer, presence of HIV infection, presence of hyperuricemia, presence of chronic inflammatory bowel disease, presence of acute biliary disease, known pork allergy, known fat absorption secondary to metabolic disease or surgery not leading to PEI, presence of viral hepatitis, known severe atopic predispositions.	change from placebo baseline in coefficient of nitrogen absorption during hospital treatment; change from placebo baseline in weight at end of each treatment period; change from placebo baseline in body mass index at the end of treatment
Results: Mean CFA was significantly higher with low- (88.9%) and high-dose (89.9%) ZENPEP versus placebo run-in (82%; P < 0.001; n = 72) with no difference between doses (P = 0.228, primary end point). In patients with baseline CFA less than 90% (n = 33), the high dose was significantly more effective (CFA: 84.1%) than the low dose (CFA: 81.1%; P < 0.001). Post hoc analysis revealed an increase in treatment effect with more severe PEI. Coefficient of nitrogen absorption (P < 0.001), body weight (P ≤ 0.021), and body mass index (P ≤ 0.020) also increased significantly with both doses compared with baseline. Percentage of days with EPI symptoms decreased with both doses. **Conclusion**: The trial demonstrates clear benefit of Zenpep over placebo. Patients with more severe baseline PEI tended to benefit more from the use of Zenpep and warranted higher dosing.		

Citation	Design	Endpoints
Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas. 2009 Aug;38(6):693-9.	Open label study in infants below the age of 24 months. Subjects had confirmed diagnosis of cystic fibrosis with exocrine pancreatic insufficiency and coefficient of fat absorption of greater than 70%. Study sample size was N=12 and study duration was 8 weeks.	• Primary endpoint was change in the coefficient of fat absorption after two weeks of treatment. • Secondary endpoints were not well defined, but loss in mean stool fat and mean fecal energy loss were also reported.
Results: After two weeks of treatment with pancrelipase (CREON), there was a statistically significant increase in the mean CFA from baseline (84.7 vs 58.0%; P=0.0013). There was a statistically significant reduction in mean stool fat (from 13.3 to 5.3 g/d; P=0.001) and mean fecal energy loss (from 238.5 to 137.9 kJ/d; P=0.018) after two weeks of pancrelipase treatment. Dietary fat intake did not change, whereas an improvement was observed in stool frequency and characteristics. Patient weight and height increased over eight weeks of treatment with pancrelipase. No serious adverse event was reported. **Conclusion**: The authors concluded that CREON significantly reduced fat malabsorption in patients when compared with placebo and was well tolerated. This trial supports the use of CREON in pediatric patients, especially in infants, however the very small sample size enables confounding and provides lesser representation of various patient characteristics.		

Citation	Design	Endpoints
Trapnell BC1, Strausbaugh SD, Woo MS, Tong SY, Silber SA, Mulberg AE, Leitz G. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due	This study had multiple phases. Initially, there was a screening phase for 7 days, followed by an open label, run-in phase, which was 14 days or shorter, followed by less than or equal to 7 days of placebo-controlled withdrawal phase. During the screening phase, patient's current PERT was discontinued, high fat meals were provided, and based on overall lipase requirements, PANCREAZE was initiated to a dose of maximum 10,000 lipase units/kg/day. Patients who achieved a coefficient of	• The primary efficacy endpoint was change in percent CFA between the 72-hour stool collections at the end of the open-label phase and double-blind phase. Fat intake (dietary fat) and fat excretion (fecal fat) data were used to

to cystic fibrosis. J Cyst Fibros. 2011 Sep;10(5):350-6	fat absorption of greater than 80% were randomized to receive placebo or PANCREAZE and were assessed based on their 72-hour stool test. This randomization was conducted during the double-blind phase. The study was conducted in US only across 11 different centers in patients ranging in age from 7 years old to 60 years old. Inclusion criteria: confirmed diagnosis of cystic fibrosis by either genetic testing or sweat test. Confirmed pancreatic exocrine insufficiency based on 72-hour stool test. Achieving coefficient of fat absorption greater than 80% to continue to the randomized, double blinded phase. Exclusion criteria: extreme cachexia, defined as BMI less than 10th percentile, severe/acute pulmonary disease unrelated to complications of cystic fibrosis; exacerbation of CF pulmonary disease≤1 month before screening; congenital anomalies of gastrointestinal tract; distal intestinal obstruction syndrome≤6 months of screening or requirement of surgical management to treat; hypersensitivity to porcine products; clinically significant gastrointestinal symptoms (e.g., vomiting, constipation); or disease or disorder that could interfere with assessment of study drug. Participants were excluded if they were taking drugs affecting blood uric acid concentrations or prokinetic agents (e.g., metoclopramide, cisapride,)≤30 days of screening; concurrent supplemental enteral nutrition; immunosuppressant agents for organ transplantation; or systemic steroid therapy. Females were excluded if pregnant, planning to become pregnant, or nursing.	calculate fecal fat excretion per 24 h, which was determined from the 72-hour stool collection. Percent CFA was calculated as: Percent CFA={[Fat intake (grams)−Fat excretion (grams)]/Fat intake (grams)}×100. • A key secondary variable was change in coefficient of nitrogen absorption (CNA), a surrogate for protein absorption, from the open-label phase to the double-blind phase. The ingested nitrogen was determined from diet records, and nitrogen excretion measurements comprised total nitrogen (fecal, in grams) for each 72-hour stool collection period. Percent CNA was calculated as: Percent CNA={[nitrogen intake (grams)−nitrogen excretion (grams)]/nitrogen intake (grams)}×100. • Another key secondary variable was prevention of the clinical signs and symptoms of EPI (abdominal pain, bloating, diarrhea, greasy stools, vomiting) during the double-blind phase. Overall improvement in health from the open-label phase to the double-blind phase was assessed using a self-reported global assessment of change (GAC) scale (0=worse, 1=same, 2=better, and 3=excellent).
Results: The mean CFA was similar in PANCREAZE® and placebo groups at baseline but was markedly higher in the PANCREAZE® group than the placebo group in the double-blind withdrawal phase. The CFA between open-label and double-blind phases (primary endpoint) was similar for the PANCREAZE® group but was markedly lower in the placebo group. The change in CFA for individual participants ranged from +8% to −16% in the PANCREAZE® group and from 0% to −75% in the placebo group. The primary endpoint results were similar for pediatric and adult patients. **Conclusion**: The study demonstrated effectiveness of PANCREAZE® in treatment of exocrine pancreatic insufficiency in cystic fibrosis patients, both children and adults, with minimal adverse events, which were not significantly different from those experienced within the placebo group.		
Citation	**Design**	**Endpoints**

Taylor CJ, Thieroff-Ekerdt R, Shiff S. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. J Cyst Fibros. 2016 Sep;15(5):675-80.	This was a randomized, double blind, active-controlled, cross-over, multinational, non-inferiority trial which compared Creon with Zenpep. Sample size was n=96. Patients were enrolled on a maintained baseline PERT regimen. Once enrolled, they initiated a diet that consisted of 100g/day of fat. Patients were assigned to either a Creon group or a Zenpep group. Without a washout, the patient was switched to the respective group, with the treatment dose being as close as possible to baseline PERT dose. After 28 days of treatment, patients were switched to the other group for another 28 day time period. Inclusion criteria: Confirmation of cystic fibrosis with a genotype test in addition to presence of a clinical feature, or with a sweat test. Documentation of pancreatic exocrine insufficiency with a 72-hour stool test. Adequate nutritional status, defined as a BMI of at least 19kg/m^2 for adults or BMI greater than or equal to 10th percentile for pediatric patients. Exclusion criteria were presence of one or more severe cardiac, renal, metabolic or gastrointestinal comorbidities.	• The primary efficacy endpoint was coefficient of fat absorption over 72-hour period • Secondary endpoints included change in body weight, coefficient of nitrogen absorption, signs and symptoms of exocrine pancreatic insufficiency, as noted in patient's self-recorded diary, as well as overall impact on overall health, activities of daily living, etc. as recorded in Cystic Fibrosis Questionnaire – Revised
Results: Overall patient characteristics and distributions were similar across both Creon and Zenpep groups. Overall, mean age was 19.2 years and males represented approximately 60% of the sample size. For the primary efficacy endpoint (coefficient of fat absorption over 72 hours), Zenpep demonstrated equivalence to Creon. Their mean coefficients of absorptions were 84.1% (SE 1.1) and 85.3 (SE 1.1), respectively. Difference in least squared means was 1.3% (95% CI: -3.6 to 1.1, p=0.297). This was well within the pre-defined non-inferiority margin of -5% to 5%. Secondary endpoints were similar as well. Coefficients of nitrogen absorption for Creon and Zenpep were 82.0 (SE 1.2) and 80.9 (SE 1.2), respectively. The LS mean difference between the two CNA was -1.1 (95% CI: -3.3 to 1.2, p=0.334). The average number of stools per day was also similar between the two groups, 1.5(SE 0.1) for Zenpep and 1.5(SE 0.1) for Creon. There were no statistically significant differences between Zenpep and Creon groups when comparing treatment emergent adverse events.		
Citation	**Design**	**Endpoints**
Konstan MW, Accurso FJ, Nasr SZ, Ahrens RC, Graff GR. Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. Clinical investigation. 2013;3(8):723-729.	This was a randomized, double blind, placebo-controlled, cross-over study. There were six well defined disparate periods during the study: A 4-day screening period (to determine eligibility), a 7 to 10 days of dose stabilization period (allowing optimal dosing of PERT), two separate 6 to 8 days of treatment periods (buffered pancrelipase and placebo cross-over) which were separated by 7 to 10 days of washout and dose stabilization periods. The dose optimization phases were open labeled. **Inclusion criteria**: age 7 years or above; confirmed diagnosis of cystic fibrosis, confirmed diagnosis of EPI; patients must currently be using PERT to manage EPI; adequate nutritional status (defined as BMI greater than or equal to fifth percentile for patients 7 years to 20 years old; for patients above the age of 20 years, BMI greater than 16.0 for females, and BMI greater than 16.5 for males. Patients received controlled, high-fat diet, with fat content calculated as 2g of fat/kg/day. 72-hour stool assessment was used to calculate the coefficients of fat and nitrogen absorption	• Primary endpoint: absolute mean difference between the coefficients of fat and nitrogen absorption. The authors determined that an overall sample size of 20 would allow for 90% power while evaluating these endpoints. • Secondary endpoint was treatment emergent adverse events.
Results: 21 subjects completed the study. Mean lipase doses during different study phases were as follows: 1406 units during dose stabilization, 1557 during washout and restabilization period, and 1565 during treatment period. A mixed-model analyses was conducted with fixed effects for age group, treatment sequence, treatment group,		

period, age × sequence interaction, age × treatment interaction and a random effect for subject within age × sequence. Mean fat intake was 109 ± 30 and 114 ± 39 g/day ± SD during active and placebo treatment, respectively (p = 0.23). Mean protein intake was 109 ± 33 and 107 ± 31 g/day ± SD during active and placebo treatment, respectively (p = 0.54), finding no statistically significant difference between the two treatment groups. Overall, there was a statistically significant improvement in both fat and nitrogen absorption for active treatment over placebo treatment. Mean CFA was 82.5% during active treatment versus 46.3% during placebo treatment, an absolute difference of 36.2 representing a 78.2% improvement for active treatment over placebo (p < 0.001). Mean CNA was 79.0% during active treatment versus 47.2% during placebo treatment, an absolute difference of 31.8%, representing a 67.4% relative improvement for active treatment over placebo (p < 0.001). Differences in CFA and CNA in favor of active treatment over placebo remained significant when comparing treatments within age subgroups. Subjects experienced statistically significant decreases in mean stool frequency (bowel movements) and mean stool weight over the 72-h stool collection period during active treatment compared with placebo treatment. Overall, the number of bowel movements decreased 40% (p < 0.001) and mean stool weight decreased by 50%. Incidence of treatment emergent adverse events was similar between the two groups. Patients within the placebo group complained more frequently of gastrointestinal symptoms.

Conclusion: Despite similar intake of fat and protein between the placebo and buffered pancrelipase groups, the coefficients of fat and nitrogen absorption were statistically significantly different between the two groups, favoring active treatment group.

Citation	Design	Endpoints
Anthera. A Phase 3, Randomized, Open-Label, Assessor-Blind, Non-Inferiority, Active-Comparator Study Evaluating the Efficacy and Safety of Liprotamase in Subjects With Cystic Fibrosis-Related Exocrine Pancreatic Insufficiency. Available from:https://clinicaltrials.gov/ct2/show/NCT03051490. NLM identifier: NCT03051490. Accessed March 8, 2018 Duffy, S. Sollpura Falls Short in Exocrine Pancreatic Insufficiency Trial. eMPR. U S A. In press March 13, 2018	This was a phase 2, randomized, open-label, assessor-blind, non-inferiority, active controlled trial comparing effectiveness of liprotamase with that of porcine pancrelipase (Pancreaze). Sample size was 140 participants. **Inclusion Criteria:** Confirmed diagnoses of cystic fibrosis and pancreatic exocrine insufficiency; good disease control with PERT prior to enrollment and good nutritional status. **Exclusion Criteria:** History of fibrosing colonopathy, distal intestinal obstruction syndrome in 6 months prior to screening, use of enteral tube feedings, chronic diarrhea unrelated to PEI, liver function test anomalies, history of liver or lung transplant, or significant bowel resection, FEV1<30%	• Primary endpoint was non-inferiority of coefficient of fat absorption between the two treatment groups. • Secondary endpoints were non-inferiority of coefficient of nitrogen absorption and treatment emergent adverse events between the two groups.

Results: The results are currently unpublished on clinicaltrials.gov and are not published in literature; however, a press release from Anthera pharmaceuticals confirms that liprotamase failed to meet both primary endpoint and one of the key secondary endpoints (i.e. coefficient of nitrogen absorption)

Conclusion: Liprotamase is inferior to Pancreaze when coefficients of fat and nitrogen absorption are compared between the two groups.

Citation	Design	Endpoints
Phillip P. Toskes, Grazyna Rydzewska, Jean-René Basque, Valérie Ratheau, Ivan T. Shaw. M1387 Safety and Efficacy of Immediate-Release Pancrelipase, Viokase®16, With Proton Pump Inhibitor Therapy for Correction of Steatorrhea in Patients With Chronic Pancreatitis With Exocrine Pancreatic Insufficiency. Gastroenterology. 2010:May;Vol. 138, Issue 5, S-394	This was a randomized, double blind, placebo controlled, parallel study which evaluated the efficacy of Viokace in comparison to placebo while treating EPI associated with chronic pancreatitis. Patients were randomized at 2:1 ratio for Viokace and placebo groups, respectively. All patients were enrolled with a baseline proton pump inhibitor (PPI) or were initiated on omeprazole 20mg per day. All subjects were confirmed to have pancreatic insufficiency by both the pancreatic elastase test and coefficient of fat absorption	• Primary endpoint was the difference between coefficients of fat absorption between placebo and Viokace • Secondary endpoints included stool frequency and safety assessments

Results: The mean CFA for subjects on VIOKASE®16 was 85.5% ± 8.9 and 58.0% ± 24.2 for subjects on Placebo (p<0.0001). Mean CFA during the washout phase was 47.6% ± 24.1 in the Viokace group and 56.6% ± 22.2 for Placebo. The change in CFA from washout phase to treatment phase for subjects on Viokace was 38.0% ± 25.4 compared to 1.4% ± 13.3 for subjects on Placebo. Viokace was superior to Placebo for improving stool frequency (1.93 ± 0.99 daily movements for Viokace and 2.33 ± 0.95 for Placebo; p=0.0083)

Conclusion: Viokace was more effective compared to placebo in the primary efficacy endpoint.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (04-01-2024 to 06-30-2024)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Enteric Coated Formulations								
Creon® 3k-9.5k-15k, 6k-19k-30k, 12k-38k-60k, 24k-76k-120k, 36k-114k-180k capsule	9	5	$10,717.86	$1,190.87	0	0 (0%)	F-AL >21	No change
Pertzye® 4k-14375, 8k-28.75k, 16k-57.5k, 24k-86.25k capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pancreaze® 4.2k-14.2k, 10.5k-35.5k, 16.8k-56.8k, 21k-54.7k, 2.6k-8.8k, 37k-97.3k capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Zenpep® 20k-63-84k, 40k-126k-168k, 5k-17k-24k, 25k-79k-105k, 10-32-42k, 15-47-63k, 3-10-14k, 60k-189,600-252,600 capsule	0	0	$0.00	$0.00	0	0 (0%)	F-AL >21	No change
Non-Enteric Coated Formulation								
Viokace® 10.4k-39.15k, 20.88k-78.3k tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**9**	**5**	**$10,717.86**	**$1,190.87**	**0**	**0 (0%)**		

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

REFERENCES

1. National Guideline Clearinghouse (NGC). Guideline summary: Cystic fibrosis: diagnosis and management. In: National Guideline Clearinghouse (NGC) [Web site]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2017 Oct 25. [cited 2018 Mar 08]. Available: https://www.guideline.gov
2. Toouli J1, Biankin AV, Oliver MR, et al. Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations.
3. Shafiq N, Rana S, Bhasin D. Pancreatic enzymes for chronic pancreatitis. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006302.
4. Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: A double-blind randomized trial. Am J Gastroenterol. 2010 Oct;105(10):2276-86. doi: 10.1038/ajg.2010.201. Epub 2010 May 25.
5. Toskes PP1, Secci A, Thieroff-Ekerdt R; ZENPEP Study Group. Efficacy of a novel pancreatic enzyme product, EUR-1008 (Zenpep), in patients with exocrine pancreatic insufficiency due to chronic pancreatitis. Pancreas. 2011 Apr;40(3):376-82. doi: 10.1097/MPA.0b013e31820b971c.
6. Colombo C, Fredella C, Russo MC, et al. Efficacy and tolerability of Creon for Children in infants and toddlers with pancreatic exocrine insufficiency caused by cystic fibrosis: an open-label, single-arm, multicenter study. Pancreas. 2009 Aug;38(6):693-9. doi: 10.1097/MPA.0b013e3181a85eaf.
7. Trapnell BC1, Strausbaugh SD, Woo MS, Tong SY, Silber SA, Mulberg AE, Leitz G. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros. 2011 Sep;10(5):350-6. doi: 10.1016/j.jcf.2011.04.005. Epub 2011 May 31.
8. Taylor CJ, Thieroff-Ekerdt R, Shiff S. Comparison of two pancreatic enzyme products for exocrine insufficiency in patients with cystic fibrosis. J Cyst Fibros. 2016 Sep;15(5):675-80. doi: 10.1016/j.jcf.2016.02.010. Epub 2016 Mar 21.
9. Ramsey, Mitchell L., Darwin L. Conwell, and Phil A. Hart. "Complications of Chronic Pancreatitis." *Digestive diseases and sciences* 62.7 (2017): 1745–1750. *PMC*. Web. 13 Mar. 2018.
10. Konstan MW, Accurso FJ, Nasr SZ, Ahrens RC, Graff GR. Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. Clinical investigation. 2013;3(8):723-729. doi:10.4155/cli.13.62.
11. Anthera. A Phase 3, Randomized, Open-Label, Assessor-Blind, Non-Inferiority, Active-Comparator Study Evaluating the Efficacy and Safety of Liprotamase in Subjects With Cystic Fibrosis-Related Exocrine Pancreatic Insufficiency. Available from:https://clinicaltrials.gov/ct2/show/NCT03051490. NLM identifier: NCT03051490. Accessed March 8, 2018
12. Duffy, S. Sollpura Falls Short in Exocrine Pancreatic Insufficiency Trial. eMPR. U S A. In press March 13, 2018
13. Whitcomb DC, Buchner AM, Forsmark CE. AGA Clinical Practice Update on the Epidemiology, Evaluation, and Management of Exocrine Pancreatic Insufficiency: Expert Review. *Gastroenterology*. 2023;165(5):1292-1301. doi:10.1053/j.gastro.2023.07.007.
14. Pancreatic Enzymes Clinical Care Guidelines. Cystic Fibrosis Foundation (2019). Available at: https://www.cff.org/pancreatic-enzymes-clinical-care-guidelines#pancreatic-enzyme-replacement-therapy-recommendations.
15. Freeman AJ, Maqbool A, Bellin MD, et al. Medical Management of Chronic Pancreatitis in Children: A Position Paper by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Pancreas Committee. *J Pediatr Gastroenterol Nutr*. 2021;72(2):324-340. doi:10.1097/MPG.0000000000003001.

Alameda MRGs for review Q3 2024 P&T Consent Agenda

Recommendation: No changes

Physician Administered Medication (PAD)/ Medical Benefit Guidelines	
Therapeutic Classes (AHFS)	N/A
Medications	Physician Administered Medications (PAD) under the medical benefit
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** Up to a 6 month duration depending upon the diagnosis and usual treatment therapies **Later Approvals** Up to a 12 month duration depending upon the diagnosis and usual treatment therapies If criteria is not met, request will be sent to a clinical reviewer for medical necessity review.
PA Review Criteria	****Medications falling under the physician administered drug/ medical benefit will be reviewed by AAH. Forward requests to AAH for review**** **Initial Authorization:** • Approve if: ○ Medication or product is administered by a healthcare professional AND ○ The medication will be provided via the Medical Benefit AND ○ Appropriate diagnosis/indication for requested medication or meets criteria below AND ▪ Medication is being requested for an accepted off-label use and is listed in the standard clinical decision support resources (as noted in Diagnosis section above) OR ▪ Requested use can be supported by at least two published peer reviewed clinical studies which must be submitted along with request ○ Requested quantity does not exceed FDA approved or standard off-label dose OR • Member is new to the plan (within the last 6 months) and the request is for continuation of therapy. Approve if: ○ Continuation of therapy is clinically appropriate AND ○ Medication or product is administered by a healthcare professional AND ○ Prescriber attests that member has been on this medication continuously before joining AAH AND ○ Request is for generic or single source brand AND ○ The diagnosis and dosage provided meets FDA labeling and/or drug-specific criteria or off-label criteria **Reauthorization:** • Continuation of therapy is clinically appropriate AND

	• Medication or product is administered by a healthcare professional under the Medical Benefit
Criteria Statement	N/A
Last P&T Review Date	9/2024

Recommendation: No changes

Off-label uses	
Therapeutic Classes (AHFS)	N/A
Medications	Formulary, Formulary PA required, Formulary, ST required, or Non-formulary medications with off-label uses
Covered Uses	Off-Label indications (medically accepted indications are defined using the following sources: American Hospital Formulary Service-Drug Information (AHFS-DI), Truven Health Analytics Micromedex DrugDEX (DrugDEX), National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium, Wolters Kluwer Lexi-Drugs, and Elsevier/Gold Standard Clinical Pharmacology and/or positive results from two peer-reviewed published studies.
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 criteria for approval:**
	• One of the following:
	  ◦ Patient has had a documented trial and or intolerance with up to two preferred medications used to treat the documented diagnosis, or 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 patient's specific diagnosis as referenced in the medical compendia
	AND
	• One of the following:
	  ◦ 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)
	  ◦ Requested use can be supported by at least two published peer reviewed clinical studies which must be submitted along with request
	AND
	• Medication is being requested at an appropriate dose per literature
	
	Reauthorization criteria for approval:
	• Patient is stable and continuing the medication AND
	• Medication is used for appropriate indication and at appropriate dose

Criteria Statement	Medications for off-label use are reserved for members who have a medication being requested at an appropriate dose per the medical literature AND have used (or cannot should not use) up to two preferred medications to treat the diagnosis, or where there is no other formulary medication with a medically accepted use for the patient's specific diagnosis as referenced in the medical compendia available AND the medication is being requested for an accepted off-label use 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	9/2024

Recommendation: No changes

Safety Edit Exception	
Therapeutic Classes (AHFS)	N/A
Medications	Formulary drugs and non-formulary drugs (non-formulary and formulary drug criteria must also be met): • Exceeding the Food and Drug Administration (FDA) or compendia max dose recommendations • Exceeding the FDA dosing or compendia administration frequency recommendations • Exceeding the FDA or compendia duration of therapy recommendations • Duplication of therapy error at Point of Service (POS) • Age Restriction error at POS • Day Supply Limit error at POS
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	See "PA Review Criteria"
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** One month approval for duplication of therapy when transitioning from one agent to another and day supply limit due to a dose increase . All other scenarios: 12 months **Later Approvals** 12 months If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	**Exceeding the Food and Drug Administration (FDA) or compendia maximum dose, administration frequency or duration of therapy recommendations.** • The member must have a documented treatment failure with the drug at the maximum tolerated dose or maximum dose (whichever is the lesser dose), administration frequency or duration of therapy. AND • The provider must submit a medical reason why the maximum dose, administration frequency or duration of therapy needs to be exceeded based on the member's condition or treatment history. **Duplication of therapy** <u>Transition from one agent to another</u> • If a provider has outlined a plan to transition a member to a similar drug or provided a dose titration schedule, the requested drug is approved for one month. <u>Concurrent Therapy with two similar agents</u> • The provider must submit a medical reason why treatment with more than one drug in the same class is required based on the member's condition and treatment history. OR

	• The provider must submit disease state specific standard of care guidelines supporting concurrent therapy. **Age Restriction** • The provider must submit a medical reason why the drug is needed for a member whose age is outside of the plan's minimum or maximum age limit. AND • The indication and dose requested is supported by the Medical Compendia or current treatment guidelines. **Day Supply Limit** • An additional fill exceeding the day supply limit is needed based on a dose increase or is needed to achieve a total daily dose OR • The provider must submit a medical reason why an additional fill is needed outside of the plan's day supply limit. AND • The indication and dose requested is supported by the Medical Compendia or current treatment guidelines.
Criteria Statement	N/A
Last P&T Review Date	9/2024

Recommendation: No changes

Quantity Limit Exception	
Therapeutic Classes (AHFS)	N/A
Medications	Formulary drugs exceeding the Alameda Alliance's published quantity limits A quantity limit is defined as a limitation in the amount of medication per fill or time period and/or limitation in the amount of fills per calendar year or other time period.
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	See "PA Review Criteria"
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	N/A
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 Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	• The provider has submitted justification for the approval of doubling (or higher) of the number of tablets/capsules per prescription for a medication that has a higher strength tablet/capsule available, stating why that higher dose tablet/capsule cannot be used (e.g. two lorazepam 0.5mg tablets to equal the dose of lorazepam 1mg, when lorazepam 1mg tablet exists). AND • The dose requested is supported by the Medical Compendia or current treatment guidelines. OR • The member must have a documented treatment failure with the drug prescribed at the health plan's quantity limit **OR** the member requires a dose within prescribing guidelines that exceeds the plan's quantity limit. AND • 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	N/A
Last P&T Review Date	9/2024

Recommendation: No changes

Antibiotic Eye Medications	
Therapeutic Classes (AHFS)	Antibacterials (EENT)
Medications	Formulary • Ciprofloxacin 0.3% eye drops • Ofloxacin 0.3% eye drops • Moxifloxacin (Vigamox) 0.5% eye drops • Neomycin-bacitracin-polymyxin B-hydrocortisone (Neo Polycin HC) 3.5 mg-400-10,000 unit/g-1 % eye ointment • Neomycin -polymyxin B-dexamethasone (Maxitrol®) 3.5 mg/g-10,000 unit/g-0.1 % eye oint Formulary, Step Therapy Required • Ciloxan (ciprofloxacin) 0.3% eye ointment Formulary, PA required • Gatifloxacin (Zymaxid) • Moxifloxacin (Moxeza) • Azasite (azithromycin) • TobraDex (tobramycin-dexamethasone) 0.3 %-0.1 % eye ointment
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	None.
Coverage Duration	**Initial Approval** If the conditions are met, the request will be approved for 1 fill with a quantity limit of 1 bottle/tube. **Later Approvals** If criteria are not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	**For the formulary, step therapy required medication Ciloxan (ciprofloxacin) 0.3% eye ointment** • Documented contraindication to or trial and failure of one of the preferred antibiotic eye drops: ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin **For gatifloxacin (Zymaxid) all of the following criteria must be met**: • For use after cataract surgery **AND** • Documented contraindication to or trial and failure of one of the preferred antibiotic eye drops: ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin **For Azasite and moxifloxacin (Moxeza) all of the following criteria must be met:** • For use after cataract surgery **AND** • Documented contraindication to or trial and failure of one of the preferred antibiotic eye drops: ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin **AND**

	• Documented contraindication to or trial and failure of gatifloxacin (Zymaxid) **For TobraDex (tobramycin-dexamethasone) 0.3 %-0.1 % eye ointment all of the following criteria must be met:** • Documented contraindication to or trial and failure of one of the preferred ophthalmic antibiotic & glucocorticoid combination eye ointments: neomycin-bacitracin-polymyxin B-hydrocortisone (Neo Polycin HC) eye ointment or neomycin -polymyxin B-dexamethasone (Maxitrol) eye ointment
Criteria Statement	Ciloxan (ciprofloxacin) eye ointment is reserved for members who cannot/should not take ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin eye drops. Gatifloxacin (Zymaxid) is reserved for members who have had cataract surgery and who cannot/should not take ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin eye drops. Azasite or moxifloxacin (Moxeza) are reserved for members who have had cataract surgery and who cannot/should not take ciprofloxacin, moxifloxacin (Vigamox), or ofloxacin eye drops AND gatifloxacin (Zymaxid) eye drops. TobraDex (tobramycin-dexamethasone) eye ointment is reserved for members who cannot/should not take neomycin-bacitracin-polymyxin B-hydrocortisone (Neo Polycin HC) eye ointment or neomycin -polymyxin B-dexamethasone (Maxitrol) eye ointment.
Last P&T Review Date	9/2024

Recommendation: Remove Zuplenz as it has been discontinued

Antiemetics	
Therapeutic Classes (AHFS)	5-HT3 Receptor Antagonists, Neurokinin-1 receptor antagonists
Medications	Formulary ondansetron (Zofran) tablet 4mg, 8mg (quantity limit) ondansetron (Zofran) ODT (quantity limit) Formulary, Prior Authorization Required ondansetron (Zofran) tablet 24mg (quantity limit) palonosetron (Aloxi) IV solution 0.25mg/5ml vial palonosetron (Aloxi) IV solution 0.25mg/2ml vial, 0.25mg/5ml syringe granisetron (Kytril) oral tablet, IV solution aprepitant (Emend) capsule Non-Formulary ondansetron (Zofran) oral solution, IV solution, injection (IV/SQ) solution Anzemet (dolasetron) tablet Sustol (granisetron ER) SQ injection Sancuso (granisetron ER) transdermal patch fosaprepitant (Emend) IV emulsion Emend (fosaprepitant) powder packet Cinvanti (aprepitant) IV emulsion Varubi (rolapitant) oral capsule Akynzeo (fosnetupitant/palonosetron) capsule, IV solution 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/Re-Approval** If all of the conditions are met, the request will be approved for up to a 6 month duration, as per chemotherapy cycle, or as recommended per FDA approved indications and/or defined medical compendium and/or per the NCCN, ASCO, NCI, or MASCC standard of care guidelines. 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 approval (Pediatric Population): • Check AAH active CCS cases for members < 21 years of age Criteria for approval (Adult Population): • Prescribed dosing is within FDA approved indications and limitations and/or supported by medical compendium and NCCN, ASCO, NCI, or MASCC standard of care guidelines, and is within quantity limits, if applicable. • Patients receiving an antineoplastic agent = HIGH or MODERATE emetic risk per the NCCN Practice guidelines can receive palonosetron hydrochloride (Aloxi) and aprepitant (Emend) capsule, as first line antiemetic agents **For*

	reference, please consult the most recent NCCN guidelines for Antiemesis which can be located under NCCN Guidelines for Supportive Care: Antiemesis @ https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf • For all other patients, if the request is for a formulary, prior authorization required or non-formulary agent, the patient has a documented treatment failure after receiving an adequate trial of formulary 5HT-3 RA (ondansetron) and/or has another documented medical reason (intolerance, hypersensitivity, contraindication, etc.) for not utilizing these medications to treat their medical condition. • The medication is recommended and prescribed by a specialist in the field to treat the patient's respective medical condition. 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	Antiemetics other than ondansetron tablets and ODT are reserved for members who have used (or cannot/should not use) oral ondansetron 4mg or 8 mg oral tablets or oral disintegrating tablets for the respective mechanism of action requested. Palonosetron (Aloxi) or aprepitant (Emend) capsule are reserved for members who are using a high or moderate emetic risk antineoplastic.
Last P&T Review Date	9/2024

Recommendation: No changes

Nuedexta (dextromethorphan/quinidine)	
Therapeutic Classes (AHFS)	Central nervous system agents, miscellaneous
Medications	Formulary, PA required Nuedexta (dextromethorphan/quinidine)
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 a neurologist or psychiatrist
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	**All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review** Criteria for initial authorization: • For a diagnosis of Pseudobulbar Affect (PBA) approve • For all other diagnoses, use off label criteria Criteria for re-authorization: • Patient is stable and continuing the medication AND • Medication is used for appropriate indication and at appropriate dose
Criteria Statement	Nuedexta is reserved for members who have a diagnosis of pseudobulbar affect.
Last P&T Review Date	9/2024

Recommendation: No changes

Cartilaginous Repair Agents	
Therapeutic Classes (AHFS)	Anti-inflammatory/antiarthritic agents, misc; devices
Medications	Formulary, PA required Euflexxa (hyaluronate sodium) – preferred agent Non-formulary (non-preferred agents) Hyalgan (hyaluronate sodium) Durolane Genvisc 850 Trivisc Synvisc Synvisc-One Orthovisc Monovisc Gel-One Visco-3 Hymovis Triluron Gelsyn-3 Supartz FX Any other hyaluronic acid/cartilaginous repair agent product
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** One complete course of treatment (based on the FDA labeled dose of the drug requested). **Later approvals** One complete course of treatment (based on the FDA labeled dose of the drug requested).
PA Review Criteria	**All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review** Initial authorization: • Diagnosis of osteoarthritis (OA)/degenerative joint disease (DJD) of the knee • Documentation (by either attestation or claims data) the patient recently (over the past 4 months) has had adequate trials on simple analgesics (acetaminophen containing products) AND NSAIDs (including 2 different prescription strength NSAIDS) on a continuous basis for 3 months without success or has a medical reason (intolerance, hypersensitivity, contraindication, etc.) for not being able to utilize simple analgesic products and NSAIDs. • Documentation patient has recently (within past 12 months) tried at least ONE steroid injection without success, per affected knee or has a medical reason for not being able to utilize steroid injections.

	• Documentation of at least one course of physical therapy for knee osteoarthritis • Attestation confirming that the patient has no contraindications to the injections (active joint infection, bleeding disorder) • If the medication request is for hyaluronic acid derivative (HAD) product other than Euflexxa, the patient has a documented medical reason (intolerance, hypersensitivity, contraindication, etc.) for not taking Euflexxa to treat their medical condition. Re-authorization • Documentation was submitted that the patient had an objective response to the treated knee(s) (e.g. decreased joint pain or stiffness, improved knee range of motion, etc) that lasted for ≥ 6 months to previous HAD therapy. • Documentation was submitted that the member has a return of symptoms of osteoarthritis that has not responded to analgesics or NSAIDs, or has a medical reason (intolerance, hypersensitivity, contraindication, etc) for not being able to utilize these therapies. • If the medication request is for hyaluronic acid derivative (HAD) product other than Euflexxa, the patient has a documented medical reason (intolerance, hypersensitivity, contraindication, etc) for not taking Euflexxa to treat their medical condition.
Criteria Statement	For osteoarthritis (OA)/degenerative joint disease (DJD) of the knee, Euflexxa is reserved for members who have used (or cannot/should not use) acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and steroids, and have had physical therapy for knee osteoarthritis. For osteoarthritis (OA)/degenerative joint disease (DJD) of the knee, other hyaluronic acid derivative products are reserved for members who have used (or cannot/should not use) Euflexxa.
Last P&T Review Date	9/2024

Recommendation: No changes

Memantine ER (Namenda XR)	
Therapeutic Classes (AHFS)	Central Nervous System Agents, Misc
Medications	Formulary, step therapy required memantine ER (Namenda XR)
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 • Documented trial and failure, intolerance, or contraindication to use donepezil AND memantine IR OR • Documentation member unable to adhere to twice daily dosing due to caregiver limitations
Criteria Statement	Memantine ER is reserved for members who have used (or cannot/should not use) donepezil AND memantine IR or for members unable to comply with twice daily dosing due to caregiver limitations.
Last P&T Review Date	9/2024

Recommendation: No changes

Ophthalmic Anti-inflammatory Immunomodulators	
Therapeutic Classes (AHFS)	EENT anti-inflammatory agents, miscellaneous.
Medications	**Formulary, step therapy required** Cyclosporine (Restasis) 0.05% dropperette **Formulary PA (prior authorization required)** Restasis multidose (cyclosporine) 0.05% drops Xiidra (lifitegrast) 5% dropperette Cequa (cyclosporine) 0.09% ophthalmic dropperette Tyrvaya (varenicline) 0.03mg nasal spray Miebo (perfluorohexyloctane) 100% drops (1.338 gm/ml) Any other newly approved 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 **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	The following criteria must be met for cyclosporine (Restasis) 0.05% dropperette: • Diagnosis of dry eye syndrome (decreased tear production) whose lack of tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, dry eye, or treatment of the signs and symptoms of dry eye disease. AND • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to at least 30-day trials each of two-different artificial tear products, one of which must be high viscosity artificial tears (e.g. methylcellulose, polyvinyl alcohol, polyethylene glycol, or oil containing) The following criteria must be met for formulary prior authorization required medications: • Diagnosis of dry eye syndrome (decreased tear production) whose lack of tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, dry eye, or treatment of the signs and symptoms of dry eye disease AND • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to at least 30-day trials each of two different artificial tear products, one of which must be high viscosity artificial tears (e.g. methylcellulose, polyvinyl alcohol, polyethylene glycol, or oil containing) AND • Documentation of trial and failure, contraindication, or intolerance to cyclosporine (Restasis) 0.05% dropperette
Criteria Statement	For dry eye syndrome, cyclosporine (Restasis) 0.05% dropperette is reserved for members who have previously used (or cannot/should not use) artificial tears. Restasis Multidose, Xiidra, Cequa, Miebo, or Tyrvaya are reserved for members who have previously used (or cannot/should not use) artificial tears and cyclosporine (Restasis) 0.05% dropperette.
Last P&T Review Date	9/2024

Recommendation: No changes

Penicillamine (Depen, Cuprimine), Trientine HCl (Syprine) for Wilson's disease	
Therapeutic Classes (AHFS)	Heavy Metal Antagonists
Medications	Formulary, PA required Penicillamine (Depen Titratabs) tablet Trientine (Syprine) Penicillamine (Cuprimine) capsule Non-Formulary Cuvrior (trientine tetrahydrochloride)
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** 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 initial approval: • Documented confirmed diagnosis of Wilson's disease • For penicillamine (Depen, Cuprimine), documented adequate trial (at least 3 months) and failure of, or intolerance to, due to significant side effects/toxicity, or a contraindication to therapy with trientine (Syprine) • For Cuvrior (trientine tetrahydrochloride), documented adequate trial (at least 3 months) and failure of, or intolerance to, due to significant side effects/toxicity, or a contraindication to therapy with BOTH trientine (Syprine) and penicillamine Criteria for re-authorization: • Documentation of positive clinical response.
Criteria Statement	Penicillamine (Depen, Cuprimine) are reserved for members who have used (or cannot/should not use) trientine (Syprine). Cuvrior (trientine tetrahydrochloride) is reserved for members who have used (or cannot/should not use) both trientine (Syprine) and penicillamine.
Last P&T Review Date	9/2024

Recommendation: No changes

Iron-chelating Agents	
Therapeutic Classes (AHFS)	Heavy Metal Antagonists
Medications	Formulary, PA required Deferasirox (Jadenu) tablet -PREFERRED Deferasirox (Jadenu) granules Deferasirox (Exjade) tablet Non-Formulary Ferriprox (deferiprone) tablet Ferriprox (2 times a day) (deferiprone) 1,000 mg tablet Ferriprox (deferiprone) 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	Physician must be a hematologist.
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 CHRONIC IRON OVERLOAD DUE TO BLOOD TRANSFUSIONS FOR DEFERASIROX** • Patient must be ≥ 2 years old. (check AAH active CCS cases for members < 21 years of age) • Diagnosis of chronic iron overload due to blood transfusions • Patient receiving blood transfusions on a regular basis/participating in blood transfusion program • Serum ferritin concentration consistently greater than 1000mcg/L. o If serum ferritin falls to <1,000 mcg/L at 2 consecutive visits, consider dose reduction (especially if dose is >17.5 mg/kg/day) o (If the serum ferritin levels fall below 500 mcg/L on any one monitoring visit, deferasirox therapy discontinued). • Documented treatment failure, contraindication, or significant intolerance to deferoxamine (Desferal) treatment. • If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferoxamine (Desferal) AND deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Jadenu) tablet must be provided. • If the request is for deferasirox (Jadenu) granules, member must meet the criteria above and have tried and failed deferoxamine (Desferal) AND deferasirox (Exjade) tablet AND (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet must be provided **REAUTHORIZATION CRITERIA FOR CHRONIC IRON OVERLOAD DUE TO BLOOD TRANSFUSIONS FOR DEFERASIROX** • If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferoxamine (Desferal) AND deferasirox (Jadenu) tablet OR a medical

reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferoxamine (Desferal) AND deferasirox (Jadenu) tablet must be provided.

- Serum ferritin concentration consistently greater than 1000 mcg/L.
    - If serum ferritin falls to <1,000 mcg/L at 2 consecutive visits, consider dose reduction (especially if dose is >17.5 mg/kg/day)
    - If the serum ferritin levels fall consistently below 500 mcg/L on any one monitoring visit, deferasirox therapy must be discontinued

INITIAL CRITERIA FOR CHRONIC IRON OVERLOAD IN NON-TRANSFUSION DEPENDENT THALASSEMIA SYNDROMES FOR DEFERASIROX

- Patient must be ≥ 10 years old (check AAH active CCS cases for members < 21 years of age)
- Diagnosis of thalassemia syndrome
- Liver iron content (LIC) by liver biopsy of ≥ 5 mg Fe/g dry weight
- Serum ferritin level on ≥ 2 measurements at least one month apart of >300 mcg/L
- If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Jadenu) tablet must be provided.
- If the request is for deferasirox (Jadenu) granules, member must meet the criteria above and have tried and failed deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Exjade) tablet AND deferasirox (Jadenu) tablet must be provided

REAUTHORIZATION CRITERIA FOR CHRONIC IRON OVERLOAD IN NON-TRANSFUSION DEPENDENT THALASSEMIA SYNDROMES FOR DEFERASIROX

- If the request is for deferasirox (Exjade) tablet, member must have tried and failed deferasirox (Jadenu) tablet OR a medical reason why member is unable to use (e.g. intolerance, contraindication, etc.) deferasirox (Jadenu) tablet must be provided.
- Serum ferritin consistently > 300 mcg/L.
- If serum ferritin < 300 mcg/L, LIC must be obtained. If LIC < 3 mg Fe/g, treatment should be discontinued.

INITIAL CRITERIA FOR TRANSFUSIONAL IRON OVERLOAD DUE TO THALASSEMIA SYNDROMES OR SICKLE CELL DISEASE AND OTHER ANEMIAS FOR FERRIPROX (DEFERIPRONE)

- Patient must be ≥ 3 years old for oral solution OR ≥ 8 years old for tablets (check AAH active CCS cases for members < 21 years of age)
- Diagnosis of thalassemia syndrome, or sickle cell disease, or other anemia
- Patient receiving blood transfusions on a regular basis/participating in blood transfusion program
- Serum ferritin concentration is consistently > 1000 mcg/L. If the serum ferritin levels fall consistently below 500 mcg/L, Ferriprox must be discontinued
- Documentation that the patient is unable to use deferoxamine (Desferal) parenterally
- Documented trial and failure of deferasirox (Exjade, Jadenu) or medical reason why deferasirox cannot be used
- Brand Ferriprox (2 times a day) 1000mg tablets and Ferriprox liquid will be approved with documentation of trial and failure, contraindication, or intolerance to generic deferiprone tablets

	REAUTHORIZATION CRITERIA FOR TRANSFUSIONAL IRON OVERLOAD DUE TO THALASSEMIA SYNDROMES OR SICKLE CELL DISEASE AND OTHER ANEMIAS FOR FERRIPROX (DEFERIPRONE) • Patient continues to receive blood transfusions on a regular basis/ or participates in a blood transfusion program • Serum ferritin concentration is consistently > 1000 mcg/L. If the serum ferritin levels fall consistently below 500 mcg/L, Ferriprox must be discontinued • If the request is for brand Ferriprox (2 times a day) 1000mg tablets or Ferriprox liquid, documentation of trial and failure, contraindication, or intolerance to generic deferiprone tablets
Criteria Statement	For chronic iron overload due to blood transfusions deferasirox (Jadenu) tablet is reserved for members who have used (or cannot/should not use) deferoxamine. Deferasirox (Exjade) tablet is reserved for members who have used (or cannot/should not use) deferoxamine AND (Jadenu) tablet. Deferasirox (Jadenu) granules are reserved for members who have used (or cannot/should not use) deferoxamine AND deferasirox (Jadenu) tablet AND deferasirox (Exjade) tablet. For chronic iron overload in non-transfusion dependent thalassemia syndromes deferasirox (Exjade) tablet is reserved for members who have used (or cannot/should not use) deferasirox (Jadenu) tablet. Deferasirox (Jadenu) granules are reserved for members who have used (or cannot/should not use) deferasirox (Jadenu) tablet AND deferasirox (Exjade) tablet. For transfusional iron overload due to thalassemia syndromes or sickle cell disease and other anemias, deferiprone (Ferriprox) tablet is reserved for members who are receiving blood transfusions who have used (or cannot/should not use) deferoxamine (Desferal) and deferasirox (Exjade, Jadenu). Brand Ferriprox (2 times a day) 1000mg tablets and Ferriprox liquid are reserved for members who have used (or cannot/should not use) generic deferiprone tablets.
Last P&T Review Date	9/2024

Recommendation: No changes

Vancomycin	
Therapeutic Classes (AHFS)	Antibacterials, miscellaneous
Medications	Formulary, with quantity limit Vancomycin 125, 250 mg capsules Firvanq 25, 50 mg/ml solution Non-Formulary Vancomycin 250mg/5ml (50mg/ml) 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), 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** Durations exceeding 10 days are approvable if vancomycin was used for initial episode of Clostridium (or Clostridioides) difficile infection (CDI) and now pulsed-tapered regimen required. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	Requests for formulary agents above the quantity limit will be approved if: • Dosing requested is appropriate based on dosing guidelines AND • Treatment with vancomycin capsules or Firvanq is being requested for treatment of a first recurrence when vancomycin capsules or Firvanq was used for initial treatment and pulsed-tapered regimen is required OR • Treatment with vancomycin capsules or Firvanq is being requested for treatment of a second or subsequent recurrence and pulsed-tapered regimen is required Requests for vancomycin 250mg/5ml (50mg/ml) oral solution will be approved if: • Dose is appropriate per label or supported by compendia/standard of care guidelines for initial treatment OR first, second, or subsequent recurrence and pulsed-tapered regimen is required AND • The patient has tried and failed both formulary dosage forms, and/or has another documented medical reason (intolerance, hypersensitivity, contraindication, etc.) for not utilizing these medications to treat their medical condition.
Criteria Statement	Vancomycin capsules or Firvanq above the quantity limits are reserved for members with a first recurrence of Clostridium (or Clostridioides) difficile infection (CDI) after initial treatment with vancomycin capsules or Firvanq or members with a second recurrence in which pulsed-tapered regimen is required. Vancomycin 250mg/5ml (50mg/ml) oral solution is reserved for members who have used (or cannot/should not use) formulary vancomycin capsules and Firvanq.
Last P&T Review Date	9/2024

Recommendation: No changes

Dronabinol	
Therapeutic Classes (AHFS)	Antiemetics, Miscellaneous
Medications	Formulary, PA required Dronabinol (Marinol): pays at point of sale for members with diagnosis of HIV ICD 10 B20, for all other diagnoses, prior authorization is required Non-formulary Syndros 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), 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	Criteria for approval:
	• Patient has anorexia or weight loss associated with AIDS/HIV OR
	• Patient has nausea or vomiting due to chemotherapy AND documentation of trial and failure, contraindication, or intolerance to at least two of the following:
	  ○ 5-HT3 antagonists (ondansetron up to 8mg BID, granisetron)
	  ○ Dopamine receptor antagonists (e.g. prochlorperazine, promethazine, or metoclopramide)
	  ○ Aprepitant
	  ○ Dexamethasone
	• OR Patient has anorexia or weight loss associated with cancer AND documentation of trial and failure, contraindication, or intolerance to megestrol or cyproheptadine.
	• If request is for Syndros, above criteria must be met AND documentation provided of inability to swallow dronabinol capsules must be provided

Criteria Statement	Dronabinol is reserved for members that have AIDS/HIV. For nausea or vomiting due to chemotherapy, dronabinol is reserved for members who have used (or cannot/should not use) ondansetron, granisetron, dexamethasone, or prochlorperazine. For weight loss due to cancer, dronabinol is reserved for members who have used (or cannot/should not use) megestrol or cyproheptadine.
Last P&T Review Date	9/2024

Recommendation: No changes

Multaq (dronedarone)	
Therapeutic Classes (AHFS)	Antiarrhythmic agents
Medications	Formulary, PA required Multaq (dronedarone)
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 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** • Diagnosis of paroxysmal or persistent atrial fibrillation (AF) or atrial flutter. • Attestation that the patient does not have NYHA (New York Heart Association) Class III or IV heart failure or symptomatic heart failure with recent decompensation in the last 4 weeks requiring hospitalization. • Attestation that the patient does not have permanent atrial fibrillation (AF) that will not or cannot be cardioverted or restored to normal sinus rhythm.
Criteria Statement	Multaq is reserved for members who have paroxysmal or persistent atrial fibrillation or atrial flutter without NYHA (New York Heart Association) class III or IV heart failure or symptomatic heart failure with recent decompensation in the last 4 weeks requiring hospitalization. Members must also not have permanent atrial fibrillation that cannot be cardioverted to normal sinus rhythm.
Last P&T Review Date	9/2024

Recommendation: No changes

Erythropoiesis-Stimulating Agents	
Therapeutic Classes (AHFS)	Erythropoiesis-Stimulating Agents
Medications	Formulary, PA required Retacrit (epoetin alfa-epbx) - **PREFERRED** Aranesp (darbepoetin alfa) Procrit (epoetin alfa) Epogen (epoetin alfa) Non-formulary Mircera (methoxy polyethylene glycol-epoetin beta)
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** If criteria are met, the request will be approved as follows: 1 month if the patient is deficient in iron, vitamin B12 or folate, and in the perisurgical setting 3 months for all other requests. If the provider attests that the preferred medication is for a chronic or long-term condition, reauthorization will be approved for 12 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Criteria for authorization of existing epoetin users who are NEW to the plan:**
	• Documentation of current dose
	• Documentation of hemoglobin level results within 30 days or member has responded to therapy (≥1-2 g/dL increase in hemoglobin (HgB) or decrease in transfusion requirements)
	
	Requests for Initial Therapy:
	• All lab results submitted must have been drawn within 30 days of request:
	• The following lab values – hemoglobin (HgB) and hematocrit (HCT)
	• Normal lab results or, if abnormally low, appropriate supplementation as follows:
	  ○ serum ferritin level (normal is > 100 ng/mL)
	  ○ transferrin saturation (TSAT) (normal is > 20%)
	  ○ vitamin B12 level(> 223 pg/mL)
	  ○ folate level (> 3.1 ng/mL)
	• For requests for non-preferred ESAs, documentation must be provided as to why preferred are not medically appropriate for the member.
	• **For anemia of CKD:**
	  ○ HgB < 10 g/dL
	
	• **For anemia related to cancer:**
	  ○ Receiving myelosuppressive therapy for palliative treatment (members receiving myelosuppressive therapy with curative intent

Erythropoiesis-Stimulating Agents	
	should not receive ESAs) **AND** documented symptomatic anemia with HgB <10 g/dL **OR** ○ The member has symptomatic anemia related to myelodysplastic syndrome AND documented serum erythropoietin level ≤ 500 mU/mL • **For zidovudine-related anemia in members with HIV:** ○ The member must currently be receiving zidovudine-containing highly active antiretroviral therapy (HAART) (zidovudine ≤ 4200 mg/week) ○ Erythropoietin level ≤ 500 mU/mL • **For ribavirin-induced anemia:** ○ Documented attempt to reduce dose was made ○ HgB < 12 g/dL • **For members undergoing surgery to reduce the need for allogenic blood transfusion:** ○ Perioperative hemoglobin must be < 13 g/dL and > 10 g/dL. ○ The member is scheduled for an elective, non-cardiac, nonvascular surgery. **Reauthorization**: • Repeat normal labs within 30 days from date of request, or appropriate supplementation as follows: ○ serum ferritin level (> 100 ng/mL) ○ TSAT (> 20%) ○ vitamin B12 level (> 223 pg/mL) ○ folate level (> 3.1 ng/mL) • For anemia of CKD: HgB ≤ 11 g/dL • For anemia related to cancer: HgB ≤ 12 g/dL • For zidovudine-related anemia in members with HIV: HgB ≤ 12 g/dL • For ribavirin-induced anemia: HgB ≤ 12 g/dL • An increase in dose has not occurred more than once every 4 weeks • If the request is a non-preferred agent, documentation must be provided as to why preferred medications are not medically appropriate for the member
Criteria Statement	Mircera, Procrit, Epogen, or Aranesp are reserved for members who have used (or cannot/should not use) Retacrit.
Last P&T Review Date	9/2024

Recommendation: No changes

Drugs for Gender Dysphoria For Less Than 21 Years Old	
Therapeutic Classes (AHFS)	Androgens; Antineoplastic Agents; Estrogens; Gonadotropins; Mineralocorticoid (Aldosterone) Antagonists; 5-Alpha-Reductase Inhibitors; Progestins
Medications	**Anti-androgens and progestins (Adjunct)** Formulary • Spironolactone (Aldactone) 25, 50, 100mg tablet • Finasteride (Proscar) 5mg tablet • Dutasteride (Avodart) 0.5mg capsule • Progesterone (Prometrium) 100, 200mg capsule • Medroxyprogesterone 2.5, 5mg tablet • Medroxyprogesterone acetate intramuscular (Depo-Provera) 150mg/mL Non-formulary: • Depo-Provera 400mg/mL injectable suspension • Progesterone 50mg/mL oil solution **Estrogen Agents for Male-to-Female (MTF)** Formulary • Estradiol (Estrace) 0.5, 1, 2mg tablet • Premarin 0.3, 0.45, 0.625, 0.9, 1.25mg tablet • Estradiol-*once*-weekly 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1mg patch: QL of #12 per 84 days • Estradiol-*twice*-weekly 0.025, 0.05, 0.075, 0.1mg patch: QL of #24 per 84 days • Estradiol valerate 20mg/mL, 40mg/mL vial: 1 vial per 30 days Non-formulary • Depo-Estradiol (estradiol cypionate) 5mg/mL **Testosterone Agents for Female-to-Male (FTM)** Formulary (first-line) • Testosterone cypionate 100mg/mL (QL #10 ml/30 days), 200mg/mL intramuscular oil (QL #5 ml/30 days) • Testosterone (Vogelxo) 1% gel pump (QL #300gm/30 days) • Testosterone (Androgel) 1.62% gel pump (QL #300gm/30 days) Formulary, PA required (second-line) • Testosterone (Androgel) 1% 50 mg packets • Testosterone (Androgel) 1% 25 mg packets • Testosterone (Testim) 1% gel tube • Testosterone (Axiron) 30mg/1.5ml solution pump • Testosterone enanthate 200mg/mL intramuscular oil (QL #5 ml/30 days) Non-formulary • Testosterone (Fortesta) 2% gel pump • Testosterone (Androgel) 1.62% gel packets • Androderm (testosterone transdermal patch) 2mg/24 hours, 4mg/24 hours • Aveed 750mg/3mL vial • Testopel pellet implant • Testosterone implant pellet • Methyltestosterone (Testred) oral capsules • Methitest (methyltestosterone) oral tablets • Testone CIK (testosterone cypionate) intramuscular injection kit

Drugs for Gender Dysphoria For Less Than 21 Years Old	
	• Natesto (testosterone) nasal gel pump • Xyosted (testosterone enanthate) subcutaneous auto-injector • Jatenzo (testosterone undecanoate) oral capsules **Gonadotropin-Releasing Hormone Receptor Agonists (GnRHa)** <u>Formulary, PA required</u> • Lupron Depot-Ped 1-Month (leuprolide) 7.5, 11.25, 15, 30 mg syringe kit (for less than 18 years) • Lupron Depot (leuprolide) 3.75, 7.5, 11.25, 22.5, 30, 45mg syringe kit • Leuprolide acetate 1mg/0.2mL solution kit <u>Non-formulary</u> • Trelstar (triptorelin) 3.75, 11.25, 22.5 mg Mixject suspension • Eligard (leuprolide acetate) 7.5, 22.5, 30, 45mg subQ • Zoladex (goserelin acetate) 3.6, 10.8mg subQ implant • Supprelin LA (histrelin) 50mg subQ implant kit • Triptodur 6-month (triptorelin) 22.5mg • Fensolvi (leuprolide acetate) syringe kit Any other newly marketed agent to treat gender dysphoria *Requests for greater than indicated quantity or age limits will be reviewed on a case by case basis
Covered Uses	Medically accepted indications are defined using the following disease specific guidelines:Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline; World Professional Association for Transgender Health (WPATH) Standards of care for the health of transgender and gender diverse people; American College of Obstetrician and Gynecologists (ACOG): Committee opinion on health care for transgender and gender diverse individuals: the TransActive Education and Advocacy Group; the World Health Organization (WHO)
Exclusion Criteria	Contraindications to any of the medications listed above
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	See "**PA Review Criteria**" below
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 24 months **Exception Approval** 3 months if requested labs are outside of recommended range or not provided; further approval requires requested labs and/or action plan submitted
PA Review Criteria	****Cosmetic medications used to treat gender dysphoria, mental health, or substance use disorder ARE approved as appropriately indicated (e.g. FDA approval, compendia supported, etc.).**** **All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review** **INITIAL CRITERIA to start treatment for non-preferred drugs and preferred drugs that require PA, the following must be met:** • Clinic notes or consult detailing the diagnosis of gender dysphoria / gender identity disorder (GID) per DSM-V diagnostic criteria made by a qualified mental health professional • Documentation of patient readiness to start GnRHa and/or cross-sex hormone therapy

Drugs for Gender Dysphoria For Less Than 21 Years Old	
	• Must meet the class specific criteria outlined below • Dosage prescribed based on recommendations from medical compendia and/or the Food And Drug Administration (FDA) as appropriate • For formulary agents with prior authorization, approve for 12 months if meet ALL of the initial criteria to start treatment; for non-formulary agents, must have documentation showing trial and failure, contraindication, intolerance and/or side effects to formulary agents, as outlined in the individual sections below **Estrogen Agents (for Male-to-Female):** INITIAL CRITERIA to start treatment: • Documentation member is at least 16 years of age AND at least in Tanner stage 2 • Documentation member does NOT have: history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • If requesting estradiol cypionate injection, documentation trial and failure, contraindication, intolerance and/or side effects to one formulary oral estrogen agent and estradiol valerate injection • If requesting transdermal estrogen patch, documentation of trial and failure, contraindication, intolerance and/or side effects to formulary oral **and** injectable estrogen agents • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Documentation of estradiol levels (less than 200 pg/ml) and testosterone levels (less than 55 ng/dL) • Documentation member does NOT have: history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration" for approval limit) **Testosterone Agents (for Female-to-Male):** INITIAL CRITERIA to start treatment: • Documentation member is at least 16 years of age **and** at least in Tanner stage 2 • No evidence of known or suspected breast cancer and/or pregnancy • If requesting formulary-prior authorization required testosterone agents, documentation trial and failure, contraindication, intolerance and/or side effects to one first-line formulary injectable testosterone agent AND one first-line formulary topical testosterone agent • If requesting non-formulary testosterone agents, documentation trial and failure, contraindication, intolerance and/or side effects to one first-line formulary injectable testosterone agent AND one first-line formulary topical testosterone agent AND at least one formulary PA-required, (second-line) testosterone agent • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Documentation of hematocrit less than 50% • Documentation of testosterone levels; discontinue or reduce dose if greater than 1000 ng/dL • No evidence of known or suspected breast cancer and/or pregnancy

Drugs for Gender Dysphoria For Less Than 21 Years Old	
	• If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") **Antiandrogens and Progesterone Agents (Adjunct):** INITIAL CRITERIA for non-formulary agents: • Documentation member is at least 18 years of age • Require documentation of trial and failure, intolerance, contraindication, or inability to use spironolactone, dutasteride, finasteride, medroxyprogesterone acetate tablet and medroxyprogesterone acetate IM. • Documentation member does NOT have known or suspected pregnancy • For medroxyprogesterone: documentation member does NOT have history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months and/or severe liver disease • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA for non-formulary agents: • No evidence that member is currently pregnant • For medroxyprogesterone: documentation member does NOT have history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months and/or severe liver disease • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") **GnRHa:** INITIAL CRITERIA to start treatment: • Documentation of baseline labs for LH, FSH, estradiol and testosterone levels at pubertal levels AND at least in Tanner stage 2 • Documentation of weight • Members less than 18 years old: Lupron Depot-Ped 1-Month and leuprolide acetate solution are preferred agents • Members greater than or equal to 18 years old: Lupron Depot (1-, 3-, 4-, and 6)-Month and leuprolide acetate solution are preferred agents • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Members less than 16 years of age: Documentation of bone age on x-ray of left hand AND bone density on x-ray absorptiometry • Documentation there is a continual need to delay puberty until at least 21 years of age (i.e. extreme short stature) **For requests over the quantity limit:** • The member must have a documented treatment failure with the drug prescribed at the health plan's quantity limit **OR** the member requires a dose within prescribing guidelines that exceeds the plan's quantity limit **AND** • 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. **Continuation of therapy for NEW members from another health plan:** • If criteria are met for initial authorization, coverage duration is 12 months • If criteria are not met for initial authorization and/or requested labs are outside of recommended range **or** not provided, allow one-time coverage duration of 3 months until all of requested labs and clinic notes are received

Drugs for Gender Dysphoria For Less Than 21 Years Old	
Criteria Statement	**Estradiol cypionate injection:** For use in gender dysphoria, estradiol cypionate injection is reserved for members who have previously used (or cannot/should not take) formulary oral estradiol or Premarin tablet and estradiol valerate injection **Estrogen patch:** For use in gender dysphoria, estradiol patches are reserved for members who have previously used (or cannot/should not take) oral estradiol or Premarin tablet and estradiol injection or members who have had a history of cardiovascular events. **Testosterone 1% packet or tube, testosterone 30mg/1.5ml solution pump or testosterone enanthate 200mg/mL intramuscular oil** For use in gender dysphoria, [Formulary, PA required (second-line) medications] <INSERT: testosterone packets/tube/solution pump or testosterone enanthate 200mg/mL intramuscular oil> are reserved for members who have previously used (or cannot/should not take) testosterone cypionate injection AND testosterone 1% gel pump or testosterone (Androgel) 1.62% gel pump. For use in gender dysphoria, non-formulary testosterone products are reserved for members who have used (or cannot/should not use) testosterone cypionate AND testosterone (Vogelxo) 1% gel pump or testosterone (Androgel) 1.62% gel pump AND testosterone 1% gel packets, tube, or testosterone 30mg/1.5ml solution pump or testosterone enanthate 200mg/mL intramuscular oil. **Quantity Limits:** Requests for quantities over the quantity or fill limit are reserved for members who have a documented medical need for quantities in excess of the limits. **Exception approval:** The criteria for approval has not been met. The Alliance cannot cover xxDRUGxx as requested because insufficient information was received from your doctor to approve this medication as requested. The Alliance uses the Gender Dysphoria Drug Coverage Guidelines to determine what information is needed. Specifically, information required that has not yet been received includes: [1] Clinic notes that describe the diagnosis and treatment plan; and [2] Lab results showing [enter required labs]. We recommend that you talk with your provider about the needed information before we can approve for the full duration as requested. We will instead approve a 3-month supply of xxDRUGxx from [enter dates of approval].
Last P&T Review Date	9/2024

Recommendation: No changes, except add 10mg available dosage for medroxyprogesterone

Drugs for Gender Dysphoria For At Least 21 Years Old	
Therapeutic Classes (AHFS)	Androgens; Antineoplastic Agents; Estrogens; Gonadotropins; Mineralocorticoid (Aldosterone) Antagonists; 5-Alpha-Reductase Inhibitors; Progestins
Medications	**Anti-androgens and progestins (Adjunct)** Formulary • Spironolactone (Aldactone) 25, 50, 100mg tablet • Finasteride (Proscar) 5mg tablet • Dutasteride (Avodart) 0.5mg capsule • Progesterone (Prometrium) 100, 200mg capsule • Medroxyprogesterone 2.5, 5, 10mg tablet • Medroxyprogesterone acetate intramuscular (Depo-Provera) 150mg/mL Non-formulary: • Depo-Provera 400mg/mL injectable suspension • Progesterone 50mg/mL oil solution **Estrogen Agents for Male-to-Female (MTF)** Formulary: • Estradiol (Estrace) 0.5, 1, 2mg tablet • Premarin 0.3, 0.45, 0.625, 0.9, 1.25mg tablet • Estradiol-*once*-weekly 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1mg patch: QL of #12 per 84 days • Estradiol-twice-weekly 0.025, 0.05, 0.075, 0.1mg patch: QL of #24 per 84 days • Estradiol valerate 20mg/mL, 40mg/mL vial: 1 vial per 30 days Non-formulary • Depo-Estradiol (Estradiol cypionate) 5mg/mL **Testosterone Agents for Female-to-Male (FTM)** Formulary (first-line) • Testosterone cypionate 100mg/mL (QL #10 ml/30 days), 200mg/mL intramuscular oil (QL #5 ml/30 days) • Testosterone (Vogelxo) 1% gel pump (QL #300gm/30 days) • Testosterone (Androgel) 1.62% gel pump (QL #150gm/30 days) Formulary, PA required (second-line) • Testosterone (Androgel) 1% 50 mg packets • Testosterone (Androgel) 1% 25 mg packets • Testosterone (Testim) 1% gel tube • Testosterone (Axiron) 30mg/1.5ml solution pump • Testosterone enanthate 200mg/mL intramuscular oil (quantity limit #5 ml/30 days) Non-formulary • Testosterone (Fortesta) 2% gel pump • Testosterone (Androgel) 1.62% gel packets • Androderm (testosterone transdermal patch) 2mg/24 hours, 4mg/24 hours • Aveed 750mg/3mL vial • Testopel pellet implant • Testosterone implant pellet • Methyltestosterone (Testred) oral capsules • Methitest (methyltestosterone) oral tablets

Drugs for Gender Dysphoria For At Least 21 Years Old	
	• Testone CIK (testosterone cypionate) intramuscular injection kit • Natesto (testosterone) nasal gel pump • Xyosted (testosterone enanthate) subcutaneous auto-injector • Jatenzo (testosterone undecanoate) oral capsules **Gonadotropin-Releasing Hormone Receptor Agonists (GnRHa)** <u>Formulary, PA required</u> • Lupron Depot-Ped 1-Month (leuprolide) 7.5, 11.25, 15, 30 mg syringe kit (for less than 18 years) • Lupron Depot (leuprolide) 3.75, 7.5, 11.25, 22.5, 30, 45mg syringe kit • Leuprolide acetate 1mg/0.2mL solution kit <u>Non-formulary</u> • Trelstar (triptorelin) 3.75, 11.25, 22.5 mg Mixject suspension • Eligard (leuprolide acetate) 7.5, 22.5, 30, 45mg subQ • Zoladex (goserelin acetate) 3.6, 10.8mg subQ implant • Supprelin LA (histrelin) 50mg subQ implant kit • Triptodur 6-month (triptorelin) 22.5mg • Fensolvi (leuprolide acetate) syringe kit Any other newly marketed agent to treat gender dysphoria *Requests for greater than indicated quantity or age limits will be reviewed on a case by case basis
Covered Uses	Medically accepted indications are defined using the following disease specific guidelines: Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline; World Professional Association for Transgender Health (WPATH): Standards of care for the health of transgender and gender diverse people); American College of Obstetrician and Gynecologists (ACOG): Committee opinion on health care for transgender and gender diverse individuals; the TransActive Education and Advocacy Group; the World Health Organization (WHO)
Exclusion Criteria	Contraindications to any of the medications listed above
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	See "**PA Review Criteria**" below
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 24 months **Exception Approval** 3 months if requested labs are outside of recommended range or not provided; further approval requires requested labs and/or physician attestation they have educated the member and explained the risks
PA Review Criteria	****Cosmetic medications used to treat gender dysphoria, mental health, or substance use disorder ARE approved as appropriately indicated (e.g. FDA approval, compendia supported, etc.).**** **All requests must be reviewed by a clinical pharmacist first and then forwarded to AAH for review** **INITIAL CRITERIA to start treatment for non-preferred drugs and preferred drugs that require PA, the following must be met:** • Clinic notes or consult detailing the diagnosis of gender dysphoria / gender identity disorder (GID) per DSM-V diagnostic criteria made by a qualified mental health professional

Drugs for Gender Dysphoria For At Least 21 Years Old	
	• Documentation of patient readiness to start GnRHa and/or cross-sex hormone therapy • Must also meet the class specific criteria outlined below • Dosage prescribed based on recommendations from medical compendia and/or the Food And Drug Administration (FDA) as appropriate • For formulary agents with prior authorization, approve for 12 months if meet ALL of the initial criteria to start treatment; for non-formulary agents, must have documentation showing trial and failure, contraindication, intolerance and/or side effects to formulary agents, as outlined in the individual sections below **Estrogen Agents (for Male-to-Female):** INITIAL CRITERIA to start treatment: • Documentation member does NOT have: history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • If requesting estradiol cypionate injection, documentation trial and failure, contraindication, intolerance and/or side effects to one formulary oral estrogen agent [or estradiol patches] and estradiol valerate injection • If requesting transdermal estrogen patch, documentation trial and failure, contraindication, intolerance and/or side effects to formulary oral **and** injectable estrogen agents • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Documentation of estradiol levels (less than 200 pg/ml) and testosterone levels (less than 55 ng/dL) • Documentation member does NOT have: history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") **Testosterone Agents (for Female-to-Male):** INITIAL CRITERIA to start treatment: • No evidence of known or suspected breast cancer and/or pregnancy • If requesting formulary-prior authorization required testosterone agents, documentation trial and failure, contraindication, intolerance and/or side effects to one first-line formulary injectable testosterone agent AND one first-line formulary topical testosterone agent • If requesting non-formulary testosterone agents, documentation trial and failure, contraindication, intolerance and/or side effects to one first-line formulary injectable testosterone agent AND one first-line formulary topical testosterone agent AND at least one formulary PA-required, (second-line) testosterone agent • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Documentation of hematocrit less than 50% • Documentation of testosterone levels; discontinue or reduce dose if greater than 1000 ng/dL • No evidence of known or suspected breast cancer and/or pregnancy **Antiandrogens and Progesterone Agents (Adjunct use):**

Drugs for Gender Dysphoria For At Least 21 Years Old	
	INITIAL CRITERIA for non-formulary agents: • Require documentation of trial and failure, intolerance, contraindication, or inability to use spironolactone, dutasteride, finasteride, medroxyprogesterone acetate tablet and medroxyprogesterone acetate IM • No evidence of known or suspected pregnancy • For medroxyprogesterone: documentation member does NOT have history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months and/or severe liver disease • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA for non-formulary agents: • Documentation member does NOT have known or suspected pregnancy • For medroxyprogesterone: documentation member does NOT have history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months and/or severe liver disease • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") **GnRHa (Adjunct use):** INITIAL CRITERIA to start treatment: • Require documentation of trial and failure, intolerance, contraindication, or inability to use spironolactone, dutasteride, finasteride, medroxyprogesterone acetate tablet and medroxyprogesterone acetate IM • Documentation of baseline labs for LH, FSH, estradiol and testosterone levels • Documentation member is on CONCOMITANT hormone replacement therapy (as verified by claims history) • No evidence of known or suspected pregnancy (if Female-to-Male transition) • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") RENEWAL CRITERIA: • Documentation of estradiol and testosterone levels • If any labs are out of recommended range or not provided, follow Exception Approval process (see "Coverage Duration") **For requests over the quantity limit:** • The member must have a documented treatment failure with the drug prescribed at the health plan's quantity limit **OR** the member requires a dose within prescribing guidelines that exceeds the plan's quantity limit **AND** • 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. **Continuation of therapy for NEW members from another health plan:** • If criteria are met for initial authorization, coverage duration is 12 months • If criteria are not met for initial authorization and/or requested labs are outside of recommended range **or** not provided, allow one-time coverage duration of 3 months until all of requested labs and clinic notes are received
Criteria Statement	**Estradiol cypionate injection:** For use in gender dysphoria, estradiol cypionate injection is reserved for members who have previously used (or cannot/should not take) formulary oral estradiol or Premarin tablets or estradiol patches and estradiol valerate injection. **Estrogen patch:**

Drugs for Gender Dysphoria For At Least 21 Years Old	
	For use in gender dysphoria, estradiol patch is reserved for members who have previously used (or cannot/should not take) oral estradiol or Premarin tablets and estradiol valerate injection or have a history of cardiovascular disease. **Testosterone 1% packet or tube, testosterone 30mg/1.5ml solution pump or testosterone enanthate 200mg/mL intramuscular oil** For use in gender dysphoria, [Formulary, PA required (second-line) medications] <INSERT: testosterone packets/tube/solution pump or testosterone enanthate 200mg/mL intramuscular oil> are reserved for members who have previously used (or cannot/should not take) testosterone cypionate injection AND testosterone 1% gel pump or testosterone (Androgel) 1.62% gel pump. For use in gender dysphoria, non-formulary testosterone products are reserved for members who have used (or cannot/should not use) testosterone cypionate AND testosterone (Vogelxo) 1% gel pump or testosterone (Androgel) 1.62% gel pump AND testosterone 1% gel packets, tube, or testosterone 30mg/1.5ml solution pump or testosterone enanthate 200mg/mL intramuscular oil. **Quantity Limits:** Requests for quantities over the quantity or fill limit are reserved for members who have a documented medical need for quantities in excess of the limits. **Any GnRHa:** For use in gender dysphoria, GnRHa products are reserved for members with ALL of the following: 1) have previously used (or cannot/should not take) ALL of the following: spironolactone, dutasteride, finasteride, medroxyprogesterone; AND 2) records showing you are currently using hormone therapy. **Exception approval:** The criteria for approval has not been met. The Alliance cannot cover xxDRUGxx as requested because insufficient information was received from your doctor to approve this medication as requested. The Alliance uses the Gender Dysphoria Drug Coverage Guidelines to determine what information is needed. Specifically, information required that has not yet been received includes: [1] Clinic notes that describe the diagnosis and treatment plan; and [2] Lab results showing [enter required labs]. We recommend that you talk with your provider about the needed information before we can approve for the full duration as requested. We will instead approve a 3-month supply of xxDRUGxx from [enter dates of approval].
Last P&T Review Date	9/2024

Recommendation: Remove Mesalamine DR (Asacol HD) tablet as it has been discontinued

Mesalamine	
Therapeutic Classes (AHFS)	Anti-Inflammatory Agents (GI Drugs)
Medications	Formulary Mesalamine (Canasa) suppository Mesalamine (Rowasa) rectal enema Mesalamine (SFRowasa) rectal enema Formulary, Step Therapy Mesalamine DR (Delzicol DR) capsule Mesalamine ER (Apriso) capsule Mesalamine DR (Lialda) tablet Formulary, PA Required Mesalamine ER (Pentasa) 500mg capsule Pentasa (mesalamine) 250mg capsule Any other mesalamine product
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	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 are not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	Criteria for Authorization Mesalamine DR (Delzicol DR), mesalamine ER (Apriso), or mesalamine DR (Lialda) are approved when all of the following criteria are met: • Documentation of a diagnosis of ulcerative colitis • Documentation of a trial and failure or contraindication to sulfasalazine or balsalazide Mesalamine ER (Pentasa) or Pentasa (mesalamine) are approved when all of the following criteria are met: • Documentation of a diagnosis of ulcerative colitis • Documentation of a trial and failure or contraindication to sulfasalazine or balsalazide AND mesalamine DR (Lialda) or mesalamine DR (Delzicol DR) or mesalamine ER (Apriso)
Criteria Statement	Mesalamine DR (Lialda) tablet, mesalamine DR (Delzicol) or mesalamine ER (Apriso) are reserved for members who have ulcerative colitis and have used (or cannot/should not use) sulfasalazine or balsalazide. Mesalamine ER (Pentasa), Pentasa (mesalamine) are reserved for members with ulcerative colitis who have used (or cannot/should not use) sulfasalazine or balsalazide AND mesalamine DR (Lialda) tablet, mesalamine DR (Delzicol), or mesalamine ER (Apriso).
Last P&T Review Date	9/2024

Recommendation: No changes, just an addition of Ortikos to coverage duration section since it was missing in this section

Corticosteroids for Ulcerative Colitis and Crohn's disease	
Therapeutic Classes (AHFS)	Corticosteroids, Adrenals
Medications	Formulary budesonide (Entocort EC) capsule (QL 540/365) Hydrocortisone (Cortenema) rectal enema Formulary, Prior Authorization Required budesonide (Uceris) tablet Cortifoam (hydrocortisone acetate) foam Budesonide (Uceris) 2mg foam Ortikos (budesonide) capsule Any other corticosteroid for ulcerative colitis or Crohn's disease
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	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial/Re-Approval** — **Budesonide (Uceris) foam, Cortifoam, Ortikos capsule, or Budesonide tablet (Uceris)** If the criteria are met, the request will be approved for up to a 2 month duration **Approval to Exceed QL:** 3 months If criteria are not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	Criteria for Authorization Budesonide (Uceris) tablet is approved when all of the following criteria are met: • Documentation of a diagnosis of mild to moderate ulcerative colitis and failed remission • Documentation of trial and failure, contraindication, intolerance, or inability to use maximum tolerated and therapeutic dose of oral aminosalicylates (i.e. sulfasalazine or balsalazide) for 8 weeks AND rectal mesalamine for up to 6 weeks Budesonide (Uceris) foam and Cortifoam are approved when all of the following criteria are met: • Documentation of a diagnosis of ulcerative colitis. • Documentation of a trial and failure, intolerance, contraindication, or inability to formulary rectal mesalamine and formulary rectal corticosteroids. Ortikos is approved when all of the following criteria are met: • Documentation of a diagnosis of mild to moderate Crohn's disease involving the ileum and/or the ascending colon • Documentation of trial and failure, contraindication, intolerance, or inability to use budesonide (Entocort EC) capsule Requests for exceeding quantity limit of 540 capsules per 365 days for budesonide (Entocort EC) capsule

	• The member must have a documented treatment failure with the drug prescribed at the health plan's quantity limit OR the member requires a dose within prescribing guidelines that exceeds the plan's quantity limit. AND • 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	Budesonide (Uceris) tablet is reserved for members who have mild to moderate ulcerative colitis and have used (or cannot/should not use) the maximum tolerated and therapeutic dose of oral aminosalicylates (sulfasalazine or balsalazide) for 8 weeks AND rectal mesalamine for up to 6 weeks Budesonide (Uceris) foam or Cortifoam are reserved for members who have ulcerative colitis and have used (or cannot/should not use) formulary rectal mesalamine and formulary rectal corticosteroids. Ortikos is reserved for members who have mild to moderate Crohn's disease involving the ileum and have used (or cannot/should not use) budesonide (Entocort EC) capsule. Requests for budesonide (Entocort EC) capsule above the quantity limit are reserved for members who have used (or cannot/should not use) this medication in doses under the quantity limit and whose prescriber has a reason why the quantity limit is inadequate.
Last P&T Review Date	9/2024

Recommendation: No changes

Atovaquone-proguanil (Malarone)	
Therapeutic Classes (AHFS)	Antimalarials
Medications	Formulary, PA required: Atovaquone-proguanil (Malarone) 62.5-25 mg tablet Atovaquone-proguanil (Malarone) 250-100 mg 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	N/A
Prescriber Restrictions	N/A
Coverage duration	For prophylaxis: If all of the conditions are met, the request will be approved for up to 3 months. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review. For treatment: If all of the conditions are met, the request will be approved for one time fill. 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 THE USE OF ATOVAQUONE/PROGUANIL FOR MALARIA PROPHYLAXIS • The medication is being prescribed at a dose that is within FDA approved guidelines. • Member is traveling to a country with mefloquine resistant malaria (see CDC website at http://www.cdc.gov/malaria/travelers/country_table/a.html) OR • Member is traveling to a country with known malaria risk and due to time constraints is unable to start prophylaxis with preferred agents 1-2 weeks prior to departure OR • Member has underlying neuropsychiatric conditions (as shown through clinical notes and/or claims history) such as: active and/or recent history of depression, chronic anxiety disorders, psychosis, and/or schizophrenia. **CRITERIA FOR THE USE OF ATOVAQUONE/PROGUANIL FOR MALARIA TREATMENT** • Diagnosis of malaria
Criteria Statement	For prophylaxis, atovaquone-proguanil is reserved for members traveling to a country with mefloquine resistance, member is unable to start therapy 1 to 2 weeks prior to travel departure, or member has condition such as depression, anxiety, psychosis, or schizophrenia.
Last P&T Review Date	9/2024

Recommendation: Remove Rhinocort Allergy brand product as it was discontinued

Intranasal Steroids	
Therapeutic Classes (AHFS)	Corticosteroids, nasal
Medications	Formulary, step therapy required Flunisolide 0.025% spray Mometasone 50 mcg actuation nasal suspension spray (quantity limit)
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	Flunisolide or mometasone nasal spray are approved when the following criteria are met: • Documentation of a trial and failure, contraindication, or inability to use (nasal burning, headache, etc.) fluticasone nasal spray OR Flonase Sensimist OR triamcinolone nasal spray OR budesonide 32mcg nasal suspension Non-formulary intranasal steroids are approved when the following criteria are met: • Documentation of a trial and failure, contraindication, or inability to use (nasal burning, headache, etc.) fluticasone nasal spray OR Flonase Sensimist OR triamcinolone nasal spray OR budesonide 32mcg nasal suspension AND • Documentation of a trial and failure, contraindication, or inability to use (nasal burning, headache, etc.) flunisolide 0.025% spray OR mometasone 50 mcg nasal spray For requests above the quantity limit • The member must have a documented treatment failure with the drug prescribed at the health plan's quantity limit OR the member requires a dose within prescribing guidelines that exceeds the plan's quantity limit. AND • 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	Flunisolide nasal spray or mometasone nasal spray are reserved for members who have used (or cannot/should not use) fluticasone nasal spray OR Flonase Sensimist OR triamcinolone nasal spray OR budesonide 32mcg nasal suspension. Non-formulary steroidal nasal sprays are reserved for members who have used (or cannot/should not use) fluticasone nasal spray or Flonase Sensimist or triamcinolone nasal spray or budesonide 32mcg nasal suspension AND flunisolide nasal spray or mometasone nasal spray.
Last P&T Review Date	9/2024

Recommendation: Remove Lindane product as it was discontinued

Scabicides and Pediculicides	
Therapeutic Classes (AHFS)	Scabicides and pediculicides
Medications	Formulary, Step therapy required Malathion (Ovide) 0.5% lotion Spinosad (Natroba) 0.9% suspension Ivermectin (Sklice) 0.5% lotion Non-Formulary Crotan (crotamiton) 10% lotion 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** If all conditions are met, the request will be approved for up to 1 treatment. **Re-approval** If conditions are met, the request will be approved for a maximum of 2 treatments in a 30 day period. If all criteria are not met, the request is referred to Clinical Reviewer for medical necessity review.
PA Review Criteria	INITIAL: **Head Lice:** For the approval of the formulary-step therapy required medications: • Diagnosis of pediculosis capitis (head lice and its eggs). • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to permethrin 1% OTC or pyrethrins/piperonyl butoxide OTC OR • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to permethrin 1% OTC or pyrethrins/piperonyl butoxide OTC, within the previous 45 days, but no earlier than 7 days after the original fill. For the approval of the non-formulary medication: • All criteria above must be met AND documented trial and failure, intolerance, or reason not to use two of the following formulary medications: malathion (Ovide) 0.5% lotion or spinosad (Natroba) 0.9% suspension or ivermectin (Sklice) 0.5% lotion **Scabies:** For the approval of the formulary-step therapy required medications: • Diagnosis of scabies (Sarcoptes scabiei) • Documented trial and failure, intolerance, or hypersensitivity to the first line agent: permethrin 5% topical cream For the approval of the non-formulary medication: • All criteria above must be met AND documented trial and failure of: spinosad (Natroba) 0.9% suspension RENEWAL:

	• For head lice: spinosad can be approved for a second treatment if live lice are present 7 days after the initial treatment. • For head lice: malathion can be approved for a second treatment if live lice are present 7-9 days after the initial treatment. • For scabies: Crotan can be approved for a second treatment if itching still present or if new burrows or lesions continue to appear 2-4 weeks after the initial treatment & also the 2nd application 24 hours later
Criteria Statement	For the treatment of head lice, malathion (Ovide) 0.5% lotion, spinosad (Natroba) 0.9% suspension, and ivermectin (Sklice) 0.5% lotion are reserved for members who have used (or cannot/should not use) permethrin 1% OTC or pyrethrins/piperonyl butoxide OTC. For the treatment of scabies, spinosad (Natroba) 0.9% suspension is reserved for members who have used (or cannot/should not use) permethrin 5% topical cream. For the treatment of scabies, Crotan lotion is reserved for members who have used (or cannot/should not use) permethrin 5% topical cream AND spinosad (Natroba) 0.9% suspension.
Last P&T Review Date	9/2024

Recommendation: No changes

Rifamycin Antibiotics	
Therapeutic Classes (AHFS)	Rifamycin Antibiotics
Medications	Formulary Prior Authorization Required Xifaxan (rifaximin) Aemcolo DR (rifamycin)
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	**Initial/Re-Approval** **Traveler's diarrhea (Xifaxan and Aemcolo):** If all of the criteria are met, approve up 1 fill up to FDA approved maximum dosing. **IBS-D (Xifaxan):** If all of the criteria are met, the request will be approved for up to #42/14 days for 3 fills for 1 year. **Hepatic encephalopathy (Xifaxan):** If all of the criteria are met, the initial request will be approved for up to 6 months. For re-approvals if all criteria are met, the request will be approved for up to 12 months. 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 For all diagnoses **(Xifaxan and Aemcolo):** • Drug is being prescribed at FDA approved dose (including patient age) For diagnosis of traveler's diarrhea **(Xifaxan and Aemcolo):** • Documented trial and failure, contraindication, or intolerance to a fluoroquinolone (e.g. ciprofloxacin) OR azithromycin For reduction of overt hepatic encephalopathy recurrence or treatment of hepatic encephalopathy **(Xifaxan):** • Documented trial and failure, contraindication, or intolerance to lactulose in previous 30 days **OR** • Patient will be using lactulose concurrently For treatment of irritable bowel syndrome – diarrhea predominant (IBS-D) **(Xifaxan):** • Patient has diagnosis of moderate to severe disease (includes one or more of the following: frequent and severe abdominal pain/discomfort; frequent bowel urgency or fecal incontinence; disability or restriction of daily activities due to IBS) **AND** • Documented trial and failure, contraindication, or intolerance to a tricyclic antidepressant (TCA) (e.g. amitriptyline)

Criteria Statement	For traveler's diarrhea, Xifaxan and Aemcolo DR are reserved for members who have used (or cannot/should not use) a fluoroquinolone (e.g. ciprofloxacin) or azithromycin. For hepatic encephalopathy, Xifaxan is reserved for members who have used (or cannot/should not use) lactulose in the prior 30 days or are concurrently using lactulose. For irritable bowel syndrome –diarrhea predominant, Xifaxan is reserved for members who have used (or cannot/should not use) a tricyclic antidepressant (TCA) (e.g. amitriptyline.
Last P&T Review Date	9/2024

Recommendation: No changes

Topical Acne Agents	
Therapeutic Classes (AHFS)	Cell stimulants and proliferants
Medications	Formulary restricted to members ≤ 21 years and quantity limit #45 g/30 days; prior authorization required for members > 21 years Tretinoin (Retin-A) 0.01%, 0.025%, 0.05% gel Tretinoin (Retin-A) 0.1%, 0.025%, 0.05% cream
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	Tretinoin criteria for approval: For members ≤ 21 years of age: • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to Differin 0.1% gel OTC For members > 21 years of age • Diagnosis of acne vulgaris • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to Differin 0.1% gel OTC AND topical antibiotics
Criteria Statement	For members ≤ 21 years of age, tretinoin gel or cream are reserved for members who have used (or cannot/should not use) Differin 0.1% OTC gel. For members > 21 years of age, tretinoin gel or cream are reserved for members who have acne, who have used (or cannot/should not use) Differin 0.1% OTC gel and topical antibiotics.
Last P&T Review Date	9/2024

Recommendation: No changes, except Aredia and Zometa brands were discontinued

Injectable/Infusible Bone-Modifying Agents for Oncology Indications	
Therapeutic Classes (AHFS)	Bone resorption inhibitors
Medications	**Preferred Agent, prior authorization required** Pamidronate disodium: 3mg/ml, 6 mg/ml, 9 mg/ml liquid in10 ml vials, 30 mg, 90 mg vials Zoledronic Acid 4 mg/5 ml vial **Non-preferred Agents, prior authorization required** Xgeva (denosumab) Prolia (denosumab)
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 an oncologist or endocrinologist
Coverage Duration	**Initial/Re-Approval** If all conditions are met, the request will be approved for up to for 6 months or as recommended per FDA approved indications and/or as defined by the medical compendium as defined above and/or per the NCCN, ASCO, NOF or NIH standard of care guidelines; if all of the above criteria are not met then, the request is referred to Clinical Reviewer for medical necessity review.

PA Review Criteria	**CRITERIA FOR APPROVAL:**
	• Prescribed dosing of medication is within FDA approved indications or is supported by the medical compendium as defined by the Social Security Act or per the NCCN, ASCO, or NIH standard of care guidelines.
	• If the request is for Xgeva (denosumab) for any of the indications below, the patient must have a documented trial and failure of pamidronate OR zoledronic acid or has a documented medical reason (intolerance, hypersensitivity, contraindication, renal insufficiency, etc) for not utilizing one of these agents to manage the medical condition
	  ○ bone metastases from solid tumors
	  ○ hypercalcemia of malignancy
	  ○ multiple myeloma osteolytic lesions
	• If the medication request if for Xgeva (denosumab) for treating **Giant Cell Tumor of Bone**, the patient has documentation submitted that the giant cell tumor of bone is unresectable, that surgical resection is likely to result in severe morbidity (e.g. denosumab is being used to aid in resection by shrinking the tumor), or that disease has recurred.
	• If the request is for Prolia (denosumab) for breast cancer, the patient has a documented trial and failure of pamidronate OR zoledronic acid that is consistent with claims history, or has a documented medical reason (intolerance, hypersensitivity, contraindication, etc) for not utilizing one of these agents to manage their medical condition
	• If the request is for Prolia (denosumab) for prostate cancer, approve.

Criteria Statement	Xgeva is reserved for treating Giant Cell Tumor of Bone in members who are not able to have surgery or who are not candidates for surgery, or in members where disease has recurred.

	Xgeva is reserved for members with cancer indications who have used (or cannot/should not use) pamidronate or zoledronic acid. Prolia is reserved for members with cancer indications who have used (or cannot/should not use) pamidronate or zoledronic acid.
Last P&T Review Date	9/2024

Recommendation: No changes

Alosetron (Lotronex)	
Therapeutic Classes (AHFS)	Anti-Inflammatory Agents (GI Drugs)
Medications	Alosetron (Lotronex)
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	None
Prescriber Restrictions	None
Coverage Duration	**Initial Approval** If the criteria are met, approve up to #2 tablets/day for 3 months initially. **Later Approvals** If patient is tolerating and responding to treatment after 3 months, subsequent requests may be approved for #2 tablets/day for 12 months. If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	<u>Criteria for Approval</u> • Patient has diagnosis of severe chronic diarrhea-predominant irritable bowel syndrome (IBS-D) and has had anatomic or biochemical GI abnormalities excluded and has symptoms that have lasted 6 months or longer (includes one or more of the following: frequent and severe abdominal pain/discomfort; frequent bowel urgency or fecal incontinence; disability or restriction of daily activities due to IBS) • • Documented trial and failure, contraindication, or intolerance to a tricyclic antidepressant (TCA) (e.g., amitriptyline)
Criteria Statement	Alosetron is reserved for women who have severe chronic diarrhea-predominant irritable bowel syndrome (IBS-D) who have used (or cannot/should not use) a tricyclic antidepressant (TCA) (e.g., amitriptyline).
Last P&T Review Date	9/2024

Recommendation: No changes

Viberzi (eluxadoline)	
Therapeutic Classes (AHFS)	GI Drugs, Miscellaneous
Medications	Viberzi (eluxadoline)
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	Viberzi is contraindicated in patients with sphincter of Oddi spasms.
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** If the criteria are met, approve up to #2 tablets/day for 3 months initially. **Later Approvals** If patient is tolerating and responding to treatment after 3 months, subsequent requests may be approved for #2 tablets/day for 12 months. If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	Criteria for Approval • Diagnosis of irritable bowel syndrome with diarrhea (IBS-D) • Provider attestation that the member has a gallbladder and does not drink more than 3 alcoholic beverages per day. • Documented trial and failure, contraindication, or intolerance to a tricyclic antidepressant (TCA) (e.g., amitriptyline).
Criteria Statement	Viberzi (eluxadoline) is reserved for members who have diagnosis of irritable bowel syndrome with diarrhea (IBS-D) who have a gallbladder, and do not drink more than 3 alcoholic beverages per day and have used (or cannot/should not use) a tricyclic antidepressant (TCA) (e.g. amitriptyline).
Last P&T Review Date	9/2024

Recommendation: No changes

Rifabutin (Mycobutin)	
Therapeutic Classes (AHFS)	Antitubercular agents
Medications	Formulary, PA required Rifabutin (Mycobutin) 150 mg 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	Prescriber is an infectious disease specialist or working in consultation with infectious disease specialist
Coverage Duration	**Initial Approval** **Diagnosis of tuberculosis** If all of the conditions are met, the request will be approved for up to 26 weeks. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review. **Prophylaxis of disseminated mycobacterium avium complex (MAC) disease** If all of the conditions are met, the request will be approved 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	For prophylaxis of disseminated mycobacterium avium complex (MAC) disease, approve if: • Documentation of advanced HIV • Documentation that the patient does not have active tuberculosis • Documented trial and failure, contraindication, intolerance, or inability to use azithromycin or clarithromycin • Requested dose is within recommended dosing guidelines For diagnosis of tuberculosis, approve if: • Documented contraindication, intolerance, or inability to use rifampin. • Requested dose is within recommended dosing guidelines
Criteria Statement	For prophylaxis of disseminated mycobacterium avium complex (MAC) disease, rifabutin is reserved for members who have used (or cannot/should not use) azithromycin or clarithromycin and do not have active tuberculosis. For tuberculosis, rifabutin is reserved for members who have used (or cannot/should not use) rifampin
Last P&T Review Date	9/2024

Recommendation: No changes

Medications for the treatment of Multi-Drug Resistant Tuberculosis	
Therapeutic Classes (AHFS)	Antitubercular agents
Medications	Formulary, Step Therapy required Cycloserine (Seromycin) 250 mg capsule Trecator (ethionamide) 250 mg tablet Moxifloxacin (Avelox) 400 mg tablet Linezolid (Zyvox) 600 mg tablet and 100 mg/5 ml suspension Formulary PA required Sirturo (bedaquiline fumarate) tablet Pretomanid 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	Diagnosis of latent tuberculosis or drug-susceptible tuberculosis
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Prescriber is an infectious disease specialist or working in consultation with infectious disease specialist
Coverage Duration	**Initial Approval** Trecator, Cycloserine, Moxifloxacin, Linezolid: Up to 20 months Sirturo: 24 months Pretomanid: 9 months
PA Review Criteria	**Formulary, Step Therapy required medications criteria for approval:** • Documentation member has intolerance, contraindication, or inability to use at least one first-line treatment: isoniazid, ethambutol, rifampin, OR pyrazinamide **Formulary PA required medications criteria for approval:** Sirturo (bedaquiline) One of the following: • Diagnosis is laboratory confirmed pulmonary multidrug-resistant tuberculosis (MDR-TB) or rifampicin-resistant tuberculosis (RR-TB) with an isolate showing genotypic or phenotypic resistance to rifampin (RIF) AND one of the following: o Short-course (generally 9-12 months) ▪ Resistance to fluoroquinolones (FQ) has been ruled out ▪ Is being prescribed in combination with other TB medications o Long-course (generally 15-24 months) ▪ Is being prescribed in combination with other TB medications • Is being used in combination with Pretomanid as below Pretomanid • Diagnosis is laboratory confirmed pulmonary extensively drug resistant (XDR)-TB or treatment-intolerant or non-responsive MDR-TB or RR-TB with an isolate showing genotypic or phenotypic resistance to RIF. • Documented FQ resistance • Is being used in combination with Sirturo (bedaquiline) and linezolid • Medical reason why other guideline-recommended regimens cannot be used For requests for therapy to continue beyond the coverage duration initial approval time period, approve if medical justification provided (e.g. extensively drug resistant [XDR]-TB) for continuation of therapy

	****For moxifloxacin and linezolid requests for diagnoses other than MDRTB, see the drug-specific criteria for each.**
Criteria Statement	For multi-drug resistant tuberculosis, Trecator, Cycloserine, moxifloxacin, or linezolid are reserved for members who have used (or cannot/should not use) isoniazid, ethambutol, rifampin, or pyrazinamide Pretomanid tablet is reserved for members with a diagnosis of multi-drug resistant or rifampin resistant tuberculosis, with documented fluoroquinolone resistance, when used as part of a 3-drug or regimen. Sirturo tablet is reserved for members with a diagnosis of multi-drug resistant or rifampin resistant tuberculosis, when used in combination with Pretomanid and other medications to treat tuberculosis.
Last P&T Review Date	9/2024

Recommendation: No changes

Tranexamic acid (Lysteda)	
Therapeutic Classes (AHFS)	Hemostatics
Medications	PA required, quantity limit (30/5), fill limit (1 fill per 28 days) Tranexamic acid (Lysteda) 650mg 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	Patients who are pregnant
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	None
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	Criteria for initial authorization: • Diagnosis of cyclic heavy menstrual bleeding (HMB) • The medication is used at the FDA-approved dose of 1,300 mg 3 times daily (3,900 mg/day) for a maximum of 5 days during monthly menstruation • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to a formulary combined oral estrogen-progestin contraceptive OR an oral progestin only contraceptive AND a non-steroidal anti-inflammatory agent. Criteria for re-authorization: • Patient is stable and has a reduction of heavy menstrual bleeding **Criteria for Quantities and Fills Greater Than Allowed:** If the patient requires doses greater than the set limits after meeting approval the following conditions must be met: • The provider has submitted a medical reason why the plan's quantity or fill limit will be inadequate based on the member's condition and treatment history
Criteria Statement	Tranexamic acid (Lysteda) is reserved for members who are experiencing heavy menstrual bleeding and have tried and failed or are unable to take oral contraceptives and non-steroidal anti-inflammatory agents (NSAIDs). Requests for quantities over the quantity or fill limit are reserved for members who have a documented medical need for quantities in excess of the limits.
Last P&T Review Date	9/2024

Recommendation: No changes

Moxifloxacin Oral Tablet	
Therapeutic Classes (AHFS)	Quinolone antibiotics
Medications	Formulary, Step Therapy Moxifloxacin 400mg tablet ****Please Note: If the request is for moxifloxacin for the treatment of multi-drug resistant tuberculosis, refer to criteria for medications for the treatment of multi-drug resistant tuberculosis *****
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 of the criteria are met, approve 1 fill up to FDA approved maximum dosing If the criteria is not met, the request will be referred to a clinical reviewer for medical necessity review.
PA Review Criteria	Criteria for approval: • Appropriate diagnosis/indication AND • Appropriate dose of medication based on age (i.e. pediatric and elderly populations) and indication AND • Documented trial and failure or intolerance to up to two formulary antibiotics that are used to treat the documented diagnosis OR • No other formulary medication has a medically accepted use for the patient's specific diagnosis as referenced in the medical compendia. OR • Based on culture and sensitivity data, moxifloxacin is the only treatment option.
Criteria Statement	Moxifloxacin tablet is reserved for members who have used (or cannot/should not use) up to two formulary antibiotic medications (if available) that are used to treat the documented diagnosis or when moxifloxacin is the only treatment option, based on culture and sensitivity data.
Last P&T Review Date	9/2024

Recommendation: No changes

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.
	
	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.
	• 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

Recommendation: No changes

Santyl Ointment	
Therapeutic Classes (AHFS)	Collagenase (enzymatic debriding ointment)
Medications	**Formulary, PA required** Santyl ointment
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** 3 months **Later Approvals** 3 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Criteria for initial approval of Santyl ointment**
	• Santyl ointment requests may be approved for up to 3 months
	  ○ For requests greater than 3 months, the provider must submit a medical reason of necessity
	• Type of wound is one of the following:
	  ○ Wounds to be debrided, severe burns, or chronic dermal ulcers
	• Verification that the requested amount does not exceed the amount on the Santyl dosing calculator: **https://www.santyl.com/hcp/dosing**
	  ○ Dimension of wound and duration of treatment required for calculation of dose and amount
	
	Criteria for reauthorization:
	• Documentation submitted indicates a clinical benefit was observed (e.g., reduction in wound size, decrease in wound-related pain, etc.)
	• Duration of time requested as therapy extension
	• Verification that the requested amount does not exceed the amount on the Santyl dosing calculator: **https://www.santyl.com/hcp/dosing**
	  ○ Dimension of wound and duration of treatment required for calculation of dose and amount

Criteria Statement	Santyl ointment is reserved for members who are undergoing wound care treatment requiring enzymatic debridement therapy.
Last P&T Review Date	9/2024

Recommendation: No changes

Topical Antibiotics	
Therapeutic Classes (AHFS)	ANTIBACTERIALS (SKIN, MUCOUS MEMBRANE)
Medications	Formulary, with quantity limits clindamycin phosphate topical gel 1% (60/30, 6 fills per 12 months) clindamycin phosphate (Cleocin T) topical lotion 1% (6 fills per 12 months) clindamycin phosphate (Cleocin T) topical solution 1% (6 fills per 12 months) clindamycin phosphate topical swab 1% (6 fills per 12 months) erythromycin-benzoyl peroxide (Benzamycin) topical gel 3-5% (6 fills per 12 months) Ery Pads (erythromycin) topical swab 2% (6 fills per 12 months) erythromycin with ethanol (Erygel) topical gel 2% (6 fills per 12 months) erythromycin with ethanol topical solution 2% (6 fills per 12 months) gentamicin topical cream 0.1% (2 fills per 12 months) gentamicin topical ointment 0.1% (2 fills per 12 months) A quantity limit is defined as a limitation in the amount of medication per fill or time period and/or limitation in the amount of fills per calendar year or other time period.
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	See "PA Review Criteria"
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** (request for more than 6 fills in 12 months, or 2 fills in 12 months for gentamicin) 3 months **Later Approvals** 6 months If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	Formulary step therapy required topical antibiotic criteria for approval: • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to topical benzoyl peroxide Initial Approval: Topical antibiotic request for exceeding quantity or fill limit • The member must have a documented clinical benefit and need to continue the drug prescribed over the health plan's quantity or fill limit OR • The member requires a dose within prescribing guidelines that exceeds the plan's quantity or fill limit. Later Approval: Topical antibiotic request: continues to exceed quantity or fill limit • Documentation that condition has improved or stabilized with therapy and the prescriber recommends continuation of therapy
Criteria Statement	Formulary topical antibiotic <insert drug> is reserved for members who have used (or cannot/should not use) topical benzoyl peroxide. Formulary topical antibiotic <insert drug> is reserved for members who have used (or cannot/should not use) quantities within the quantity and/or fill limits.
Last P&T Review Date	9/2024

Recommendation: No changes

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 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 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

Recommendation: No changes, except remove IFE PG20 as it has been discontinued

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: No changes

Vowst	
Therapeutic Classes (AHFS)	OTHER MISCELLANEOUS THERAPEUTIC AGENTS
Medications	Vowst (fecal microbiota spores, live-brpk)
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	Treatment of Clostridioides difficile infection (CDI)
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	If all the criteria are met, the request will be approved for 1 treatment course.
PA Review Criteria	**Initial Authorization:** • Medication is prescribed at an FDA approved dose • Diagnosis of at least 1 recurrent episode of CDI (≥2 total CDI episodes) • Current episode of CDI must be controlled (<3 unformed/loose stools/day for 2 consecutive days) • Positive stool test for C. difficile within 30 days before prior authorization request • Administration will occur 24–72 hours following completion of antibiotic course for CDI treatment • Confirmation patient will bowel cleanse using magnesium citrate or polyethylene glycol electrolyte solution the day before the first dose of Vowst *Vowst is limited to 1 treatment course*
Criteria Statement	Vowst is reserved for members who have a diagnosis of at least 1 recurrent episode of CDI (≥2 total CDI episodes), with the current episode of CDI being controlled (<3 unformed/loose stools/day for 2 consecutive days) and a positive stool test for C. difficile within 30 days before prior authorization request. Administration must be24–72 hours following completion of antibiotic course for CDI treatment and the member must bowel cleanse using magnesium citrate or polyethylene glycol electrolyte solution the day before the first dose of Vowst.
Last P&T Review Date	9/2024

Alameda PADs for review Q3 2024 P&T Consent Agenda

Recommendation: No changes

Adakveo	
Medications	Adakveo (crizanlizumab-tmca)
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 Member must be 16 years of age or older
Prescriber Restrictions	Prescriber must be a hematologist
Coverage Duration	If the criteria are met, the initial request will be approved for up to a 12 month duration; reauthorization requests will be approved for up to 12 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Member has a confirmed diagnosis of sickle cell disease
	• Documentation was provided that the member has had 2 or more pain crises in the last 12 months
	• Documentation was provided that the member has been taking hydroxyurea at the maximum tolerated dose and has been compliant within the last 6 months (or a medical reason was provided why the patient is unable to use hydroxyurea)
	• Documentation of the member's current weight
	• Request is for an FDA-approved dose
	
	Reauthorization:
	• Documentation has been submitted that the member has demonstrated or maintained ONE of the following changes from baseline:
	  ○ Reduction in pain crises
	  ○ Increased time between crises
	  ○ Decrease in days hospitalized
	• Documentation of the member's current weight
	• 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	~~9/2023~~9/2024

Recommendation: No clinical changes, minor grammatical correction

Exondys 51	
Medications	Exondys 51 (eteplirsen) 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), 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	Prescribed by neurologist or provider who specializes in the treatment of DMD
Coverage Duration	If the criteria are met, the initial request will be approved for a maximum 6 month duration. Further authorizations will be for 6 months.
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** Exondys 51 is approved when all of the following criteria are met: • Documentation of a diagnosis of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping • Dose is within FDA approved dosing • Member has been on a stable dose of corticosteroids for at least 6 months • Baseline dystrophin levels are provided • Results of motor function tests are provided [e.g. 6-Minute Walk Test (6MWT), Time to Stand Test (TTSTAND), Time to Run/Walk Test (TTRW), North Star Ambulatory Assessment (NSAA), Time to Climb 4 Steps Test (TTCLIMB)] • The member is ambulatory (e.g. able to walk with ~~our~~or without assistance, and not wheelchair dependent) **Criteria for Re-Authorization:** **Documentation of all of the following:** • The member is ambulatory • Improvement or stabilization demonstrated by scores of motor function tests [e.g. 6-Minute Walk Test (6MWT), Time to Stand Test (TTSTAND), Time to Run/Walk Test (TTRW), North Star Ambulatory Assessment (NSAA), or Time to Climb 4 Steps Test (TTCLIMB)] • Improvement in dystrophin level from baseline • Documentation of tolerability • Dose is within FDA approved dosing If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~9/2023~~9/2024

Recommendation: No changes

Erythropoiesis-Stimulating Agents	
Medications	Retacrit (epoetin alfa-epbx) - biosimilar Procrit (epoetin alfa) Epogen (epoetin alfa) Mircera (methoxy polyethylene glycol-epoetin beta) Aranesp (darbepoetin alfa) 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 "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Maximum Billable Units	variable
Coverage Duration	**Initial Approval** If criteria are met, the request will be approved as follows: 1 month if the patient is deficient in iron, vitamin B12 or folate, and in the perisurgical setting 3 months for all other requests. If the provider attests that the preferred medication is for a chronic or long-term condition, reauthorization will be approved for 12 months

Other Criteria	**** When this biosimilar is indicated, and available, the member must have documented dates of trial and failure, intolerance, inability to use, or contraindication to the biosimilar medication prior to the brand medication approval, OR 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, in addition to meeting all applicable criteria below.**
	
	<u>Criteria for authorization of existing epoetin users who are NEW to the plan:</u>
	• Documentation of current dose
	• Documentation of hemoglobin level results within 30 days or member has responded to therapy (≥1-2 g/dL increase in hemoglobin (HgB) or decrease in transfusion requirements)
	
	<u>Requests for Initial Therapy:</u>
	• All lab results submitted must have been drawn within 30 days of request:
	• The following lab values – hemoglobin (HgB) and hematocrit (HCT)
	• Normal lab results or, if abnormally low, appropriate supplementation as follows:
	  ○ serum ferritin level (normal is > 100 ng/mL)
	  ○ transferrin saturation (TSAT) (normal is > 20%)
	  ○ vitamin B12 level(> 223 pg/mL)
	  ○ folate level (> 3.1 ng/mL)
	
	• **For anemia of CKD:**
	  ○ HgB < 10 g/dL

Erythropoiesis-Stimulating Agents	

	• **For anemia related to cancer:**
	  ○ Receiving myelosuppressive therapy for palliative treatment (members receiving myelosuppressive therapy with curative intent should not receive ESAs) **AND** documented symptomatic anemia with HgB <10 g/dL
	  OR
	  ○ The member has symptomatic anemia related to myelodysplastic syndrome AND documented serum erythropoietin level ≤ 500 mU/mL
	
	• **For zidovudine-related anemia in members with HIV:**
	  ○ The member must currently be receiving zidovudine-containing highly active antiretroviral therapy (HAART) (zidovudine ≤ 4200 mg/week)
	  ○ Erythropoietin level ≤ 500 mU/mL
	
	• **For ribavirin-induced anemia:**
	  ○ Documented attempt to reduce dose was made
	  ○ HgB < 12 g/dL
	
	• **For members undergoing surgery to reduce the need for allogenic blood transfusion:**
	  ○ Perioperative hemoglobin must be < 13 g/dL and > 10 g/dL.
	  ○ The member is scheduled for an elective, non-cardiac, nonvascular surgery.
	
	Reauthorization:
	• Repeat normal labs within 30 days from date of request, or appropriate supplementation as follows:
	  ○ serum ferritin level (> 100 ng/mL)
	  ○ TSAT (> 20%)
	  ○ vitamin B12 level (> 223 pg/mL)
	  ○ folate level (> 3.1 ng/mL)
	• For anemia of CKD: HgB ≤ 11 g/dL
	• For anemia related to cancer: HgB ≤ 12 g/dL
	• For zidovudine-related anemia in members with HIV: HgB ≤ 12 g/dL
	• For ribavirin-induced anemia: HgB ≤ 12 g/dL
	• An increase in dose has not occurred more than once every 4 weeks
	• Dose continues to be appropriate per label or supported by compendia/standard of care guidelines
	
	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	~~9/2023~~9/2024

Recommendation: No changes

Iron-containing Products	
Medications	Injectafer (ferric carboxymaltose) injection, solution Ferumoxytol (Feraheme) Monoferric (ferric derisomaltose)
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	If all of the criteria are met, request may be approved for: • Injectafer: two (2) doses of up to 750mg maximum at least seven (7) days apart, or 1 dose of up to 1000mg maximum once. May reapprove for recurrent anemia • Ferumoxytol (Feraheme): 2 doses of 510mg maximum at least 3-8 days apart. May re-approve for persistent or recurrent anemia • Monoferric (ferric derisomaltose): 1 dose of up to 1000mg maximum once. May re-approve for recurrent anemia
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Diagnosis of iron deficiency anemia
	  ○ Members who have intolerance to oral iron or have tried and failed oral iron, or
	  ○ Members for whom initiation of oral iron would be medically contraindicated (such as malabsorption syndromes, severe blood loss, etc.) or
	  ○ Members is a dialysis patient
	• Medication is being prescribed at an age appropriate FDA approved dose or is supported by compendia or standard of care guidelines
	• The member has tried and failed, has an intolerance, or inability to use one of the following: iron dextran (Infed), iron sucrose (Venofer), or sodium ferric gluconate complex (Ferrlecit)
	OR
	• Diagnosis of iron deficiency in adult patients with heart failure and New York Heart Association class II/III (Injectafer only)
	
	Re-authorization:
	• Medication is being prescribed at an FDA approved dose or is supported by compendia or standard of care guidelines
	• Documentation provided that member had a positive response to therapy (as evidenced by improved lab values such as hemoglobin, ferritin, transferrin saturation) but continues to have iron deficiency or iron deficiency anemia
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~9/2023~~9/2024

Recommendation: No clinical changes, minor formatting change

Tepezza	
Medications	Tepezza (teprotumumab-trbw)
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	Member must be 18 years age or older
Prescriber Restrictions	Prescriber must be an ophthalmologist or endocrinologist
Coverage Duration	If all of the criteria are met, the request will be approved for up to 24 weeks of treatment (8 total infusions). Retreatment requests will not be allowed beyond the 8 dose limit.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	Tepezza is approved when all of the following are met:
	• Dosing does not exceed dosing guidelines as outlined in the package insert
	• Member has a confirmed diagnosis of Graves' disease
	• Documentation of moderate-severe thyroid eye disease as evidenced by one or more of the following:
	  ○ Lid retraction of >2mm
	  ○ Moderate or severe soft-tissue involvement
	  ○ Proptosis ≥3mm above normal values for race and sex
	  ○ Periodic or constant diplopia
	• Member must be euthyroid or thyroxine and free triiodothyronine levels are less than 50% above or below normal limits (submit laboratory results with request)
	• Members of reproductive potential: attestation the member is not pregnant, and appropriate contraception methods will be used before, during, and 6 months after the last infusion
	• Member has had a trial and therapy failure of, or contraindication to:
	  ○ For active disease: oral or IV glucocorticoids
	  ○ For chronic/inactive disease: rehabilitative surgery
	
	Re-authorization:
	• Retreatment or renewal requests beyond a total of 24 weeks of treatment (8 total infusions) will not be allowed.
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~9/2023~~9/2024

Recommendation: No changes

Fecal microbiota	
Medications	Rebyota (fecal microbiota, live-jslm) Vowst (fecal microbiota spores, live-brpk)
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 Healthcare Professional (USP DI), and the Drug Package Insert, and/or per the National Comprehensive Cancer Network (NCCN)
Exclusion Criteria	Treatment of Clostridioides difficile infection (CDI)
Required Clinical Information	See “other criteria”
Age Restrictions	According to package insert
Prescriber Restrictions	N/A
Coverage Duration	If all the criteria are met, the request will be approved for 1 treatment course
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** • Medication is prescribed at an FDA approved dose • Diagnosis of at least 1 recurrent episode of CDI (≥2 total CDI episodes) • Current episode of CDI must be controlled (<3 unformed/loose stools/day for 2 consecutive days) • Positive stool test for C. difficile within 30 days before prior authorization request • Administration will occur 24–72 hours following completion of antibiotic course for CDI treatment • For Vowst only: confirmation patient will bowel cleanse using magnesium citrate or polyethylene glycol electrolyte solution the day before the first dose of Vowst *Rebyota and Vowst are limited to 1 treatment course* If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review
Last Review Date	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Omisirge	
Medications	Omisirge (omidubicel-onlv)
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	Patient has previously received this medication
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescribed by an oncologist
Coverage Duration	If all the criteria are met, the initial request will be approved for a one-time treatment.
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** • Patient has a hematologic malignancy planned for umbilical cord blood transplantation (UCBT) following myeloablative conditioning • Prescriber attests that the patient is eligible for myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) AND does not have a readily available matched related donor, matched unrelated donor, mismatched unrelated donor, or haploidentical donor • Patient has not received a prior allogenic HSCT • Patient does not have known allergy to dimethyl sulfoxide (DMSO), Dextran 40, gentamicin, human serum albumin, or bovine material **The safety and effectiveness of repeat administration of Omisirge have 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 Review Date	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Qalsody (tofersen)	
Medications	Qalsody (tofersen)
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	See "other criteria"
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescribed by a neurologist, neuromuscular specialist, or physician specializing in the treatment of amyotrophic lateral sclerosis (ALS)
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	**Initial Authorization:** • Diagnosis of ALS • Documentation of genetic test confirming a mutation in the superoxide dismutase 1 (SOD1) gene • Member is not dependent on invasive ventilation or tracheostomy • Documentation of slow vital capacity (SVC) ≥ 50% • Medication is prescribed at an FDA approved dose **Re-Authorization:** • Documentation or provider attestation of positive clinical response (e.g., reduction in the mean concentration of neurofilament light [NfL] chains in the plasma, reduction in concentration of SOD1 in cerebrospinal fluid (CSF), or improvement in the Revised ALS Functional Rating Scale (ALSFRS-R) total score) • Member is not dependent on invasive ventilation or tracheostomy • 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 Review Date	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Lamzede	
Medications	Lamzede (velmanase alfa-tycv)
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	Prescribed by a specialist in the treatment of alpha-mannosidosis or other lysosomal storage disorders
Coverage Duration	If all of the criteria are met, the request will be approved for 12 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of alpha-mannosidosis as confirmed by one of the following:
	  ○ Deficiency in alpha-mannosidase enzyme levels or activity in blood leukocytes
	  ○ DNA testing
	• Prescriber attests that medication will only be used to treat non-central nervous system manifestations of alpha-mannosidosis
	• Prescriber attests patient can walk without support
	• Patient's weight
	• Dosing is consistent with FDA-approved labeling or is supported by compendia or standard of care guidelines
	
	Reauthorization
	• Patient has demonstrated a clinical response (i.e., reduction in serum oligosaccharide concentrations, stabilization or improvement in 3-minute stair climbing test [3MSCT], 6-minute walking test [6-MWT], forced vital capacity [FVC], etc.)
	• Prescriber attests that medication will only be used to treat non- central nervous system manifestations of alpha-mannosidosis
	• Prescriber attests patient can walk without support
	• 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	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Enzyme Replacement Therapies for Fabry Disease	
Medications	Fabrazyme (agalsidase beta) Elfabrio (pegunigalsidase alfa)
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	Prescribed by a geneticist, cardiologist, nephrologist or specialist experienced in the treatment of Fabry disease
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:** • Male members must have a documented diagnosis of Fabry disease confirmed by one of the following: 1. An undetectable (<1%) alpha galactosidase A (alpha-Gal-A) activity level OR 2. A deficient alpha-Gal-A activity level AND a documented detection of pathogenic mutations in the galactosidase alpha (*GLA*) gene by molecular genetic testing • Female members must have a documented diagnosis of Fabry disease confirmed by detection of pathogenic mutations in the *GLA* gene by molecular genetic testing AND evidence of clinical manifestation of the disease (e.g. kidney, neurologic, cardiovascular, gastrointestinal) • Member must not be using concurrently with Galafold (migalastat) • Documentation of the member's current weight • Request is for an FDA-approved dose **Re-Authorization:** • Documentation that member has experienced an improvement in symptoms from baseline including but not limited to: decreased pain, decreased gastrointestinal manifestations, decrease in proteinuria, stabilization of increase in eGFR, reduction of left ventricular hypertrophy (LVH) on echocardiogram, or improved myocardial function, or has remained asymptomatic • Member must not be using concurrently with Galafold (migalastat) • Documentation of the member's current weight • 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	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Roctavian	
Medications	Roctavian (valoctocogene roxaparvovec-rvox)
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	Prior use of gene therapy for Hemophilia 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 hematologist
Coverage Duration	If all the criteria are met, the initial request will be approved for a one-time treatment
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** • Diagnosis of severe hemophilia A (congenital factor VIII deficiency with factor VIII activity < 1 IU/dL) • Documentation of a current prophylactic regimen of Factor VIII infusions or bispecific monoclonal antibodies (i.e. Hemlibra) • Documented FDA-approved anti-AAV5 antibody test showing the patient is negative for anti-AAV5 antibodies • Documented Factor VIII inhibitor titer test showing the patient is negative for Factor VIII inhibitors • Prescriber attestation of performed liver health assessments • Patient weight • Medication is prescribed at an FDA approved dose **The safety and effectiveness of repeat administration of Roctavian 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 Review Date	~~9/2023~~9/2024

Recommendation: No clinical changes, addition of medical necessity review statement

Enzyme replacement therapy for acid sphingomyelinase deficiency (ASMD)	
Medications	Xenpozyme (olipudase alfa-rpcp)
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	Specialists experienced in the treatment of ASMD
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 12 months.
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Medication is prescribed at an FDA approved dose
	• Member has a diagnosis of ASMD confirmed by one of the following:
	  ○ Deficiency in acid sphingomyelinase (ASM) enzyme activity (as measured by peripheral blood leukocytes, cultured skin fibroblasts, or dried blood spots)
	  ○ Sphingomyelin phosphodiesterase-1 (SMPD1) gene mutation
	• Member has a clinical presentation consistent with ASMD type B or type A/B
	• Documentation of members height and weight
	• Documentation of baseline ALT and AST within 1 month prior to initiation of treatment
	
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response (i.e. improvement in splenomegaly, hepatomegaly, pulmonary function, 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	~~9/2023~~9/2024

Alameda Alliance for Health (IHSS)

Q3 2024 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
Fasenra Subcutaneous Solution Prefilled Syringe 10 MG/0.5ML	NF to F-PA
Acthar Gel Subcutaneous Auto-injector 80 UNIT/ML	NF to F-PA
Acthar Gel Subcutaneous Auto-injector 40 UNIT/0.5ML	NF to F-PA
Entresto Oral Capsule Sprinkle 6-6 MG	NF to F-QL (240/30 days)
Entresto Oral Capsule Sprinkle 15-16 MG	NF to F-QL (240/30 days)
Afluria Intramuscular Suspension	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Afluria Preservative Free Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Fluad Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (65 years and up) (1 fill per 270 days)
Fluarix Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Flublok Intramuscular Solution Prefilled Syringe 0.5 ML	NF to F-AL-QL (18 years and up) (1 fill per 270 days)
Flucelvax Intramuscular Suspension	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Flucelvax Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Flulaval Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Fluzone High-Dose Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (65 years and up) (1 fill per 270 days)
Fluzone Intramuscular Suspension	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
Fluzone Intramuscular Suspension Prefilled Syringe 0.5 ML	NF to F-AL-QL (12 years and up) (1 fill per 270 days)
FluMist Nasal Liquid	NF to F-AL-QL (12-49 years) (1 fill per 270 days)

Alameda Alliance for Health

Q3 2024 INTERIM PAD UPDATES

These changes have been made to the Alliance's Physician Administered Drugs recently. Changes were made to enhance prior authorization process.

HCPCS Code	HCPCS Description	Action
J7682	TOBRAMYCIN NON-COMP UNIT	Remove from PA
J9057	COPANLISIB	Remove from PA
J9070	CYCLOPHOSPHAMIDE	Remove from PA

ALAMEDA Alliance FOR HEALTH

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

POLICY AND PROCEDURE

Policy Number	RX-002
Policy Name	Pharmacy Benefit Prior Authorization Review Process
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	IHSS
Effective Date	12/01/1997
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	9/24/2024~~3/19/2024~~
Compliance Committee Approval Date	TBD~~4/10/2024~~

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 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. The Alliance covers medications for treating gender dysphoria or alleviating mental health or substance use.

This policy and the associated procedures pertain to general prior authorizations for medications.

PROCEDURE

I. Prior Authorization Process Guidelines

A. Prior authorization review and approval criteria (or Medication Review Guidelines) are required for the drugs or dosage forms included in the Alliance formulary that require prior authorization.

B. The Alliance's prior authorization requirements and review processes are available to practitioners and providers through the Alliance's Provider Manual, provider newsletters and on the Alliance's website. Likewise, they are available to members through the Alliance's Evidence of Coverage documents, member newsletters, and on the Alliance's website. 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.

II. Submitting a Prior Authorization (PA) or Appeal

Prior authorizations and appeals may be filed either orally or in writing by the member/member's representative or the member's provider/provider's office authorized representative. Prior Authorizations ~~and appeals~~ are received by telephone via PerformRx help desk, PerformRx PA fax number or our direct pharmacy telephone number. Appeals are received by the Alliance grievance and appeals (G&A) department orally or in writing by the member/member's representative or member's provider/provider's office representative. The Alliance provides a prompt review of prior authorizations and appeal requests (24 hours for prior authorizations and up to 30 days for an appeal).

III. Prior Authorization Requirements and Processes

A. The Alliance supplies all providers with the Medication Prior Authorization (PA) form and instructions for its use. The member may initiate the PA review process by calling the Alliance customer service number and requesting a review. The Alliance will supply the member's provider with the PA form and instructions for use.

B. The Alliance does not accept PA forms completed by members or members' caretakers (although members and members' caretakers may initiate a request by phone, email, or any other communication method utilized by the Alliance Member Services Department).

C. The PA form shall be in compliance with Title 28, Division 1, Chapter 2, Article 7 § 1300.67.241. PA request can be made telephonically or through a web portal or a fax.

D. The Alliance shall not request the provider to submit more than "Minimum Amount of Material Information" in the prior authorization process to determine if the PA request should be approved or disapproved.

E. Providers are responsible for submitting a complete PA form to request authorization requests for medical necessity review. A PA form for an authorization request is only complete when all the information required to review the request and render a decision is provided.

F. Additional information that may be requested from the pharmacy, provider, member, or family member can include but are not limited to:
   1. Reason for the medication 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. Laboratory testing results
   11. Patient psychosocial history
   12. Evaluations from other health care practitioners and providers
   13. Diagnostic images
   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

G. Outreach calls (up to 2 attempts within 24-hr TAT) may be made to the requesting provider to

request reasonably necessary clinical information when needed to make a PA decision for medication requests. For each outreach attempt, the reviewer is to document the following:

a) Name and title of person spoken to
b) Phone number called (if different from one already noted in the PA system)
c) What specific information was requested

H. The Alliance utilizes criteria that have been approved by the Alliance Pharmacy and Therapeutics (P&T) Committee. The criteria are objective in nature and utilize evidence-based guidelines, national guidelines, and current medical and pharmaceutical literature. The review guidelines are maintained in the Medication Request Guidelines (MRG) document.

I. The criteria in the MRG are reviewed quarterly by the P&T Committee, which is co-chaired by the Alliance's Chief Medical Officer and the Alliance's Senior Director of Pharmacy Services. The P&T Committee is made up of currently licensed pharmacists and physicians with expertise in developing, adopting, and reviewing criteria. This committee has the responsibility to apply relevant evidence-based guidelines and current medical evidence when recommending and approving revisions to the criteria. These criteria and process revisions are then applied to the MRG to be used by reviewers.

J. The criteria are applied with consideration to individual needs. This includes but is not limited to:
1. Allergy, intolerance, or resistance to a medication
2. Availability of a formulary alternative
3. The age of the member and comorbidities
4. Additional clinical complications
5. Home environment and transportation issues that may impact the member's ability to comply with the treatment plan
6. Clinical progress or lack of responsiveness to medications
7. Ability to safely self-administer drugs and whether specialized home care services may be required
8. Any psychosocial conditions which may impact medication administration

K. The local delivery system may also be factored into the criteria. Examples include:
1. Medications with limited distribution through specialty pharmacy vendors
2. Pharmacy does not have a formulary medication in stock
3. Member is not able to pick up medication from pharmacy and requires delivery

L. If a reviewer is not able to review a request using the MRG based on individual needs or delivery system considerations the request will be considered an Exception Request (***see RX-003 Exception Review Process***). The reviewer then adheres to the following process:
1. The reviewer documents the reason why the MRG cannot be used and refers the case to a pharmacist for review.
2. The pharmacist reviews the case and background materials. When appropriate, the pharmacist can approve the request, documenting the rationale for the authorization.
3. The pharmacist can modify or deny the request for the following reasons:
   a) Insufficient information was received to make a decision (as determined by the Alliance Medication Request Guidelines, national standard guidelines, prescribing information, or other sources of standard prescribing information).
   b) Not a covered benefit: The requested medication is not a covered benefit (<u>unless treating gender dysphoria or alleviating mental health or substance use</u>):
      (1) The product requested is a dietary supplement, Medical Food, or other products not approved by the FDA.
      (2) The product requested is being used for a cosmetic purpose.

(3) Appetite/weight suppressants being used for cosmetic purposes and with no medical necessity (as documented by clinic notes)
(4) The product requested is being used to aid/improve hair growth or impair/stop/reduce hair growth.
(5) The product requested is to be used by the member as part of a medical or clinical study protocol. Note that supporting medications that may be needed for the study (but are not directly a part of the study) are covered by Alameda Alliance.

c) Generic Substitution Required: The request is for a Brand Name Drug that has at least one Food and Drug Administration (FDA) A-B rated generic formulation available. Requests for "brand-name drug only" will be handled in accordance with the Alameda Alliance Medication Request Guideline for Brand Name Requests When Generic is Available.

d) Biosimilar Substitution Required: The request is for a Brand Name Drug that has at least one Food and Drug Administration (FDA) approved biologically similar product available. Requests for "brand-name drug only" will be handled in accordance with the Alameda Alliance Medication Request Guideline for Brand Name Requests when Biosimilar is Available.

e) **Non-Formulary:** The product requested is not on the formulary and the member has not met the non-formulary approval criteria as outlined by the Alameda Alliance Medication Request Guidelines for non-formulary medications.

f) **Criteria not met**: The product requested and accompanying information submitted does not meet the approval criteria (as reviewed and approved by the Alameda Alliance Pharmacy & Therapeutics Committee) and is outlined in the Alameda Alliance Medication Request Guidelines.

g) **Investigational:** The request is for off-label or investigational use that is not supported by drug compendia and its use is not supported by nationally recognized treatment guidelines or by two (2) peer reviewed articles.

h) **Medical Necessity**: Use of the requested product does not meet medical necessity. To meet medical necessity, the treatment must be ALL the following:
(1) Safe, effective, and within national standards of practice.
(2) Not experimental or part of a current clinical trial or study.
(3) Specific and treat the identified condition.
(4) Expected to improve health or prevent or delay progression of the condition from getting worse.
(5) Not primarily for convenience.
(6) Not being used to avoid legal consequences.
(7) Not to be contraindicated, dangerous to the patient, or have other reasons why the requested drug should not be used.

i) **Other Payor Responsibility**: There is documentation available showing that the medication should be covered by another payor (e.g., Medi-Cal, other commercial, Medicare, Fee-for-service, California Children's Services).

j) **Benefit Limit Exceeded**: The benefit limit for a drug or service (as reviewed and approved by the Alameda Alliance Pharmacy & Therapeutics Committee) and is outlined in the Alameda Alliance Medication Request Guidelines has been reached without documentation why further therapy is necessary.

k) Request for additional clinical information goes unanswered

l) **Retro Requests:** These requests will only be reviewed when received within 90 days of the given pharmacy product. Requests made on the 91st day and afterwards will be subject to denial.

M. Of the above listed denial reasons, the pharmacist will review the requests for medical necessity

(essentially becoming an ***Exception Request***, refer to ***RX-003 Exception Review Process***) if:

1. Clinical information provided does not meet criteria for use based on MRG.
2. The member has not tried and failed the initial treatment option for drugs that require step therapy.
3. Benefit rules cannot be applied AND there is no MRG.

N. The pharmacist will defer cases that cannot be denied based on the above listed denial reasons (and do not qualify as an ***Exception Request, see RX-003 Exception Review Process)***. These requests and any other highly complicated cases will be sent to an Alliance board-certified Medical Director for review.
   1. 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.
   2. The Medical Director may render one of 3 decisions: approve, deny, or modify.
   3. The Medical Director finalizes the review and returns the case to the reviewing pharmacist with documentation of their decision and the rationale.

O. The reviewer documents the criteria and rationale for the decision in the pharmacy authorization system. If the decision is a denial, the specific reasons or missing information are clearly and concisely included.

P. The plan ensures that only licensed pharmacists, physicians, or other licensed health care professionals competent to evaluate the clinical issues can make decisions regarding medically necessary non-formulary drugs.

Q. Members receive a notice of action (NOA) letter with the outcome of the request, their rights, and the process to appeal the decision. The provider also receives a NOA via fax or regular mail. (see *RX-011 – Member and Provider Decision and Notification Requirements*)

IV. Authorization Processing Time Frames (***See RX-011 – Review and Notification Time Frames)***

For processing times of authorizations, the Alliance conforms to standards issued by the National Committee on Quality Assurance, and California state law. Please see Table 2 for detailed turnaround time requirements.

A. Prospective Standard Requests
   1. **Group Care (IHSS):** The plan makes decisions to approve, modify, or deny prescription drug authorization requests within 24 hours from time of receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases, and notifies the requesting provider by telephone or fax of the plan's determination within in 24 hours from time of receipt for urgent/emergent cases and for non-urgent cases in accordance with Title 28, Division 1, Chapter 2, Article 7 §1300.67.241
      a) The requested treatment shall be deemed authorized if the required information is provided and the Alliance fails to make a determination by the expiration of the applicable time frame.

V. 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. The Alliance allows for payment of the three (3) day supply of the drugs even if the prior authorization request is subsequently denied.
F. 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. Provision of Contraceptive Drugs

A. The Alliance covers all FDA approved contraceptive drugs, devices, and other products, including all FDA-approved contraceptive drugs, devices, and products available over the counter, as prescribed by the member's provider.
   1. The Alliance provides coverage of at least one FDA approved contraceptive drug, device, or product without cost sharing for the original, brand name contraceptive if there is no therapeutic equivalent generic substitute available in the market.
   2. The Alliance defers to the determination and judgment of the provider and provide coverage for the alternative prescribed contraceptive drug, device, product, or service without imposing any cost sharing requirements if the covered therapeutic equivalent of a drug, device, or product is deemed medically inadvisable by the member's provider.
   3. The Alliance does not infringe upon a member's choice of contraceptive drug, device, or product and shall not impose any restrictions or delays on the coverage required, including prior authorization, step therapy, or utilization control techniques.
   4. The Alliance clarifies that the exclusion from contraception coverage for religious employers does not apply to a contraceptive drug, device, procedure, or other product that is used for purposes other than contraception.
   5. The Alliance does not require a member to make any formal request (i.e., prior authorization requests, any utilization controls, or any other forms of medical management restrictions), other than a pharmacy claim, for coverage of receiving a 12-month supply of self-administered hormonal contraceptives at one time.

VII. Annual Review of Pharmacy Prior Authorization and UM Criteria

A. All pharmacy utilization management criteria undergo annual evaluation for appropriateness and effectiveness. Criteria are updated when necessary. The P&T committee reviews the pharmacy UM program, including delegated elements. The review encompasses scope, policies and procedures, and criteria as appropriate.

VIII. Monitoring of the PA process

A. The Alliance provides oversight of its PBM through an annual audit of the PA review process.
B. The Senior Director of Pharmacy Services reviews a monthly authorization report, which provides statistics on all approvals, denials, modifications to ensure that providers and members have been notified in accordance within the mandated turnaround times.
C. Inter-rater Reliability- the Alliance evaluates the consistency of decision making for those health care professionals involved in applying Pharmacy Criteria

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DEFINITIONS / ACRONYMS

Terminal Illness: 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)).

"Minimum Amount of Material Information": the information generated by or in the possession of the prescribing provider related to the patient's clinical condition that enables an individual with the appropriate training, experience, and competence in prescription drug prior authorization processing to determine if the prescription authorization request should be approved or disapproved. (Title 28, Division 1, Chapter 2, Article 7 § 1300.67.241)

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)).

NCQA: National Committee on Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently PerformRx)

RELATED POLICIES AND PROCEDURES

RX-003 Exception 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 Types
Table 2: Turn-Around Times based on Regulatory Bodies
Table 3: Decision & Notification Time Frames for Alameda Alliance
Figure 1: Prior authorization and exception request workflow

REVISION HISTORY

12/01/1997, 3/25/2016, 10/12/2017, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 9/20/2022, 6/20/2023, 9/26/2023, 4/10/2024, 9/24/2024

REFERENCES

- California Code of Regulations (CCR), Health & Safety Code, §§1367.01, 1367.21, 1367.22,1367.24, 1367.25 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 5 (Timeliness of UM Decisions)
- NCQA, 2016 HP Standards & Guidelines, UM 7 (Denial Notices)
- NCQA, 2016 HP Standards & Guidelines, UM 13 (Procedures for Pharmaceutical Management)
- 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 – MediCal Rx

MONITORING

This P&P is reviewed annually to ensure effectiveness.

APPENDIX

Table 1: Decision Types

a. IHSS

Reviewer Type	Approval	Denial	Modification	Deferral
PBM Clinicians	Yes	Yes	Yes	N/A
Plan Pharmacist	Yes	Yes	Yes	N/A
Plan Medical Director	Yes	Yes	Yes	N/A

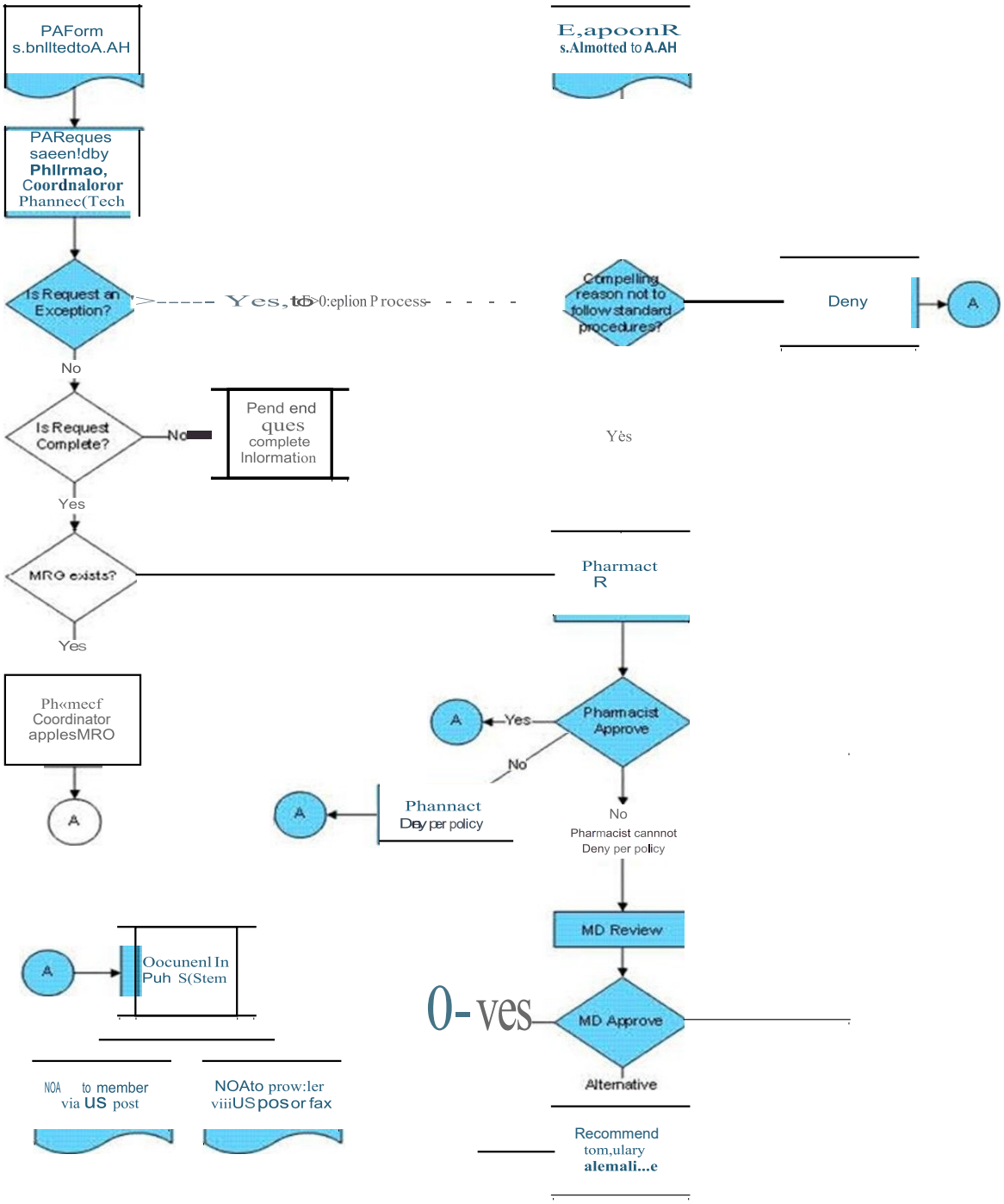
Table 2. Pharmacy Benefit Determination Turnaround Timetable of Different Regulatory Bodies

Type of Request	NCQA	DHCS	DMHC	**Alliance**
Prospective, Urgent	72 hours	72 hours	24 hours	**24 hours**
Prospective, Non-Urgent	15 calendar days	5 business days	72 hours	**72 hours**
Post-service	30 calendar days	30 calendar days	30 calendar days	**72 hours**

Table 3: Decision & Notification Time Frames

Type of Request	**Decision**	**Initial Notification**	**Written Notification**
Prospective, Urgent	Approval Modification Denial	A fax is sent to the requesting provider within 24 hours of receipt of the request	NONE 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
Prospective, Non-Urgent	Approval Modification Denial	A fax is sent to the requesting provider within 72 hours of receipt of the request	NONE 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
Post-service	Approval Modification Denial	A fax is sent to the requesting provider within 72 hours of receipt of the request	NONE 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)



ALAMEDA Alliance FOR HEALTH
Health care you can count on.
Service you can trust.

POLICY AND PROCEDURE

Policy Number	RX-005
Policy Name	P&T Committee Roles and Scope
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	IHSS
Effective Date	02/01/2012
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date	9/24/2024~~3/19/2024~~
Compliance Committee Approval Date	TBD~~4/10/2024~~

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 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.

PROCEDURE

To help assure continuing patient access to a quality-driven, cost-effective, rational, drug benefit through the Alliance Drug Formulary, the P&T Committee will complete the following activities and adhere to the following operating procedures.

All pharmacy criteria decisions made by the Committee will be based upon a thorough review of the relevant findings of government agencies, medical associations, national commissions, peer-reviewed journals, and authoritative compendia consulted in pharmaceutical determinations.

The Committee will apply the above findings in adopting the pharmaceutical management procedures, including those used in constructing the formulary or preferred status. Evidenced based guidelines and guidelines will be applied when determining the following:

A. For the non-covered pharmaceuticals, making available an exceptions process to obtain the drugs
B. Considerations regarding limiting access to drugs in certain classes
C. Considerations on whether a pharmaceutical class is covered, not covered, or covered with restrictions and within each class of pharmaceuticals the following considerations are made:
    a. Which pharmaceuticals are preferred or covered at any level
    b. The criteria for prior authorizations of any pharmaceutical not covered
    c. Exceptions process available to members
    d. Substitutions made automatically or with physician permission
    e. Evidence showing how preferred-status pharmaceuticals can produce similar or better results for a majority of the population than other pharmaceuticals in the same class

I. Organization and Operation

A. Membership

1. The Committee shall be comprised of the following members:
    a) Alliance Chief Medical Officer (Co-Chair) or designee
    b) Alliance Senior Director of Pharmacy Services (Co-Chair) or designee
    c) Practicing physician(s) representing Family Practice and/or Internal Medicine
    d) Practicing physician(s) representing Pediatrics
    e) Practicing physician(s) representing a medical specialty as needed in accordance with the agenda
    ~~e)~~f) Practicing psychiatric specialist (e.g., psychiatric pharmacist/physician)
    ~~f)~~g) Practicing community pharmacist(s) contracted with Alliance (not to exceed three)
2. Non-voting members:
    a) Alliance Pharmacy Benefit Management Company representative pharmacist(s)
    b) Alliance Director of Provider Relations or designee
    c) Designated personnel (physician, pharmacist, nurse, etc.) representing Quality Assurance.
3. Membership should represent health care providers who serve the Alliance's patient population.
4. All Committee members shall complete a conflict-of-interest form pertaining to any financial or other relationship with pharmaceutical manufacturers. All Committee members' affiliations with outside interests shall not impair the responsible exercise of his or her duties as a P&T Committee member. If they have financial interest with a particular pharmaceutical manufacturer, they will be excluded from discussing and voting on evaluations or policies regarding the manufacturer's product line. (Refer to Appendix 1)
5. Compensation: Voting P&T members who are not Alliance staff are eligible to receive a financial stipend for each attended meeting and e-voting completed

B. Quorum

A quorum, is defined as a simple majority of voting members, must be present to conduct the P&T Committee meeting. A consensus decision will be made on formulary additions, deletions, and drug use/benefit policies. If no consensus is established, the issue will be put to a vote with the decision determined by majority vote of the quorum.

C. Schedule

The P&T Committee shall meet quarterly, at least four times per year. If urgent matters (as determined by the Alliance Chief Medical Officer) pertaining to the selection or utilization of drugs arise between meetings, a telephone or electronic voting will be conducted with the members. All relevant matters discussed between meetings will be presented formally at the next meeting.

D. Materials

An agenda and supplementary materials, including minutes of the previous meeting, shall be prepared, and submitted to the Committee members at least 7 days prior to the meeting to ensure proper review of the material.

1. Minutes of the Committee proceedings shall be prepared and maintained in the permanent records of Alliance.

E. Formulary Change Requests

Alliance providers may request additions, deletions, and modifications to the Alliance Drug Formulary by completing Formulary Request Form found in the Alliance Provider Manual. All requests shall be communicated in writing or by fax to:

Alameda Alliance for Health
Pharmacy Services
1204 South Loop Road
Alameda, CA 94502
Fax: 877-748-4524

F. Pharmaceutical Management Procedures

1. The P&T Committee will review pharmaceutical management procedures including medication guidelines, criteria, and clinical evidence, at least once every 12-month period and update those procedures as necessary as a result of that review.

2. Newly approved and marketed drugs will not be a pharmacy benefit until reviewed for addition to the Drug Formulary. FDA AA or P rated drugs (drug indicated for treatment of AIDS and HIV related illness and drugs with important therapeutic gain over existing therapies) may be an exception to the rule.

3. Addition or deletion to the Drug Formulary will be conducted at least once a year. Exceptions will be a drug product with clinical evidence supporting a significant improvement or decline in reported efficacy,

safety, or cost as determined by the Committee.

4. All decisions by the Committee to add or delete a drug from the Drug Formulary will take effect the first calendar day of the second month after the meeting unless otherwise specified. This is to allow time to notify physicians and other providers and change systems if needed.

5. Appeals to the Committee decisions may be made in writing within one month of the decision notification to the Chair of the Committee. These will be addressed on a case-by-case basis at the discretion of the Committee Chair.

II. Functions and Scope

The functions and scope of this Committee are designed to meet the following goals: to provide quality health care, to manage and control drug costs, and to continue to grow while ensuring the necessary management of resources.

A. Drug Formulary (See RX-004, Formulary Management)

1. Maintain a list of routinely covered drugs acceptable for use in the ambulatory care setting and provide for its constant revision
2. The selection of items to be included in the Drug Formulary shall be based on objective pharmacoeconomic evaluation of their relative therapeutic efficacy, safety, and cost. Therapeutic efficacy, safety, and adverse effects will be considered as the primary reasons for formulary inclusion/exclusion. If those are deemed to be equivalent or similar, the committee will also consider the Pharmacoeconomics of formulary inclusion/exclusion of the drug.
3. The Committee will attempt to minimize duplication of the same basic drug type, drug entity or drug product.

B. Guidelines and Protocols

1. To review drug utilization patterns and establish guidelines, protocols, programs, and procedures that help ensure high quality, cost-effective drug therapy.

C. Drug Use Review (DUR)

1. To recommend, initiate or direct Drug Use Review (DUR) and quality assurance programs. This includes recommending target drug or disease states to review, approving criteria for use before review, reviewing results when completed, making recommendations to appropriate departments, providers, etc., to take corrective action when less than optimal therapy is discovered, and measure for change after corrective action is in place. When recommendations for corrective action involve an individual provider, particularly change in a provider's scope of practice, such recommendation will be reported to the HCQC.

D. Scope of Decisions

1. The committee will make decisions on the following concerns:
2. Classes of pharmaceuticals

3. Classes preferred or covered at any level
4. An exceptions process available to members for obtaining non-covered pharmaceuticals
5. Considerations regarding limiting access to drugs in certain classes Within each class of pharmaceuticals

    (1) The pharmaceuticals preferred or covered at any level
    (2) The criteria for prior authorization of any pharmaceutical
    (3) An exceptions process available to members
    (4) Substitutions made automatically or with physician permission
    (5) This evidence can show how preferred-status pharmaceuticals can produce similar or better results for a majority of the population than other pharmaceuticals in the same class.

E. Evidence-Based Decision Making

These decisions are based on appropriate external evidence to support continued use of revisions of procedures or criteria set forth in section D.

The following are considered by the P&T Committee when reviewing the formulary:

1. The formulary will contain drugs which represent each mechanism of action sub-class within all major therapeutic categories of prescription drugs.. Drugs newly approved by the Federal Drug Administration (FDA) are reviewed by the P&T Committee within (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 in the Alliance's formulary.
2. In accordance with the Health and 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 use which that drug had been approved for marketing by the FDA, provide that all the following conditions are met.
    a) The drug is prescribed by a participating licensed health care professional for the treatment of:
        (1) A life-threatening condition
        (2) 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'srequest is reviewed in accordance with Health & Safety Code, CCR, Section 1367.24.

    b) The drug has been recognized for the treatment of that condition by one of the following:
        (1) The American Medical Association Drug Evaluations
        (2) The American Hospital Formulary Service Drug Information.

(3) The United States Pharmacopoeia Dispensing Information, Volume 1, "Drug Information for the Health Care Professional."
(4) 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.

3. Alliance Provider recommendations for addition or deletion of drugs to the formulary
4. Bioavailability data
5. Cost comparisons against other drugs available to treat the same medical condition(s)
6. Current therapeutic guidelines
7. Dosage ranges by route and age
8. Findings from the following agencies: governmental agencies, medical and pharmaceutical associations, the National Institutes of Health, and regulatory body publications
9. Off-label uses
10. Patient risk factors relative to contraindications, warnings, and precautions
11. Patient utilization and experience
12. Pharmacoeconomic data
13. Pharmacokinetic data
14. 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)
15. Risks versus benefits regarding clinical efficacy clinical efficacy and safety of a particular drug relative to other drugs with the same indication
16. Special monitoring or medication administration requirements

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.

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services Department
Pharmacy Benefit Manager (Currently – *PerformRx*)

RELATED POLICIES AND PROCEDURES

P&T Charter
Alliance Bylaws – Section 6
RX-002 Prior Authorization Review Process
RX-004 Formulary Management

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENT

Appendix 1: Confidentiality & Conflict of Interest Form

REVISION HISTORY

11/13/2020, 3/16/2021, 6/21/2022, 3/28/2023, 6/20/2023, 4/10/2024, 9/24/2024

REFERENCES

- NCQA UM 12.A.1
- NCQA UM 12.D. 1 and 2
- H&SC 1367.24
- H&SC 1367.21
- 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.

Alameda Alliance for Health
1240 South Loop Road
Alameda, CA 94502
Phone Number: **1.510.747.4567**
Toll-Free: **1.877.932.2738**
People with hearing and speaking impairments (CRS/TTY): **711/1.800.735.2929**

www.alamedaalliance.org

90-Day Supply on Maintenance Medications

Medications are available for Alliance Group Care Members through choice in-network retail pharmacies or Walgreens Mail Service pharmacy. Prescriptions are filled with generic versions, when available and medically necessary. Certain medications are subject to prior authorization (PA) review by Alameda Alliance for Health (Alliance).

This list may not include all 90-day maintenance medications as product updates are being made periodically. Questions about drugs not included on this list should be directed to the Alliance Pharmacy Services Department at **1.510.747.4541**. Products in red are new additions to the list.

Asthma & COPD

Arnuity Ellipta
Atrovent HFA
Combivent
Flovent Diskus
Flovent HFA
Fluticasone/Salmeterol blister w/device
Fluticasone/Salmeterol Respiclick
Montelukast
Qvar Redihaler
Spiriva HandiHaler
Spiriva Respimat
Stiolto Respimat
Theophylline
Tudorza Pressair

Blood Pressure & Heart Health

Acetazolamide
Aliskiren
Aliskiren/Amlodipine
Amiloride
Amiodarone
Amlodipine/Benazepril
Aspirin/Dipyridamole
Atenolol
Atenolol/Chlorthalidone
Azilsartan
Benazepril
Benazepril/HCTZ
Bisoprolol Bisoprolol/HCTZ
Bumetanide

Blood Pressure & Heart Health (cont.)

Candesartan
Captopril
Carvedilol
Chlorthalidone
Cilostazol
Clonidine
Clopidogrel
Digoxin
Diltiazem
Dipyridamole
Dronedarone
Enalapril
Enalapril/HCTZ
Eprosartan

Blood Pressure & Heart Health (cont.)

Eprosartan/HCTZ
Felodipine
Flecainide
Fosinopril
Furosemide
Guanfacine
Hydralazine
Hydrochlorothiazide
Indapamide
Irbesartan
Irbesartan/HCTZ
Isoproterenol
Isosorbide Dinitrate
Isosorbide Mononitrate
Labetalol
Lisinopril
Lisinopril/HCTZ
Methyldopa
Methyldopa/HCTZ
Metolazone
Metoprolol Succinate
Metoprolol Tartrate
Mexiletine
Midodrine
Minodixidil
Nadolol
Niacin
Nicardipine
Nifedipine
Nitroglycerin
Olmesartan

Blood Pressure & Heart Health (cont.)

Pentoxifyline
Pindolol
Prazosin
Propafenone
Propranolol
Propranolol/HCTZ
Quinidine gluconate
Quinidine sulfate
Ramipril
Reserpine
Sotalol
Spironolactone
Spironolactone/HCTZ
Telmisartan
Telmisartan/HCTZ
Terazosin
Triamterene/HCTZ
Valsartan/HCTZ
Verapamil
Warfarin

Diabetes

Chlorpropamide
Glimepiride
Glipizide
Glyburide
Glyburide, micronized
Glyburide/Metformin
Metformin
Nateglinide
Pioglitazole/Metformin

Diabetes (cont.)

Pioglitazone
Rosiglitazone
Rosiglitazone/Metformin
Tolazamide
Tolbutamide

Gastrointestinal Health

Balsalazide
Sulfasalazide
Ursodiol

Gout

Allopurinol
Probenecid

High Cholesterol

Atorvastatin
Cholestyramine/Aspartame
Colestipol
Docosahexanoic Acid/EPA
Ezetimibe/Simvastatin
Fenofibrate
Fenofibrate, nanocrystalized
Fluvastatin
Gemfibrozil
Lovastatin
Omega-3 Fatty Acids/Fish Oil
Omega-3 Fatty Acids/Vitamin E
Simvastatin

Liver Disease
Adefovir
Baraclude solution
Entecavir
Lamividine
Tenofovir 300mg tablets
Vemlidy
Viread

Men's Health
Alfuzosin
Doxazosin
Finasteride
Tamsulosin
Terazosin

Mental Health
Bupropion
Duloxetine
Escitalopram
Fluoxetine
Mirtazapine
Paroxetine
Sertraline
Trazodone

Miscellaneous
Cabergoline
Fludrocortisone
Hydroxychloroquine
Hydroxyurea
Leflunomide
Methazolamide

Miscellaneous
Methotrexate
Methylsulfate
Neostigmine

Myasthenia Gravis
Edrophonium Chloride
Physostigmine Salicylate
Pyridostigmine Bromide

Osteoporosis & Paget's Disease
Alendronate
Calcitonin (Salmon)
Raloxifene

Parkinson's & Alzheimer's
Bromocriptine
Carbidopa/Levodopa
Donepezil
Entacapone
Pramipexole
Ropinirole

Seizures & Epilepsy
Carbamazepine
Clobazam
Clonazepam
Divalproex sodium
Ethosuximide
Ezogabine
Gabapentin
Levetiracetam
Levetiracetam NaCl

Seizures & Epilepsy
Phenobarbital
Phenytoin
Primidone
Rufinamide
Tiagabine
Topiramate
Valproic Acid
Zonisamide

Thyroid Conditions
Armour Thyroid
Levothyroxine
Liothyronine
Methimazole
Propylthiouracil

Transplant
Azathioprine
Mycophenolate Mofetil
Mycophenolate Sodium
Tacrolimus

Urinary Incontinence & Retention
Bethanechol
Desmopressin
Oxybutinin

Vitamins & Nutritional Health
B Complex with Vitamin C
Calcitriol
Calcium Acetate 667 mg
Calcium Carbonate

Vitamins & Nutritional Health

Calcium Carbonate/Vitamin D2
Calcium Carbonate/Vitamin D3
Calcium Citrate/Vitamin D2
Calcium Citrate/Vitamin D3
Calcium Glubionate
Calcium Gluconate
Calcium Lactate
Calcium Phosphate/Vitamin D3
Cholecalciferol (Vitamin D3)
Cyanocobalamin (Vitamin B-12)
Ferrous Sulfate
Folic Acid
Folic Acid with Multivitamins
Magnesium Oxide
Multivitamins
Potassium Bicarbonate
Potassium Chloride
Pyridoxine
Thiamine

Women's Health

Estradiol
Estrogens, Conjugated
Estrogens, Conjugated/Medroxyprogesterone Acetate
Estrogens, Esterified
Estrogens, Esterified/Methyltestosterone
Norethindrone Acetate/Ethinyl Estradiol

ALAMEDA Alliance FOR HEALTH

Up to 365-Day Supply on Contraceptives

Generic products are listed under **LABEL NAME** by their ingredient components.

LABEL NAME	GENERIC NAME	STRENGTH	DOSAGE FORM
ALYACEN 1/35	NORETHINDRONE & ETHINYL ESTRADIOL	1 MG-35MCG	TABLET
ALYACEN 7/7/7	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG/0.75MG/1MG- 35MCG	TABLET
AMETHIA	LEVONORGESTREL & ETHINYL ESTRADIOL & ETHINYL STRADIOL	0.15MG-30MCG/10MCG 3 MONTH DOSE PACK	TABLET
AMETHIA LO	LEVONORGESTREL/ETHINYL ESTRADIOL & ETHINYL ESTRADIOL	0.10MG-20MCG/10MCG 3 MONTH DOSE PACK	TABLET
AMETHYST	ETHINYL ESTRADIOL & LEVONORGESTREL	90MCG-20MCG	TABLET
APRI	ETHINYL ESTRADIOL & DESOGESTREL	0.15MG-0.03MG	TABLET
BALZIVA	ETHINYL ESTRADIOL & NORETHINDRONE	0.4MG-35MCG	TABLET
BEYAZ	DROSPIRENONE/ ETHINYL ESTRADIOL/ LEVOMEFOLATE CALCIUM	3MG-0.02MG-0.45MG	TABLET
BRIELLYN	ETHINYL ESTRADIOL & NORETHINDRONE	0.4MG-35MCG	TABLET
CAMRESE	LEVONORGESTREL/ETHINYL ESTRADIOL & ETHINYL ESTRADIOL	0.15MG-30MCG 3 MONTH DOSE PACK	TABLET
CAMRESE LO	ETHINYL ESTRADIOL & LEVONORGESTREL	0.10MG-20MCG 3 MONTH DOSE PACK	TABLET
CONCEPTROL	NONOXYNOL 9	4%	VAGINAL GEL
CONDOMS	CONDOMS, LATEX, LUBRICATED	N/A	TOPICAL
DROSPIRENONE-ETHINYL ESTRADIOL	DROSPIRENONE-ETHINYL ESTRADIOL	3MG-0.03MG	TABLET
ELLA	ULIPRISTAL	30MG	TABLET
ENSKYCE	DESOGESTREL & ETHINYL ESTRADIOL	0.15MG-0.03MG	TABLET
GENERESS FE	NORETHINDRONE & ETHINYL ESTRADIOL & FERROUS FUMARATE	0.8MG-25MCG/75MG	TABLET
GIANVI	DROSPIRENONE & ETHINYL ESTRADIOL	3MG-20MCG	TABLET

LABEL NAME	GENERIC NAME	STRENGTH	DOSAGE FORM
GILDESS 1.5/30	NORETHINDRONE & ETHINYL ESTRADIOL	1.5MG-30MCG	TABLET
GILDESS 1/20	NORETHINDRONE & ETHINYL ESTRADIOL	1MG-20MCG	TABLET
GILDESS FE 1/20	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL & FERROUS FUMARATE	1MG-20MCG/75MG	TABLET
GILDESS FE 1.5/30	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL & FERROUS FUMARATE	1.5MG-30MCG/ 75MG	TABLET
GYNOL II	NONOXYNOL 9	3%	VAGINAL GEL
INTROVALE	LEVONORGESTREL & ETHINYL ESTRADIOL	0.15MG-30MCG	TABLET
JOLESSA	LEVONORGESTREL & ETHINYL ESTRADIOL	0.15MG-30MCG	TABLET
JUNEL 1.5/30	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL	1.5-0.03MG	TABLET
JUNEL 1/20	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL	1MG-20MCG	TABLET
JUNEL FE 1.5/30	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL & FERROUS FUMARATE	1.5-0.03MG	TABLET
JUNEL FE 1/20	NORETHINDRONE ACETATE & ETHINYL ESTRADIOL & FERROUS FUMARATE	1MG-20MCG	TABLET
KARIVA	DESOGESTREL-ETHINYL ESTRADIOL	0.15MG/0.02MG-0.01MG	TABLET
LEVONORGESTREL-ETHINYL ESTRADIOL	LEVONORGESTREL-ETHINYL ESTRADIOL	0.1MG-20MCG (84)/10MCG (7) 3 MONTH PACK	TABLET
LEVONORGESTREL-ETHINYL ESTRADIOL	LEVONORGESTREL-ETHINYL ESTRADIOL	0.1MG-20MCG	TABLET
LEVONORGESTREL-ETHINYL ESTRADIOL	LEVONORGESTREL-ETHINYL ESTRADIOL	0.15MG-30MCG 3 MONTH PACK	TABLET
LEVONORGESTREL	LEVONORGESTREL	0.75 MG	TABLET
LEVONORGESTREL	LEVONORGESTREL	1.5 MG	TABLET
LO LOESTRIN FE	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG-10MCG/75MG	TABLET
LOMEDIA 24 FE	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG-20MCG/75MG	TABLET
LORYNA	DROSPIRENONE & ETHINYL ESTRADIOL	3MG-20MCG	TABLET
LOW-OGESTREL	NORGESTREL & ETHINYL ESTRADIOL	0.3MG-30MCG	TABLET
LUTERA	LEVONORGESTREL & ETHINYL ESTRADIOL	0.1MG-20MCG	TABLET
MARLISSA	LEVONORGESTREL & ETHINYL ESTRADIOL	0.15MG-30MCG	TABLET

LABEL NAME	GENERIC NAME	STRENGTH	DOSAGE FORM
MICROGESTIN 1.5/30	NORETHINDRONE & ETHINYL ESTRADIOL	1.5MG-30MCG	TABLET
MICROGESTIN 1/20	NORETHINDRONE & ETHINYL ESTRADIOL	1MG-20MCG	TABLET
MICROGESTIN FE 1.5/30	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1.5MG-30MCG/ 75MG	TABLET
MICROGESTIN FE 1/20	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG-20MCG/75MG	TABLET
MINASTRIN 24 FE	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG-20MCG/75MG	TABLET
NATAZIA	DIENOGEST & ESTRADIOL VALERATE	3MG/2MG-2MG/ 2MG-3MG-1MG	TABLET
NECON 0.5/35	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG-35MCG	TABLET
NECON 1/35	NORETHINDRONE & ETHINYL ESTRADIOL	1MG-35MCG	TABLET
NECON 1/50	NORETHINDRONE-MESTRANOL	1MG-50MCG	TABLET
NECON 10/11	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG-35MCG/ 1MG-35MCG	TABLET
NECON 7/7/7	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG/0.75MG/1MG-35MCG	TABLET
NEXPLANON	ETONOGESTREL	68MG	SUBDERMAL
NORETHINDRONE	NORETHINDRONE	0.35MG	TABLET
NORGESTIMATE-ETHINYL ESTRADIOL	NORGESTIMATE-ETHINYL ESTRADIOL	0.25MG-35MCG	TABLET
NORGESTIMATE-ETHINYL ESTRADIOL	NORGESTIMATE-ETHINYL ESTRADIOL	0.18MG/0.215MG/ 0.25MG-25MCG	TABLET
NORGESTIMATE-ETHINYL ESTRADIOL	NORGESTIMATE-ETHINYL ESTRADIOL	0.18MG/0.215MG/ 0.25MG-35MCG	TABLET
NORINYL 1+50	NORETHINDRONE-MESTRANOL	1MG-50MCG	TABLET
NORTREL 1/35	NORETHINDRONE & ETHINYL ESTRADIOL	1 MG-35MCG	TABLET
NORTREL 7/7/7	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG/0.75MG/ 1MG-35MCG	TABLET
NUVARING	ETONOGESTREL/ETHINYL ESTRADIOL	0.12MG-0.015MG	VAGINAL RING
OGESTREL	NORGESTREL & ETHINYL ESTRADIOL	0.5MG-50MCG	TABLET
PORTIA	LEVONORGESTREL-ETHINYL ESTRADIOL	0.15MG-0.03MG	TABLET
QUARTETTE	LEVONORGESTREL-ETHINYL ESTRADIOL	0.15MG-20MCG/ 0.15MG-25MCG 3 MONTH DOSE PACK	TABLET
QUASENSE	LEVONORGESTREL-ETHINYL ESTRADIOL	0.15MG-30MCG 3 MONTH DOSE PACK	TABLET
RECLIPSEN	DESOGESTREL-ETHINYL ESTRADIOL	0.15MG-0.03MG	TABLET

LABEL NAME	GENERIC NAME	STRENGTH	DOSAGE FORM
SAFYRAL	DROSPIRENONE-ETHINYL ESTRADIOL-LEVOMEFOLATE	3MG-0.03MG-0.451MG	TABLET
TILIA FE	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG/20MCG-30MCG-35MCG (75MG)	TABLET
TODAY CONTRACEPTIVE SPONGE	NONOXYNOL 9	1000MG	VAGINAL SPONGE
TRI-LEGEST FE	NORETHINDRONE & ETHINYL ESTRADIOL (FERROUS FUMARATE)	1MG/20MCG-30MCG-35MCG (75MG)	TABLET
TRI-NORINYL	NORETHINDRONE & ETHINYL ESTRADIOL	0.5MG/1MG/0.5MG-35MCG	TABLET
TRI-LO-SPRINTEC	NORGESTIMATE-ETHINYL ESTRADIOL	0.18MG/0.215MG/ 0.25MG-25MCG	TABLET
TRIVORA	LEVONORGESTREL/ETHINYL ESTRADIOL	0.05MG-0.075MG-0.125MG/ 0.03MG-0.04MG-0.03MG	TABLET
VAGINAL CONTRACEPTIVE FILM	NONOXYNOL 9	28%	VAGINAL FILM
VAGINAL CONTRACEPTIVE FOAM	NONOXYNOL 9	12.5%	VAGINAL FOAM
VELIVET TRIPHASIC REGIMEN	DESOGESTREL/ETHINYL ESTRADIOL	0.1MG-0.125MG-0.15MG/25MCG	TABLET
VESTURA	DROSPIRENONE-ETHINYL ESTRADIOL	3MG-20MCG	TABLET
XULANE	NORELGESTROMIN-ETHINYL ESTRADIOL	4.86MG-0.53MG	TRANSDERMAL PATCH
ZENCHENT FE	NORGESTIMATE-ETHINYL ESTRADIOL (FERROUS FUMARATE)	0.4MG-35MCG/75MG	TABLET
ZOVIA 1/35E	ETHYNODIOL DIACETATE-ETHINYL ESTRADIOL	1MG-35MCG	TABLET
ZOVIA 1/50E	ETHYNODIOL DIACETATE-ETHINYL ESTRADIOL	1 MG-50MCG	TABLET

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

PHARMACY & THERAPEUTICS COMMITTEE

Record of Committee Meeting Minutes

Tuesday, June 11, 2024 | 5:00pm – 7:00pm

Status	Voting Committee Members	Organization	Initials	Officer / Notes
P	Donna Carey, MD	Interim Chief Medical Officer-Alliance	DC	Chairman
P	Helen Lee, PharmD	Senior Director of Pharmacy Services – Alliance	HL	Co-Chair
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	Betsy Yuan, PharmD	Alameda County Behavioral Health Dept.	BY	

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	Role / Department
P	Iryna Makukh	PerformRx	Pharmacy Formulary Management.
P	Liza Rosendale	PerformRx	Clinical Program Manager
P	Pat DeHoratius	PerformRx	Manager Formulary/DUR
P	Barrie Cheung	PerformRx	Regional Pharmacy Director
P	Rahel Negash, PharmD	Alameda Alliance	Pharmacy Supervisor
A	Ramon Tran Tang, PharmD	Alameda Alliance	Clinical Pharmacist
P	Jefferey Bencini, Pharm D	Alameda Alliance	Clinical Pharmacist
P	Timothy Tong, Pharm D	Alameda Alliance	Clinical Pharmacist
A	Beverly Juan, MD	Alameda Alliance	Medical Director
A	Sanjay Bhatt, MD	Alameda Alliance	Medical Director
A	Darryl Crowder	Alameda Alliance	Provider Relations
P	Bibek Sandhu, PharmD, MBA	PillarRX	Consulting Pharmacist

Other Guests	

Follow-up Items:

Clerk of the Committee: Benita Ochoa

Agenda Item	Discussion Leader	Discussion Summary	Action	Notes
I) Call to Order	D. Carey	• Agenda Overview	Called to order at: 5:03PM	
II) Informational Updates	D. Carey H. Lee	Informational Updates • CalAIM Updates (ECM, CS, TCS, LTC, ICF-DD, BH/ABA) - We are still moving forward as a reminder for those of you who are not as involved with it this is the States revamping of our Medi-Cal system to encourage people to work together across all sectors. Two of the components we have are enhanced care management. Which is case management services for the most vulnerable of our vulnerable population. We had two vulnerable populations of focus that went live in January which was our just as involved population and our birth equity. So, ECM is our benefits side and community support is our services side that really allows us as a plan to pay for social determinants of health. So, we are continuing to expand our network for things such as meals, home modifications, asthma remediation. We also do personal care giver and services. So, these are things that we can now as a plan can pay for that we couldn't pay for before. • DHCS Audit - DHCS audit is June 17th through June 28th, two weeks we have been preparing for that audit. That has taken a lot of our time, effort, and energy. • DSNP Readiness - We are moving to our Medicare members we are getting ready to be a Medicare advantage plan in January of 2026. Right in parallel with our focus on the audit is our focus on getting ready for the DSNP plan. - HL: We have decided we will be using PerformRx as our PBM for DSNP line of business. As well for MTM we are still looking into whether we should work with PerformRx or if we will use a different vendor. In case you are not familiar with MTM that is Medication Therapy Management. • New P&T Member – Dr. Betsy Yuan - Introduction to new P&T psychiatric pharmacists Dr. Betsy Yuan. - HL: Appreciate you joining us this was based on DMHC recommendation to have behavioral health focus pharmacists or doctor to join our P&T. - Introductions continued. • Medi-Cal Rx MCDAC Drugs - MCDAC stands for Medical Drug Advisory committee drugs. For Medi-Cal Rx state took over pharmacy benefit as of 2022 and they do not have formulary, but they do have CDL which is covered drug list. Once a quarter they will send us drugs for review and see if we want to add these drugs to		

the covered drug lists. First drug is Opvee and is for the treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older. Our recommendation is to add as a formulary to the covered drugs list with prior authorization. The second product is Tyenne. This is for Rheumatoid arthritis, Giant Cell Arteritis, polyarticular Juvenile Idiopathic Arthritis, and Systemic Juvenile Idiopathic Arthritis. Recommendation to add to covered drug list with prior authorization.

Questions:

PB: Is the Opvee a higher dose of Narcan? What is the difference between this and Narcan?
BY: The opvee has a longer half-life so it's supposed to last longer and is supposed to spike stronger to work against synthetic opioids.
PB: Would that apply to fentanyl?
BY: Yes, that is the marketing around it at least. Most of the studies are modeling studies.
HL: Narcan is now over the counter, but Opvee is now the only one that requires a prescription and of course the ingredient is different. Narcan contains naloxone and Opvee contains nalmefene. So, its slightly different and as Dr. Yuan mentioned Opvee stays in the body longer than Narcan.
PB: Are there PA criteria on the CDL?
HL: The criteria will get developed by DHCS but certainly this is a new alternative to Narcan.

MCDAC Drug	Indication	CDL Status	Recommendation Based on - Safety, Efficacy, Essential Need, Misuse Potential, etc.
Opvee®(nalmefene) 2.7mg/0.1ml Nasal Spray	Emergency treatment of known or suspected overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older.	F-PA	Keep F-PA
Tyenne®(tocilizumab-aazg)	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, and Systemic Juvenile Idiopathic Arthritis.	F-PA	Keep F-PA

III) Pharmacy Utilization Reports (Quarter 1, 2024) — H.Lee

(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.)

- Top 50 Drugs by Cost (IHSS)

- Reporting period is first quarter January to March of 2023 as of now we have less than 6,000 patients.
- The top 50 drugs accounted for **1,076 claims** for **590 members** and cost **$1,357,202,** which is an increase of $237,924 in spend from the previous quarter.
- Biktarvy remains at number one, claims have gone up by 5, and there is one additional member since the previous quarter.
- Zejula is up to number 2 with 3 claims for 1 member. This medication is managed via the Oral and Injectable Oncology Medications MRG.
- Vemlidy is down to number 3 with 47 claims for 19 members. This medication is managed via the Hepatitis B MRG, which was loosened during Q4 2022 P&T to require trial and failure of, or reason not to use, entecavir (previously generic Viread and entecavir).
- Ozempic is at numbers 4, 6 and 11, with 181 total claims for 89 members. There was an increase of 40 claims and of 17 members from the previous quarter.
- Tagrisso is at number 5 with 4 claims for one member. There was an increase of one claim for one member from the previous quarter. This medication is managed via the Oncology MRG.

- Top 50 Drugs by Cost (Medi-Cal)
  - The top 50 drugs accounted for 36,007 claims for 30,640 members and cost $48,416,394.87, which is an increase of $6,868,129.68 in spend from the previous quarter.
  - Biktarvy remains at the number 1 spot with 850 claims for 653 members. An increase of 174 claims from last quarter.
  - Ozempic has risen from number 3 to number 2, with 1,877 claims for 1,521 members. This is an increase of 403 claims from last quarter.
  - Humira has also risen from the number 4 from the number 3 spot with 129 claims for 106 members. This is an increase of 20 claims since last quarter.
  - Jardiance 10mg has moved up to the number 4 spot from number 6, with 1,647 claims for 1,485 members. This is an increase of 496 claims from last quarter.
  - Jardiance 25mg remains at the number 5 spot with 1,536 claims for 1,435 members. This is an increase of 139 claims from last quarter.

- Top 50 PA Reviewed Drugs by Volume (IHSS)
  - Top 50 PA requests = 200. There were 258 total PA requests for quarter 1.
  - 69 requests (35%) were approved. This approval rate is lower, by 13%, than what was observed last quarter.
  - 131 requests (65%) were denied or partially approved.
  - Wegovy is up at numbers 1, 10, 13, 23, and 24 with 39 total requests and 5 approvals (13%).

- Wegovy 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.

- Jardiance is at numbers 2 & 8 with 21 total requests and 6 approvals (29%).
  - The formulary alternative is Steglatro, with trial and failure of metformin.
  - During the Q1 Alameda P&T meeting the SGLT2 Inhibitors and Combinations criteria were updated to include a 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.
- Lidocaine 5% patch and Ozempic 0.25-0.5 mg/dose is at number 3 and 4 with 12 requests and 1 approval (8%) for each drug.
  - Lidocaine requires a diagnosis of neuropathic pain and a trial and failure of gabapentin or pregabalin and one other formulary alternative used for neuropathic pain or morphine MME < 50 for 3 months.
  - Ozempic requires a trial and failure of metformin.
- Vemlidy 25 mg is down to number 5 and had a total of 11 requests, from which there were 7 approvals (64%).
  - Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets.
- Xiidra is at number 6 with 10 requests and 2 approvals (20%).
  - Xiidra requires trial and failure or inability to use artificial tears and cyclosporine (Restasis) 0.05% dropperette.

- Top 50 PA Reviewed Drugs by Volume (Medi-Cal)
  - The top 50 drugs accounted for 208,531 claims for 187,022 members and cost $4,636,174.09.
  - Albuterol remains at the number 1 spot with 14,230 claims for 11,733 members. An increase of 684 claims from last quarter.
  - Ibuprofen remains at the number 2 spot with 9,506 claims for 8,516 members. This is an increase of 1,661 claims from the last quarter.
  - Aspirin also remains at the same spot with 9144 claims for 8,444 members. This is an increase of 1,305 claims from last quarter.
  - Fluticasone remains at number 4 with 8,636 claims for 8,028 members. There was an increase of 1,252 claims from the last quarter.
    - Loratadine has risen from the number 6 spot to number 5 with 6,680 claims for 5,985 members. This is an increase of 1,496 claims from the last quarter.

IV) E-Voting Material/Consent Agenda

B. Ochoa

Monographs/Class Reviews	Changes
Opioid Use Disorder Agents Class Review (with PA criteria)	• No changes
Phosphate Binders Class Review (with PA criteria)	• No changes
Benign Prostatic Hyperplasia (BPH) Class Review	• No changes
Contraceptives foams, devices Class	• No changes
Gaucher Disease Class Review	• No changes
Ridaura Monograph	• No changes
Medication Request Guidelines	**Changes**
Opioid Use Disorder (OUD) Agents	• No changes
Phosphate Binders	• No changes
Formulary, step therapy required *For drugs without specific criteria	• No changes
Non-formulary and prior authorization required oral liquid formulations	• No changes
Cholinesterase Inhibitors	• No changes
febuxostat (Uloric)	• No changes
Lamotrigine ER	• No changes
Levalbuterol (Xopenex/Xopenex HFA)	• No changes
Lidocaine Patch	• Remove Gen7T and Synera as they have been
Potassium-removing agents	• No changes

Approved via e-voting:
Yes: 6
No: 0
Abstained: 1

		Healthcare professional (HCP) administered/IV Disease Modifying Therapies (DMTs) for Multiple Sclerosis (MS)	• Minor wording change for clarity			
		Fenofibrates	• Remove generic Antara as it has been discontinued			
		Nutritional formulas, infant formulas (STC C5F C5C)	• Remove STC information, as this refers to FDB			
		Lipotropics	• No changes			
		Long acting opioids	• No changes			
		Serotonin Receptor Agonists (Triptans)	• No changes			
		Pregabalin (Lyrica and Lyrica CR)	• No changes			
		Rufinamide (Banzel)	• No changes			
		vigabatrin (Sabril)	• Corrected minor grammar error to be consistent with package insert			
		Sedative Hypnotics	• Remove Zolpimist as it has been discontinued			
		Epidiolex (cannabidiol)	• No changes			
		Tiagabine (Gabitril)	• No changes			
		Topiramate (Topamax) sprinkles	• No changes			
		Hepatitis C Medications	• Change to treatment summary in recommended regimens for patients who have failed Mavyret treatment and require Vosevi			
		Short acting opioid containing products	• No changes			
		Hemlibra (emicizumab-kxwh)	• No changes			
		Aptiom (eslicarbazepine)	• No changes			
		Alprazolam (Xanax)	• No changes			
		Rectiv (nitroglycerin) ointment	• No changes			
		Diuretics	• No changes			
		Sleep Disorder Therapy	• No changes			
		Palforzia	• No changes			
		Gonadotropin Releasing Hormone Antagonists	• Streamlining language and abbreviations			

Lupkynis	• Update diagnostic requirement wording for simplicity
Radicava ORS (edaravone)	• No changes
Daybue (trofinetide)	• No changes
Filspari	• No changes
Joenja	• No changes
Skyclarys (omaveloxolone)	• No changes
Physician Administered Drug (PAD) Guidelines	**Changes**
Leqembi	• Update coverage duration language for clarity
B-Cell Maturation Antigen (BCMA) Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy	• No changes
Naglazyme	• No changes
Radicava (edaravone)	• No changes
Interim Formulary Updates	
• See p. 154 in packet	
Summary of Physician Administered Drug (PAD) Updates	
• None	
Pharmacy Policy & Procedure Updates	
• RX-012 - DU Policies - Pharmacy Portal DU Access	• Cleaned and updated document to reflect current policy post Magellan to Prime transition.
• RX-013 -Physician Facility-Administered Drugs	• Updated policy for clarity (e.g., COC).
ED Oversight	
• None	
90 Day Maintenance List updates	
• Annual review – no additions	
P&T Meeting Minutes	
• P&T Meeting Minutes Q1 March 19, 2024	

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
Xolair Subcutaneous Solution Auto-injector 75 MG/0.5ML	NF to F-PA
Xolair Subcutaneous Solution Auto-injector 150 MG/ML	NF to F-PA
Xolair Subcutaneous Solution Prefilled Syringe 300 MG/2ML	NF to F-PA
Xolair Subcutaneous Solution Auto-injector 300 MG/2ML	NF to F-PA
Opill Oral Tablet 0.075 MG	NF to F
Glucagon-like peptide 1 (GLP-1) agonists and Dipeptidyl peptidase-4 (DPP-4) inhibitor	Claims for a GLP-1 will no longer reject when a member has recent history of use of a DPP-4 (and vice versa) and will instead send an educational message to the pharmacy

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

- **No Changes**

V) New Business	Iryna Makukh	**New PADs**	Move to approve: 1st: PB	

		HL - Ok, now if there aren't any other questions, we can now move onto New Business. Irina, now you can talk about new PAD's**.** **<u>Amtagvi</u>** - **<u>Amtagvi</u>** - IM - Thank you, so on page 202 Amtagvi. The cost for $550, 000 for one time administration with prescriber must be oncologist and the exclusion criteria is based on the trial exclusion criteria and that includes uncontrolled brain metastases, Melanoma of uveal or ocular origin, and no systemic steroid therapy for any reason. All these were exclusion criteria in the trial. - It's a onetime treatment because effectiveness and safety has not been studied for more than one treatment and the authorization treatment is based on the study and the prescriber's information that includes diagnosis of unresectable or metastatic melanoma Stage IIIc or Stage IV and the patient 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 and this is indication. Also, members must have at least one resectable lesion of a minimum 1.5 cm in diameter post-resection and was exclusion criteria in the trial as well as Eastern Cooperative Oncology Group of either 0 or 1. No authorization as it is a one-time treatment**<u>.</u>** **<u>Lenmeldy</u>** - The next PAD criteria is called Lenmeldy on page 203. Lenmeldy is a gene therapy indicated for children with pre-symptomatic late infantile, pre-symptomatic early juvenile, and Early symptomatic early juvenile metachromatic leukodystrophies or MLD. - MLD is a rare genetic disorder that causes fatty substances to build up in cells particularly in the brain spinal cord and peripheral nerves. This build is caused by a deficiency of enzyme ARSA that helps break down lipids called sulfatides. Symptoms include loss of ability to attack sensation such as toxic pain, loss of intellectual ability, rigid muscles, poor muscle function, and paralysis. So, a very devastating disease. - The prevalence of MLD ranges from 1/40, 000 to 1/100,000 in North European and North American population and Lenmelfy is made from the patients own stem cells which have been genetically modified to include a functional copy of the ARSA gene. After infusion, Lenmeldy re-populates part of bone marrow with CD34+ cells which produce ARSA enzyme and that can break down and prevent harmful accumulation of sulfatides. - Lenmeldy is a one-time IV infusion and costs $4.25 million. That is the most expensive therapy on the market currently. - Full criteria, we are asking the prescriber to be a neurologist or geneticist. The authorization criteria include diagnosis of an approved indication at an approved dose and ARSA enzyme	2nd: AB	

activity below normal range and indication of 2 causes of two disease-causing ARSA alleles. This is based on clinical trials where all children had ARSA activity below the normal range and had two disease-causing ARSA alleles identified. Again, it is a one-time treatment, so authorization of Any questions?

Questions:
Comments:
DC: Do we have a motion to approve our new PADS?
PB: So, moved.
DC: Great, thank you. Second?
AB: I'll second.
BD: second
DC: Great, thank you. Alright all-in favor of approval of our new PADS, please say "I".
Group- "I"!
DC: Any "no's"? Any abstention?
Group-(silence)
DC: Great, thank you, adding our new PADS.
HL: Irina, now you can go through our new Medication Review Guidelines please this criteria for this medication.

New MRGs
IM- Lets review new Medication Review Guidelines policies**.**

Filsuvez

- **IM-** The first new MRG policy is for Filsuvez. It's on page 204.
- Filsuvez is a topical gel, for the treatment of wounds associated with dystrophic or junctional epidermolysis bullosa. Epidermolysis bullosa is a rare inherited connective tissue disorder that causes abnormalities in cohesion of the layers of the epidermis that can result in blisters, erosion, non-healable serrations, and scars in response to even a small skin trauma. Estimated incidents of EB is 1/20,000 with approximately 30,000 individuals affected in the United States.

		- Filsuvez is applied topically to affect its wound surface and covered with wound dressing. It can be applied at home; it doesn't have to be a doctor's office. - The price is $12,600 to $54,000 per month depending on how often patient's use of the product. In the study it was used every 1 to 4 days. Each tube is billed to us for one time use only. As for criteria, we're asking for a specialist prescriber, dermatologist specialist in the treatment of epidermolysis bullosa. For coverage duration, we have 3 months in initial and 6 months for subsequent requests. We require diagnosis of dystrophic or junctional epidermolysis bullosa, with genetic mutation(s) confirmed via genetic testing, we're asking for documentation that's wounds so not appear to be infected, are clean adequate granulation tissue, excellent vascularization, and no evidence of squamous cell carcinoma as these patients were excluded from the trials. Also added, maximum dispensable amount of one tube per day and that's based on the dose calculator the healthcare provider packaged for this drug and trials with dressing changes every 1 to 4 days. - In the re-authorization criteria, looking for clinical benefit of treatment and documentation of need for continued treatment as well as the same requirements, for the clean wound without squamous cell carcinoma. - Next, we have MRG criteria for Complement Inhibitors for the Treatment of Myasthenia Gravis Agents and that's on page 206. - So, the agent we have is Zilbrysq subcutaneous injection indicated generalized myasthenia gravis for patients with positive serological test for Anti-AChR antibodies. Myasthenia gravis is a chronic auto immune disorder that is characterized by fluctuating muscle weakness and fatigue. Typically, it affects the skeletal and ocular muscles. The reported annual incidents is 8 to 10 cases per one million. And Zilbrysq is the first medication that can be self-administered by subcutaneous injection. It's a single dose prefilled syringe. - The price is $22,680 to $44,250 per month and dosing is based on weight. - For the criteria, the prescriber must be neurologist or rheumatologist. We are looking for the diagnosis of generalized myasthenia gravis with positive serological tests for Anti-AChR antibodies and clinical classification of class II, III or IV. This is based on patient population and trials. - The member should try and failed two (2) or more conventional therapies such as acetylcholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressive therapies or 1 - conventional therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin. The second category signifies the more severe disease. - There should be no concurrent use of Vyvgart, Vyvgart Hytrulo, Rystiggo, Soliris, or Ultomiris which are also complement inhibitors that weren't studied together. - Because of the risk for serious meningococcal infections Zilbrysq is only available through REMS program so documentation is required for patient to compliant with recommendations for vaccination against meningococcal infections. - For re-authorization, we are looking for documentation of clinical response to therapy.		

- So that's it for these criteria, any questions?
- **PB**-I think Vyvgart works differently than complements, but I agree it shouldn't be used together since they're both relatively new.
- **IM**- Thank you Doctor Bayard.

Eohilia

- **IM-** So let's go to the next criteria. The criteria for Eohilia on page 207
- **IM-** Eohilia is indicated for adult and pediatric patients eleven years of age or older with eosinophilic esophagitis or "EOE". It's a chronic inflammatory disease. The exact cause is unknown. However, it can be triggered by certain foods and environmental allergens. Chronic inflammation of EOE can lead to difficulty swallowing, vomiting, and pain and the prevalence is estimated from 0.5-1 case in 1000 people.
- Eohila is a budesonide in a form of an oral suspension and the limitation of its use is that it has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks. So, it is not for long term maintenance treatment.
- The price is 1,875 per month and the prescriber must be gastroenterologist, allergist, immunologist, or other provider who specializes in the treatment of eosinophilic esophagitis (EoE).
- The request will be approved for 3 months since Eohilia is not indicated for use longer than 12 weeks and we ask for a diagnosis of EOE confirmed by biopsy indicating more or equal to 15 eosinophils per high-power field (eos/hpf) which was part of exclusion criteria for clinical trials and is used in clinical practice as well to confirm diagnosis.
- Members must have experienced difficulty swallowing for at least 4 days over a 2 week period which was part of exclusion criteria. Documented trial and failure, intolerance, or contraindication to an inhaled corticosteroid that can be swallowed.
- Proton pump inhibitors are considered first line as well as topical corticoids like Eohilia and inhaled corticosteroids are off label use for EoE but are considered first line along with PPI's along with FDA approved dose. Again, no re-authorization as it's only used for 12 weeks.

Wegovy

- IM-The next new MRG is for Wegovy on page 208,209
- Wegovy is GLP-1 agonist that recently received a new indication to reduce the risk of major adverse cardiovascular in adults with established cardiovascular disease and who meet body mass index requirements either overweight or obesity. Major cardiovascular events are defined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke per PI.
- It's the first drug in weight reduction space which **** risk reduction and the price is $1349 per month at maintenance dose.

		- Criteria requires that members must be at least 45 years of age. This was part of trial exclusion criteria as well. - Exclusion criteria are requests for Wegovy for a diagnosis of weight reduction, history of diabetes as diabetes patients were excluded from the trial, personal or family history of medullary thyroid carcinoma, which is black box warning, multiple Endocrine Neoplasia syndrome type 2 which is a contraindication in the PI, and concurrent use of any GLP-1 agonist. - Authorization criteria includes Wegovy is prescribed for reducing the risk of adverse cardiovascular events in adults with established cardiovascular disease. That documentation needs to be provided to demonstrate has history of at least one of the following: prior MI, prior stroke, or symptomatic peripheral arterial disease. These were all part of the exclusion criteria. Also, documentation is needed to show a member is overweight or obese, receive standard of care treatment for CVD as appropriate/indicated, including an antiplatelet drug, lip lowering drug, hypertensive medication as appropriate. Documentation should be provided that patient's Hb A1c less than or equal to 6.5% because patients with A1c greater than 6.5 were excluded from the trials. - For re-authorization, we are asking patients should be continuing treatments from the demographics requirements from the trial and do not have diabetes. **Questions:** **Comments:** DC-So we need approval for the new MRG's. Can I get a motion? BD-I motion. PB-Second DC-Great. Thank you so much. All in favor of approving say "I". Group- "I"! DC-any no's? Any abstentions? Alright thank you so much.		
VI) Class Reviews, Monographs, and Recommendations-	Iryna Makukh	**Rezdiffra monograph** **a. New MRG: Rezdiffra** - IM-so we have a new monograph and MRG and page 210. - IM-So Rezdiffra is the first drug that proved to treat adults noncirrhotic nonalcoholic steatohepatitis or NASH with moderate to advanced liver fibrosis consistent with stages F2 to F3 fibrosis and is intended to be used in conjunction with diet and exercise. Use of Rezdiffra should be avoided in patients with decompensated cirrhosis and that is a limitation of use. NASH is the most severe form of non-alcoholic fatty liver disease which is a chronic liver condition must commonly associated with type 2 diabetes and obesity. NASH is characterized in the abnormal accumulation of fat in the liver and in fact an estimated 1.5 to 6.5 percent of US adults. - The FDA approval of Rezdiffra had accelerated approval pathway and the end point in the case was the extent of inflammation and scaring at 12 months. - Continued approval of Rezdiffra is contingent of the result of an ongoing 54-month trial to identify and assess clinical benefit after 54 months of treatment. It is a partial agonist of the thyroid hormone receptor-beta and THR-β is the major form of thyroid hormone receptors in the liver and stimulation of it reduces intrahepatic triglycerides,		

		- The dosing is based on patients' actual body weight. It's 80mg one daily for patients less than 100kg and 100mg daily for patients greater than or equal to 100kg. - The cost of the monthly therapy is $3950 and in the phase 3 MAESTRO-NASH trials with a 2 point or higher reduction score with no worsening of fibrosis and improvement of fibrosis in at least one stage with no worsening of the NAFLD activity score at week 52. - The NASH trials are still ongoing and will be used to confirm and verify clinical benefits and potentially support full approval of Rezdiffra. - Guidelines have not been updated since the release of Rezdiffra and focus primarily on diet and exercise as the main forms of treatment and although no alternatives are available there are many therapies that many be approved in the next few years. - Normally there are GLP-1 receptor agonists in phase 2 and 3 trials as well. - We also have a new MRG for Rezdiffra on page 216. - Here we ask for the prescriber must be a hepatologist, gastroenterologist, or a specialist in the treatment of liver disease. We are excluding patients with complicated cirrhosis or with specific types of thyroid disease as they were excluded from the trials. - For initial authorization, we require diagnosis of NASH with moderate to advances liver fibrosis via documentation of stage F2 to F3 fibrosis per PI confirmed by biopsy or noninvasive test (NIT), attestation to providing lifestyle changes including alcohol avoidance and exercise and being prescribed at an FDA approved dose. - For re-authorization, member has clinically benefited from the medication continues to have a fibrosis stage less than 3 - So that's the proposed MRG		
		<u>Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists Class Review</u> - We recommend preferring an additional agent. - Add preferred Emgality and Ajovy. - For Acute Migraine Treatment we are recommending adding Zavzpret as a preferred agent with Ubrevely and recommending expanding provider restrictions and we are updating quantity limits for Ubrevely increasing it to align with label indication and package size. - No other recommendations.		
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. Hepatitis B Drugs** - Pg. 249 We did do a quarterly DUR review and as a result, we did notice that the entecavir 0.5 and 1 mg tablets in Q4 of last year and Q1 of this year all had approvals for requests that we received. As we're approving a lot of these products, we're going to go ahead and propose recommendation here to add entecavir to the formulary just to relieve that PA burden as well, since it's highly utilized and highly approved.	Move to approve: 1st: DB 2nd: PB	

- Pg. 250 And throughout the policy, you can also see that we're striking the entecavir language here since it would no longer PA and review. And that's the only change to this policy based on our DUR review this quarter.

Comments:

Guideline (Changes): **2. Transthyretin-mediated Amyloidosis Agents**

- Pg. 252 We're making a change in the medication section to add the indication polyneuropathy because we have Amvuttra and Wainua that are used to treat this condition. And then for cardiomyopathy there are two products available. The change that we can see here as well is that we're adding Wainua since it's a new indicated product that's approved by the FDA. So, we're adding that to our policy for review if we get and when we get these requests. It's available in the initial authorization section and also throughout the policy as appropriate. We're making updates to the diagnosis of polyneuropathy of hereditary TTR-mediated amyloidosis, just rephrasing to make it more clear.
- Pg. 252 At the bottom of the page, there's two products there (Vyndaqel and Vyndamax). Those are the medications to treat when a diagnosis of cardiomyopathy is present.
- Pg. 253 And we're adding for wild-type or hereditary TTR-mediated amyloidosis and striking the requirement to have documentation with genotyping since these products can be used for wild-type or when it's hereditary.

Comments:

Guideline (Changes): **3. Medications for Attention Deficit Hyperactivity Disorder (ADHD) and Narcolepsy**

- Pg. 254 For ADHD we're just switching from brand to generic to comply with the market availability, and if we scroll through the policy, we'll see that there's no other change.

Comments:

Guideline (Changes): **4. Roflumilast (Daliresp)**

- Pg. 256 For Daliresp there's a change in the PA review criteria section and this is to align with the guideline recommendation. So, we're just adding the long-acting muscarinic antagonist (LAMA) here since they can be used in conjunction with Daliresp, and there's no other changes to this policy.

Comments:

Guideline (Changes): **5. Injectable Atypical Antipsychotic Medications**

- Pg. 257 So here's our policy for the injectable atypical antipsychotics. You can see the first change there in the medication section is that brand and generic switch, and then we're also adding three products that have been recently approved by the FDA to this list. There's no other changes for content on here.

Comments:

Guideline (Changes): **6. Hereditary Angioedema (HAE)**

- Pg. 259 This is our hereditary angioedema policy. We're updating the coverage duration approval length from 3 to 6 months, and this is just to allow for more review of clinical benefit and response based on guideline recommendations. If we scroll down to the PA review criteria, we also see that there's an addition of two more genetic test mutation examples as they align with the C1INH for HAE. This is to document for appropriate review and treatment monitoring, and then also adding for acute treatment and prophylaxis the very products that are indicated for each. This is just to add clarity for reviewers, for appropriate request determination.

Comments:

Guideline (Changes): **7. Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors**

- Pg. 262 So here we have our Adenosine Triphosphate-Citrate Lyase (ACL) inhibitors, and we're just making update to the title there, since there's a typo and just adding Antilipemic Agents. In our PA review criteria, we're updating this section in three parts to simplify. There is a new indication for cardiovascular risk reduction and so we'll add that and we're also going to start based on the top. We have our initial authorization sections, so for all requests that are received, we'll need to have a trial and failure of high intensity statins. And then also, indication that the provider has counseled the member for smoking cessation and also heart healthy diet and then also appropriate dose.
- Pg. 263 Secondly, we can see the criteria for hyperlipidemia, so there's differentiation here with the cardiovascular risk reduction for clarity. So, when we get requests for hyperlipidemia, we'll review for appropriate diagnosis. We will look for that heterozygous familial hypercholesterolemia (FH) or primary hyperlipidemia, and then also treatment failure of ezetimibe.
- For cardiovascular risk reduction, we look for established cardiovascular disease here or member with a high risk of having this, and so they would need to have one of the following: either type 1 or 2 diabetes in females over 65 years of age or males over 60 years of age, Reynolds Risk score > 30% or a SCORE Risk score > 7.5%, or coronary artery calcium score over 400.
- Everything else there is struck because you can see it in the initial authorization review criteria and we're keeping the LDL level over 70 for reference for appropriate review.
- Pg. 264 And the reauthorization criteria we're just updating that to remove the requirement for continued statin therapy since the trials show that these products can be used as monotherapy.

Comments:

		Guideline (Changes): **8. Xolair for Asthma and Urticaria** - Pg. 265 This is our Xolair policy, so first we're changing this to add IgE-mediated food allergy to the policy. Also, the exclusion criteria has additionally two items that we will add: we will also exclude Xolair concomitant use with Palforzia and also exclude Xolair for emergency treatment of allergic reactions, so this includes anaphylaxis. - The prescriber restrictions section we're simply updating all of those providers to one sentence just to simplify. - Pg. 266 There's additional change in the PA review criteria section. So, here's where we're adding that IgE-mediated food allergy. For Xolair, we're looking for a diagnosis for appropriate use, so we're looking for peanut, milk, egg, wheat, cashew, hazelnut, or walnut allergy. And then we also want to see attestation that Xolair will be used in conjunction with food allergy avoidance, so we want to make sure that the overall patient care is being monitored well and then of course appropriate FDA dose is being utilized for the weight of the patient, as its weight based. There are no other changes for this policy. **Comments:** Guideline (Changes): **9. Anti-Obesity Medications** - Pg. 267 Our last policy is our anti-obesity medications, and this change is pretty simple, it relates to that Wegovy policy that we just saw in the new MRGs. We're just adding language here to make it clear that if we get requests for Wegovy to treat or to reduce the risk of major adverse cardiovascular events, the reviewer would need to refer to the appropriate policy, which is the Wegovy policy. - There's no other changes in content for any of our weight reducing products. That would conclude our medication request guideline updates. **Comments:** **Comments:** No changes recommended at this time. No further discussion.		

VIII) Physician Administered Drug (PAD) Policies-	Iryna Makukh	Guideline (Changes): **1. Aduhelm** - Pg. 270 This policy we're recommending retiring because the manufacturer announced they are discontinuing the development of the drug along with the termination of the Envision clinical study. This was due to challenge effectiveness in safety before and after its approval, especially because of the risk of brain swelling and bleeding. - Biogen said they would shift their resources to other treatments such as Leqembi. **Comments:** N/A Guideline (Changes): **2. Anti-CD19 CAR-T Immunotherapies** - Pg. 272 we're making recommendations here based on two new indications for Breyanzi. The two new indications are chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). Both for relapsed or refractory disease. This is in addition to the previous indication for Large B cell lymphoma also for relapsed or refractory disease. - We're adding a bullet point to initial authorization to require that use is supported by a labeled indication or NCCN guidelines for all requests. - We're adding CLL indication for Breyanzi that has requirements based on the prescribing information that the patient is 18 years of age or older and has relapsed or refractory disease and that's defined per PI that patient has failed at least 2 prior lines of therapy including BTK inhibitor and BCL-2 inhibitor. - For the next section, non-Hodgkin's lymphoma we broke the section down by the specific types of lymphoma and added a section for SLL indication for Breyanzi. Here we specified which drugs are treating each type of lymphoma and the requirements for them for simplicity for the reviewer. - Otherwise, this section is exactly the same as what it used to be for other forms of NHL. Just with spelled out types of lymphoma and conditions required for the 3 drugs that treat them. No clinical changes here. - Below we added SLL indication. Small Lymphocytic lymphoma is another new indication for Breyanzi and here requirements are also based on prescribing information that patient is 18 years of age or older and has relapsed refractory disease. Which is defined that the patient received 2 prior lines of therapy including BTK inhibitor and BCL-2 inhibitor. - No other changes to this policy. **Comments:** Guideline (Changes): **3. SMN2 Splicing Modifiers for the Treatment of Spinal Muscular Atrophy (SMA)** - Pg. 275 in this policy we're adding to the exclusion criteria that's Evrsdi and Spinraza and they should not be used concurrently as they have similar mechanism of action. - Also, we're removing the exclusion criteria for the use of Spinraza after the previous use of Zolgensma. This is based on an ongoing phase 4 open label trial for Spinraza, where results		

already show promise for both efficacy and safety in treating patients with Spinraza after Zolgensma in therapy.
- These are all the changes here; everything else is the same in this policy.

Comments:

Guideline (Changes): **4. Generalized Pustular Psoriasis (GPP) Agents**

- Pg. 276 here we have recommendations for Generalized Pustular Psoriasis agents for Spevigo. It received an expanded indication for GPP maintenance in adult and pediatric patients 12 years or older. This is in addition to the existing indication for acute GPP flares.
- We're adding coverage duration for maintenance statement for 12 months since end points for maintenance treatment were evaluated after 48 weeks.
- We separated initial authorization criteria into 2 sections for each indication and specified a request is for acute flare the IV vial is used, and if the request is for maintenance treatment the Sub Q syringe is used and that's for PI.
- For maintenance treatment we added criteria based on inclusion criteria of a failed trial, that's history of at least 2 flares in the past year of moderate or severe intensity and global assessment score of 0 or 1.
- Also, we're requiring trial and failure of two of the following agent's oral retinoids and methotrexate. These are preferred initial treatments, and cyclosporine which is used for a more severe disease in patients with GPP.
- We added a reauthorization section, where we're requiring positive clinical response to the therapy.
- These are all the changes for this policy.

Comments:

Guideline (Changes): **5.Vyjuvek**

- Pg. 278 we're recommending some updates for Vyjuvek for treatment of epidermolysis bullosa.
- There was approval of a new drug for Filsuvez for this indication and we created a new criteria for the agent since it doesn't have to be administered by a healthcare provider.
- Vyjuvek must be administered by a healthcare provider, and we made some changes based on the new drug approval.
- We're updating exclusion criteria for no concurrent use of Vyjuvek and Filsuvez since they have not been studied together.
- Also, we're adding the maximum authorization amount of 1 vial per week and that's based on max dosing and once weekly administration of Vyjuvek. This is to reduce excessive volume requests.
- No other changes in this criteria.

		Comments:		
IX) Informational Updates on New Developments in Pharmacy	N. Felten	New Product Review • New Products were discussed.		

BRAND NAME	GENERIC NAME/DOSAGE FORM	RECOMMENDATION
Alvaiz	eltrombopag 9 mg, 18 mg, 36 mg, 54 mg oral tablets	Non-formulary
Xolair	omalizumab 75 mg/0.5 mL, 150 mg/mL, 300 mg/2 mL subcutaneous auto-injector; 300 mg/2 ml subcutaneous syringe	F; PA (See updated MRG) (already added via CRF)
Eohilia	budesonide 2 mg/10 ml oral suspension	Non-formulary (see new MRG)
Amtagvi	lifileucel intravenous suspension	Non-formulary (see new PAD)
Filsuvez	birch triterpenes 10% topical gel	Non-formulary (see new MRG)
FreeStyle Libre	FreeStyle Libre 3 Reader Device	Non-formulary
Zymfentra	infliximab-dyyb 120 mg/ml subcutaneous syringe; 120 mg/ml subcutaneous auto-injector	Non-formulary
Opill	norgestrel 0.075 mg oral tablet	F (already added via CRF)
Hemlibra	emicizumab-kxwh 12 mg/0.4 ml subcutaneous vial	Non-formulary

			Pemrydi RTU	pemetrexed 100 mg/10 ml, 500 mg/50 ml intravenous vials	Non-formulary			
			RiVive	naloxone 3 mg nasal spray	Non-formulary			
			Yuflyma	adalimumab-aaty 20 mg/0.2 ml subcutaneous syringe	Non-formulary			
			Alyglo	immune globulin (human)-stwk 5 g/50 ml, 10 g/100 ml, 20 g/200 ml intravenous vials	Non-formulary			
			Rezdiffra	resmetirom 60 mg, 80 mg, 100 mg oral tablets	Non-formulary (see new MRG)			
			Simlandi	adalimumab-ryvk 40 mg/0.4 ml subcutaneous auto-injector	Non-formulary			
			Lenmeldy	atidarsagene autotemcel 1.8 to 11.8 x 10^6 CD34+ cells/ml intravenous suspension	Non-formulary (see new PAD)			
			Winrevair	sotatercept-csrk 45 mg, 60 mg subcutaneous vials	Non-formulary			
			Spevigo	spesolimab-sbzo 150 mg/ml subcutaneous syringe	Non-formulary (see updated PAD)			
			Voydeya	danicopan 50 mg, 100 mg oral tablets	Non-formulary			

			Baclofen	baclofen 15 mg oral tablets	Non-formulary			
			Opsynvi	macitentan/tadalafil 10 mg-20 mg, 10 mg-40 mg oral tablets	Non-formulary			
			Cyclophosphamide	cyclophosphamide 500 mg/5 ml, 1000 mg/10 ml, 2000 mg/20 ml intravenous vials	Non-formulary			
			Tyenne	tocilizumab-aazg 80 mg/4 ml, 200 mg/10 ml, 400 mg/20 ml intravenous vials	Non-formulary			
			Ogsiveo	nirogacestat 100 mg, 150 mg tablets	Non-formulary			
			Adalimumab-aaty	adalimumab-aaty 20 mg/0.2 ml, 40 mg/0.4 ml subcutaneous syringe; 40 mg/0.4 ml, 80 mg/0.8 ml subcutaneous auto-injector	Non-formulary			
			Xcopri	cenobamate 25 mg oral tablets	Non-formulary			
			Adalimumab-ryvk	adalimumab-ryvk 40 mg/0.4 ml subcutaneous auto-injector	Non-formulary			
			Extencilline	penicillin G benzathine 1,200,000 units, 2,400,000 units intramuscular vials	Non-formulary			
			Libervant	diazepam 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg buccal films	Non-formulary			

			Anktiva	nogapendekin alfa inbakic-pmln 400 mcg/0.4 ml intravesical vial	Non-formulary		
			Ojemda	tovorafenib 100 mg oral tablets; 25 mg/mL oral suspension	Non-formulary		
X) Old Business		None					
XI) Public Comment	N. Felten	• No comment					
Adjournment	D. Carey	• P&T Committee Member Forms **Meeting adjourned at 6:36PM**				None	

DocuSigned by:
Rahel Negash
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Rahel Negash, PharmD
Supervisor, Pharmacy Services,
Alameda Alliance for Health

07/23/2024 | 1:01 PM PDT
Date

DocuSigned by:
Donna Carey
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Donna Carey, MD
Interim Chief Medical Officer,
Alameda Alliance for Health

07/24/2024 | 6:14 AM PDT
Date

New

Xolremdi	
Therapeutic Classes (AHFS)	Hematopoietic Agents
Medications	Xolremdi (mavorixafor)
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	12 years of age and older
Prescriber Restrictions	Prescriber must be an immunologist or a hematologist
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. 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 WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) syndrome confirmed by genotype variant of chemokine receptor 4 (CXCR4) and absolute neutrophil count (ANC) of ≤ 400 cells/μL • Documentation of baseline ANC and absolute lymphocyte count (ALC) • Documentation of member weight • Medication is prescribed at an FDA approved dose **Re-Authorization:** • Documentation or provider attestation of positive clinical response (i.e. improvement from baseline in ANC and/or ALC) • Documentation of member weight • Medication is prescribed at an FDA approved dose
Criteria Statement	Xolremdi is reserved for members who have a confirmed diagnosis of WHIM syndrome with documented member weight and baseline ANC and ALC.
Last P&T Review Date	9/2024

New

Rytelo (imetelstat)	
Medications	Rytelo (imetelstat)
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	Member must be 18 years of age or older Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a hematologist or oncologist
Coverage Duration	Initial requests will be approved for 6 months. Reauthorization requests will be approved for 6 months.
Maximum Billable Units	Variable
Other Criteria	**Criteria for initial approval:** • Diagnosis of myelodysplastic syndromes (MDS) with transfusion-dependent anemia • Myelodysplastic Syndrome Revised International Prognostic Scoring System (IPSS-R) categorization as low or intermediate-1 risk of progression • Member has transfusion burden of 4 or more red blood cell (RBC) units within an 8 week period over the last 4 months • Prescriber attestation that complete blood cell count (CBC) will be obtained prior to initiation, weekly for first two cycles, and prior to each cycle thereafter • Member’s weight has been provided with request • Medication is prescribed at an FDA approved dose **Reauthorization:** • Documentation or provider attestation of reduction in RBC transfusion burden as compared with baseline • Provider attestation that patient is tolerating the medication and is not experiencing any serious adverse reactions • Member’s weight has been provided with request • Medication is prescribed at an FDA approved dose 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	9/2024

Drug Name: Duvyzat (givinostat)

Manufacturer: ITF Therapeutics, LLC

Approval Date: 3/21/2024

Marketing Date: 6/11/2024

Recommendation

Implement the newly developed Duvyzat (givinostat) MRG Criteria with no changes to formulary status.

Prescribing Information

Indication

Duvyzat™ is indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older.

Mechanism of Action

Duvyzat™ is a histone deacetylase inhibitor. The precise mechanism by which Duvyzat™ exerts its effect in patients with DMD is unknown.

Dosage and Administration

The recommended dosage of Duvyzat™ is based on body weight and administered orally twice daily.

Table 1: Recommended Dosage in Patients 6 Years of Age and Older for the Treatment of DMD

Weight±	Dosage	Oral Suspension Volume
10 kg to less than 20 kg	22.2 mg twice daily	2.5 mL twice daily
20 kg to less than 40 kg	31 mg twice daily	3.5 mL twice daily
40 kg to less than 60 kg	44.3 mg twice daily	5 mL twice daily
60 kg or more	53.2 mg twice daily	6 mL twice daily

± Based on actual body weight

Duvyzat™ may cause adverse reactions which may necessitate dosage modifications. See package insert for full prescribing information.

Black Box Warning

None

Adverse Reactions

Most common: diarrhea, abdominal pain, thrombocytopenia, nausea/vomiting, hypertriglyceridemia, and pyrexia

Serious: hematological changes, increased triglycerides, gastrointestinal disturbances, QTc prolongation

Use in Specific Populations, Pregnancy

Duvyzat™ is indicated for the treatment of DMD, which is a disease of predominantly young male patients. Therefore, there are no adequate data available to assess the use of Duvyzat™ in pregnant women. In animal studies, oral administration of givinostat during organogenesis resulted in decreased fetal body weight and increased structural variations; oral administration during pregnancy and lactation resulted in increased embryofetal and offspring mortality and neurobehavioral changes in the offspring.

Drug Interactions

- Closely monitor when Duvyzat™ is used in combination with an oral CYP3A4 sensitive substrate or a sensitive substrate of the OCT2 transporter, for which a small change in substrate plasma concentration may lead to serious toxicities.
- Avoid concomitant use with other drugs that prolong the QTc interval; monitor ECG if concomitant use cannot be avoided.

How Supplied

Oral suspension: 8.86 mg/mL

Price

$55,500

(Per month for a 30 kg child, based on WAC.)

Clinical Studies

Completed

Title	Randomized, Double Blind, Placebo Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients With Duchenne Muscular Dystrophy (EPIDYS) NCT: 02851797 PMID: 38508835
Design	Phase 3, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of givinostat in ambulant subjects with DMD
Population	N= 179 At baseline, patients had a mean age of 9.8 years, 90% were White, 3% were Asian, 3% were Black.
Arms	Patients were randomized 2:1 to receive either Duvyzat (n = 118) or placebo (n = 61) twice daily for 72 weeks, stratified by concomitant steroid use.
Endpoint(s)	Primary: • Change from baseline to Month 18 in 4-stair climb (4SC) time for Duvyzat compared to placebo Secondary:

<table>
<tr><td></td><td>

- Change from baseline to Month 18 in physical function as assessed by the North Star Ambulatory Assessment (NSAA)

</td></tr>
<tr><td>Inclusion Criteria</td><td>

- Ambulant males aged ≥6 years with a diagnosis of DMD confirmed by genetic testing
- Able to complete 2 Four Stairs Climb test (4SC) screening assessments
- Have the mean of 2 screening 4SC assessments ≤8 seconds
- Time to rise from floor between ≥3 and <10 seconds at screening
- Manual muscle testing (MMT) of quadriceps at screening Grade ≥- 3
- Use of systemic corticosteroids for a minimum of 6 months immediately prior to the start of study treatment

</td></tr>
<tr><td>Exclusion Criteria</td><td>

- Exposure to any dystrophin restoration product (e.g., Ataluren, Exon skipping) within 6 months prior to the start of study treatment
- Exposure to idebenone within 3 months prior to the start of study treatment
- Diagnosis of other uncontrolled neurological diseases or presence of relevant uncontrolled somatic disorders that are not related to DMD
- Current or history of liver disease or impairment
- Triglycerides > 300 mg/dL (3.42 mmol/L) in fasting condition at screening visit
- Baseline QTcF >450 msec, or history of additional risk factors for torsades de pointes

</td></tr>
<tr><td>Results</td><td>

Primary:

- Patients treated with Duvyzat showed statistically significant less decline in the 4-stair climb compared to placebo (see Table 4).

Secondary:

- Patients treated with Duvyzat experienced less worsening on the NSAA compared to placebo, which was nominally significant but not statistically significant based on the prespecified multiplicity adjustment.

Table 4. Change from Baseline to Month 18 on 4SC Compared to Placebo*

	Mean Baseline 4SC (seconds)	Mean Change from Baseline	Treatment Difference from Placebo (95% CI)	p-value
DUVYZAT (n = 81)	3.39	1.25	-1.78 (-3.46, -0.11)	0.037
Placebo (n = 39)	3.48	3.03		

*Givinostat or placebo were administered in addition to a stable dose of corticosteroids throughout the study

</td></tr>
<tr><td>Conclusion</td><td>Among ambulant boys with Duchenne muscular dystrophy, results of the four-stair climb assessment worsened in both groups over the study period; however, the decline was significantly smaller with givinostat than with placebo. The dose of givinostat was reduced after an interim safety analysis, but no new safety signals were reported. An ongoing extension study is evaluating the long-term safety and efficacy of givinostat in patients with Duchenne muscular dystrophy.</td></tr>
</table>

Interpretation	Duvyzat™ represents the first nonsteroidal drug option for patients with DMD regardless of their genetic mutation. While the primary endpoint results worsened in both groups, Duvyzat™-treated individuals showed a slower decline in performing the four-stair climb assessment compared to placebo-treated individuals. These results are not generalizable to all patients with DMD as inclusion was limited to ambulant patients. There is a phase 3 study underway to investigate givinostat in non-ambulant patients with DMD. Due to its unique mechanism of action and overall efficacy and safety profile, Duvyzat™ helps fill an unmet need for treatment options in the DMD population. An ongoing extension study is evaluating the long-term safety and efficacy of Duvyzat™.

Ongoing

Title	Givinostat in Duchenne's Muscular Dystrophy Long-term Safety and Tolerability Study NCT: 03373968
Design	A phase 2/3, open label, long-term safety, tolerability, and efficacy study of givinostat in all DMD patients who have been previously treated in one of the givinostat studies.
Completion Date	12/2025

Title	Efficacy, Safety, and Tolerability of Givinostat in Non-ambulant Patients with Duchenne Muscular Dystrophy (ULYSSES) NCT: 05933057
Design	A phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy, safety, and tolerability of givinostat in non-ambulant male pediatric (aged 9 to <18 years) patients with DMD.
Completion Date	2/2028

Guidelines

Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar; 17(3):251-267.

Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopedic management. Lancet Neurol. 2018 Apr; 17(4):347-361.

Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. 2018 May; 17(5):445-455.

Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(5):465-72.

Clinical guidelines and recommendations for the management of DMD have not been updated since the approval of Duvyzat™. The 2016 American Academy of Neurology Practice Guidelines were reaffirmed in January of 2022. Current treatment recommendations for DMD primarily revolve around orthopedic interventions, health maintenance, management of complications and the use of glucocorticoids. Glucocorticoids are used in the management of DMD due of their anti-inflammatory and immunomodulatory effects on muscle function.

This is a summary of the American Academy of Neurology (AAN) guideline update, "Corticosteroid treatment of Duchenne muscular dystrophy."

Please refer to the full guideline at *AAN.com/guidelines* for more information, including the definitions of the classifications of evidence and recommendations.

What is the efficacy of corticosteroids with regard to Duchenne muscular dystrophy (DMD) progression, specifically their effect on survival, quality of life (QoL), motor function, scoliosis, pulmonary function, and cardiac function?

Prednisone	
Moderate Evidence	Prednisone, offered as an intervention for patients with DMD, should be used to improve strength and pulmonary function (**Level B**).
Weak Evidence	Prednisone, offered as an intervention for patients with DMD, may be used to improve timed motor function, to reduce the need for scoliosis surgery, and to delay the onset of cardiomyopathy by 18 years of age (**Level C**).
Insufficient Evidence	Data are insufficient to support or refute the benefit of prednisone for survival in DMD (**Level U**).
	Data are insufficient to support or refute the benefit of bisphosphonates for improving survival of patients with DMD who are taking prednisone (**Level U**).
	Data are insufficient to support or refute an effect of prednisone on QoL in patients with DMD (**Level U**).

Deflazacort	
Weak Evidence	Deflazacort, offered as an intervention for patients with DMD, may be used to improve strength and timed motor function and delay the age at loss of ambulation by 1.4 to 2.5 years (**Level C**).
	Deflazacort, offered as an intervention for patients with DMD, may be used to improve pulmonary function, to reduce the need for scoliosis surgery, and to delay the onset of cardiomyopathy by 18 years of age (**Level C**).
	Deflazacort, offered as an intervention for patients with DMD, may be used to increase survival at 5 and 15 years of follow-up (**Level C**).
Insufficient Evidence	Data are insufficient to support or refute the benefit of bisphosphonates for improving survival of patients with DMD who are taking deflazacort (**Level U**).
	Data are insufficient to support or refute an effect of deflazacort on QoL in patients with DMD (**Level U**).

Clinical Opinions

Duchenne muscular dystrophy (DMD) is rare, fatal, X-linked genetic disease whereby a mutation in the DMD gene causes defects or absence of dystrophin protein. These mutations lead to an absence or a defect of the dystrophin protein, resulting in progressive muscle degeneration, leading to loss of ambulation and eventually respiratory, orthopedic, and

cardiac complications. Clinically, DMD presents as progressive and irreversible muscle deterioration. DMD primarily affects boys but can affect girls in rare cases. The incidence is estimated to be approximately one in 3,500-5,000 newborn boys, and prevalence estimates ranging between 10,000 and 15,000 males. Most DMD patients are diagnosed at 3 to 5 years of age. Patients commonly require wheelchairs by age 12, breathing support by age 20, and die by age 30, generally due to respiratory or cardiac failure.

Currently, pharmacological treatment with corticosteroids, such as prednisone and Emflaza®, are the mainstay of DMD treatment strategies because of their beneficial effects for improving motor function and pulmonary function, reducing the risk of scoliosis, delaying the loss of ambulation, and possibly for delaying progression of cardiomyopathy and improving survival. Agamree®, a dissociative steroid, represents another treatment option for DMD. Although Agamree binds to the same receptors as glucocorticoid steroids, it exhibits a different mechanism of action downstream, allowing for better tolerability and safety. Other treatment options include the "exon-skipping" drugs, Exondys® 51, Vyondys® 53, Viltepso™, Amondys® 45, and the gene therapy, Elevidys™.

Duvyzat™, an oral histone deacetylase inhibitor, represents the first nonsteroidal treatment option for patients with DMD ages six years and older. Duvyzat™ works by counteracting disease pathology and slowing down muscle deterioration. Unlike the previously mentioned therapies, Duvyzat™ is the only treatment option for the broad DMD population regardless of genetic mutation. Approval is based on results from the Phase III EPIDYS trial. The study met its primary endpoint demonstrating that patients on Duvyzat™ showed a statistically significant and clinically meaningful difference in time to complete the four-stair climb assessment. There is a phase 3 study underway to investigate givinostat in non-ambulant patients with DMD. Through its unique mechanism of action, Duvyzat™ has shown a positive risk/benefit profile and the ability to delay disease progression. Duvyzat™ helps fill a tremendous unmet need for treatment options in the DMD population. An ongoing extension study is evaluating the long-term safety and efficacy of Duvyzat™ in patients with DMD.

Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Prednisone	F	5 mg/5 mL (120 mL, 500 mL) oral solution 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, 50 mg oral tablet	$516** $5**
Emflaza® (deflazacort)	F-PA	22.75 mg/mL (13 mL) oral suspension 6 mg, 18 mg, 30 mg, 36 mg oral tablets	$24,264† $18,419†
Agamree® (vamorolone)	NF	40 mg/mL oral suspension	$22,800^

^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).*

***Based on maximum recommended dose of 40 mg/day*

† Dose for ~30 kg child

^ Based on max dose of 300mg/day.

Medication Request Guideline

New:

Duvyzat	
Therapeutic Classes (AHFS)	Other Miscellaneous Therapeutic Agents
Medications	Duvyzat (givinostat)
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 a neurologist or provider or specializes in the treatment of Duchenne Muscular Dystrophy (DMD)
Coverage Duration	If all the criteria are met, the initial request will be approved for 12 months. For continuation of therapy, the request 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:** • Medication is prescribed at an FDA approved dose according to body weight • Genetically confirmed diagnosis of Duchenne Muscular Dystrophy (DMD) and copies of testing were submitted with request • Patient has been stable on baseline corticosteroids for at least 6 months • Patient is ambulatory **Re-Authorization:** • Documentation or provider attestation of positive clinical response (such as improved muscle function, muscle strength, or disease stabilization) • Patient is on concurrent corticosteroid treatment • Patient is ambulatory • Medication is prescribed at an FDA approved dose according to body weight
Criteria Statement	Duvyzat is reserved for members who have a diagnosis of DMD, who are ambulatory and have been stable on baseline corticosteroids for at least 6 months.
Last P&T Review Date	9/2024

References

1. Duvyzat (givinostat) [prescribing information]. ITF Therapeutics, LLC, Concord, MA; March 2024.
2. AMCP eDossier System. Dymaxium Healthcare Innovations, Ltd. Available at: https://amcp.edossiers.com/. Accessed on April 2, 2024.
3. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on April 2, 2024.
4. Facts & Comparisons eAnswers, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on April 2, 2024.
5. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on April 2, 2024.
6. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on April 2, 2024.
7. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Available at: http://www.fda.gov/. Accessed on April 2, 2024.
8. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management [published correction appears in Lancet Neurol. 2018 Apr 4;:]. *Lancet Neurol*. 2018;17(3):251-267. doi:10.1016/S1474-4422(18)30024-3
9. Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(5):465-72.
10. Mercuri E, Vilchez JJ, Boespflug-Tanguy O, et al; EPIDYS Study Group. Safety and efficacy of givinostat in boys with Duchenne muscular dystrophy (EPIDYS): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2024 Apr;23(4):393-403. doi: 10.1016/S1474-4422(24)00036-X. PMID: 38508835.

PERFORMRx℠

Glaucoma

Executive Summary

CLASS OVERVIEW

Glaucoma is an optic neuropathy which can lead to progressive vision loss and blindness and may be (but is not always) accompanied by an increase in intraocular pressure (IOP). The two main classifications for glaucoma are open- or angle-closure (referring to the angle of the anterior chamber). Glaucoma can further be categorized as acute, subacute or chronic, and primary (unknown cause) or secondary etiology (known cause such as uveitis, trauma, or glucocorticoid therapy). Glaucoma is the second leading cause of blindness worldwide, and the most common cause of blindness in African Americans. While glaucoma more commonly affects older individuals, certain types of glaucoma may occur in infants and children as well. The scope of this review will cover pharmacotherapy agents used mainly for primary open-angle glaucoma (POAG).

Risk factors for POAG include older age, African race or Latino/Hispanic ethnicity, higher level of IOP, family history, low ocular perfusion pressure, type 2 diabetes mellitus, myopia, and thin central cornea. Regardless of the level, reduction of IOP is the main goal of therapy for open-angle glaucoma and reduces risk of disease progression (visual field loss, optic disc changes). This is generally approached by presuming the patient's baseline IOP (regardless of whether this is an elevated pressure) has caused the glaucomatous changes and can cause further damage to the optic nerve, and treatment is focused on achieving a target pressure reduction which is not clearly defined (typically by 20%-30%) and can vary depending on patient risk factors and overall prognosis/disease course.

The main treatment options include pharmacotherapy agents, laser therapy, or surgery. Pharmacotherapy agents include prostaglandins, beta blockers, alpha-2 adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, rho-kinase inhibitors, acetylcholinesterase inhibitors, or a combination of agents in these categories. Pharmacotherapy is generally the initial treatment strategy, and per the American Academy of Ophthalmology, prostaglandin analogs are the initial choice in most situations due to their efficacy, tolerability/safety, and convenient once-daily dosing. Agents should be selected based on patient-specific factors and can be switched or used in combination to achieve IOP in the target range. Laser therapy or surgery are generally reserved as treatment options after pharmacotherapy has failed but can be employed in conjunction with pharmacotherapy agents as well.

There have not been any novel drug launches in the glaucoma treatment category since the previous update, and the majority of topical agents used in treatment of POAG are available generically. However, novel administration methods in the form of ocular implants are the most recent advancements in care. Druysta® (bimatoprost) and iDose® TR (travoprost) provide options for patients with poor adherence to use of topical therapies, delivering drug for extended lengths of time. Currently, neither product is FDA approved for repeat administration. Durysta® is expected to provide efficacy for IOP lowering for 6-12 months, and iDose TR may last up to 3 years.

UTILIZATION FINDINGS

There were 196 claims for 100 members, for a total cost of $4,792.42 and an average cost per claim of $24.45. The most highly utilized medication was Latanoprost 0.005% ophthalmic drops, with 120 claims, followed by Brimonidine 0.2% ophthalmic drops with 30 claims. There were 2 prior authorizations with 1 approval (50%).

RECOMMENDATIONS

- Change from F-PA to NF based on no utilization and adequate alternatives
    - Apraclonidine (Iopidine®) 0.5% ophthalmic drops
- Implement new Rho Kinase Inhibitor MRG criteria with no formulary changes

CLINICAL SUMMARY

Primary open-angle glaucoma is defined by the American Academy of Ophthalmology as, "a chronic, progressive optic neuropathy in adults in which there is a characteristic acquired atrophy of the optic nerve and loss of retinal ganglion cells and their axons. This condition is associated with an open anterior chamber angle by gonioscopy." The progressive loss of visual field often goes unnoticed by patients in its initial stages and diagnosed during routine eye examination vs patients seeking provider care for complaints of pain, redness, or visual symptoms. Left untreated, patients will progressively lose vision and mean progression rate to blindness is approximately 25 years. While many patients with a diagnosis of POAG have elevated IOP, nearly 40% may not. Regardless of the level, reduction of IOP is the main goal of therapy for open-angle glaucoma and reduces risk of disease progression (visual field loss, optic disc changes). This is generally approached by presuming the patient's baseline IOP (regardless of whether this is an elevated pressure) has caused the glaucomatous changes and can cause further damage to the optic nerve, and treatment is focused on achieving a target pressure reduction which is not clearly defined (typically by 20%-30%) and can vary depending on patient risk factors and overall prognosis/disease course.

The main treatment options for POAG include pharmacotherapy agents, laser therapy, or surgery. Pharmacotherapy agents include prostaglandins, beta blockers, alpha-2 adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, rho-kinase inhibitors, acetylcholinesterase inhibitors, or a combination of agents in these categories. In general, topical pharmacologic agents for treatment of glaucoma work to reduce intraocular pressure by either increasing aqueous humor outflow or decreasing its production.

Agents which increase aqueous outflow:

- Prostaglandins
- Alpha-2 adrenergic agonists
- Cholinergic agonists
- Acetylcholinesterase inhibitors
- Rho kinase inhibitors

Agents which decrease aqueous production:

- Alpha-2 adrenergic agonists
- Beta blockers
- Carbonic anhydrase inhibitors
- Rho kinase inhibitors

Per the American Academy of Ophthalmology Preferred Practice Parameter Guidelines, prostaglandin analogs are considered initial choice of therapy in most situations due to their efficacy, tolerability/safety, and convenient once-daily dosing. Agents should be selected based on patient-specific factors and can be switched or used in combination to achieve IOP in the target range. Laser therapy or surgery are generally reserved as treatment options after pharmacotherapy has failed but can be employed in conjunction with pharmacotherapy agents.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Betaxolol (Betoptic®, Betoptic S®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Solution: Instill 1 to 2 drops into affected eye(s) twice daily. Suspension (Betoptic S®): Instill 1 drop into affected eye(s) twice daily.
Carteolol (Ocupress®)	Elevated intraocular pressure (chronic open-angle glaucoma and intraocular hypertension)	Instill 1 drop in affected eye(s) twice daily.
Levobunolol (Betagan®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 to 2 drops into affected eye(s) once daily; may increase to 1 drop twice daily in patients with severe or uncontrolled glaucoma. Doses >1 drop twice daily are generally not more effective.
Timolol (Timoptic®, Timoptic-XE®, Istalol®, Betimol®)	Elevated intraocular pressure (open-angle glaucoma or ocular hypertension)	Gel-forming solution (Timolol GFS, Timoptic-XE®): Instill 1 drop (either 0.25% or 0.5% solution) once daily. Solution: Initial: Instill 1 drop (0.25% solution) into affected eye(s) twice daily; if response is not adequate, increase to 1 drop (0.5% solution) twice daily. May decrease dose to 1 drop once daily if intraocular pressure is well controlled. Istalol®: Instill 1 drop (0.5% solution) once daily in the morning.
Apraclonidine (Iopidine®)	Intraocular pressure reduction: 0.5% solution: Short-term, adjunctive therapy in patients who require additional reduction of IOP 1% solution: Prevention and treatment of postsurgical intraocular pressure (IOP) elevation following argon laser trabeculoplasty, argon laser iridotomy or Nd:YAG posterior capsulotomy	0.5%: Instill 1 to 2 drops in the affected eye(s) 3 times daily. 1%: Instill 1 drop in operative eye 1 hour prior to anterior segment laser surgery, second drop in same eye immediately upon completion of procedure.
Brimonidine (Alphagan®, Alphagan P®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Ophthalmic (0.1%, 0.15%, 0.2% solution): Instill 1 drop in affected eye(s) 3 times/day (approximately every 8 hours).
Brinzolamide (Azopt®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 drop in affected eye(s) 3 times daily.
Dorzolamide (Trusopt®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 drop in the affected eye(s) 3 times daily.
Acetazolamide (Diamox®, Diamox Sequels®)	• Altitude illness • Edema • Elevated intraocular pressure in patients with chronic open-angle glaucoma or acute angle-closure glaucoma prior to surgery or as part of a 4-drug medical management regimen when a patient cannot be seen by an ophthalmologist for ≥1 hour • Epilepsy	Angle-closure glaucoma, acute: Oral (immediate release) or IV: 500 mg as part of a 4-drug regimen. Note: Reserve medical management for emergency situations when an assessment by an ophthalmologist will be delayed by ≥1 hour. Open-angle glaucoma: Oral: 250 mg 1 to 4 times/day (immediate release) or 500 mg twice daily (extended release). Note: Reserve for management of acute ocular pressure increases, including after surgery or trauma.

Medication	Indications	Dosing/Administration
Methazolamide (Neptazane®)	• Treatment of chronic open-angle or secondary glaucoma • Short-term therapy of acute angle-closure glaucoma prior to surgery	Oral: 50 to 100 mg 2 to 3 times/day.
Bimatoprost (Lumigan®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 drop into affected eye(s) once daily in the evening; do not exceed once-daily dosing (may decrease IOP-lowering effect). If used with other topical ophthalmic agents, separate administration by at least 5 minutes.
Latanoprost (Xalatan®, Xelpros®, Iyuzeh®)	Elevated intraocular pressure (chronic open-angle glaucoma and ocular hypertension)	One drop in the affected eye(s) once daily in the evening; do not exceed the once daily dosage (may decrease the IOP-lowering effect).
Travoprost (Travatan Z®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 drop into affected eye(s) once daily in the evening; do not exceed once-daily dosing (may decrease IOP-lowering effect).
Tafluprost (Zioptan®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	One drop in the affected eye(s) once daily in the evening; do not exceed the once daily dosage because it has been shown that more frequent administration may decrease the IOP-lowering effect.
latanoprostene bunod (Vyzulta®)	Elevated intraocular pressure (chronic open-angle glaucoma and ocular hypertension)	Instill 1 drop into affected eye(s) once daily in the evening; do not exceed the once daily dosage (may decrease the IOP-lowering effect).
Pilocarpine (Isopto Carpine®)	• Elevated intraocular pressure (open-angle glaucoma or ocular hypertension) • Angle closure glaucoma • Miosis • Prevention of postoperative elevated IOP	Elevated intraocular pressure: Ophthalmic: Instill 1 drop of 1%, 2%, or 4% solution into the affected eye(s) up to 4 times daily; initiate pilocarpine-naive patients on the 1% concentration. Note: Strength of solution and frequency of instillation dependent on degree of pressure elevation and patient miotic response. Glaucoma (acute angle closure): Ophthalmic: Instill 1 drop of 2% solution into the affected eye as part of a 4-drug regimen; may repeat in 30 to 60 minutes if intraocular pressure remains elevated (eg, >40 mm Hg). Note: Reserve medical management for emergency situations when an assessment by an ophthalmologist will be delayed by ≥1 hour. Miosis: Ophthalmic: Instill 1 drop (or 2 drops 5 minutes apart) of 1%, 2%, or 4% solution into the affected eye(s). Prevention of postoperative elevated IOP: Ophthalmic: Instill 1 drop (or 2 drops 5 minutes apart) of 1%, 2%, or 4% solution into the affected eye(s) 15 to 60 minutes prior to surgery.
Miochol-E® (Acetylcholine)	To obtain miosis of the iris in seconds after delivery of the lens in cataract surgery, in penetrating keratoplasty, iridectomy, and other anterior segment surgery where rapid miosis may be required	Ophthalmic surgery: Intraocular: Usual dosage: 0.5 to 2 mL.

Medication	Indications	Dosing/Administration
Miostat® (Carbachol)	• Lowers intraocular pressure in the treatment of glaucoma • Cause miosis during surgery	Glaucoma: Ophthalmic: Instill 1-2 drops up to 3 times/day. Ophthalmic surgery (miosis): Intraocular: 0.5 mL instilled into anterior chamber before or after securing sutures.
Netarsudil (Rhopressa®)	Elevated intraocular pressure (chronic open-angle glaucoma or ocular hypertension)	Instill 1 drop into affected eye(s) once daily in the evening (maximum: 1 drop into affected eye(s) once daily).
Echothiophate iodide (Phospholine Iodide®)	Accommodative esotropia: Concomitant esotropias with a significant accommodative component Elevated intraocular pressure: Reduction of elevated intraocular pressure	Initial: Instill 1 drop in affected eye(s) twice daily (prior to bedtime and in the morning). Maintenance: Twice-daily dosing is preferred, but some patients have been treated with once-daily or every-other-day dosing (with 1 dose just prior to bedtime).
Brimonidine tartrate-timolol (Combigan®)	Elevated intraocular pressure (glaucoma or ocular hypertension)	Instill 1 drop into affected eye(s) twice daily.
Brinzolamide-brimonidine (Simbrinza®)	Elevated intraocular pressure (open-angle glaucoma or ocular hypertension)	Instill 1 drop in affected eye(s) 3 times daily.
Dorzolamide-timolol (Cosopt®)	Elevated intraocular pressure (open-angle glaucoma or ocular hypertension) and insufficiently responsive to beta-blockers	Instill 1 drop in affected eye(s) twice daily.
Rocklatan® (netarsudil-latanoprost)	Elevated intraocular pressure (open-angle glaucoma or ocular hypertension)	One drop in the affected eye(s) once daily in the evening.
Durysta® (bimatoprost)	Reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension.	Durysta is an ophthalmic drug delivery system for a single intracameral administration of a biodegradable implant. Durysta should not be readministered to an eye that received a prior Durysta. See prescribing information for administration detail.
iDOSE® TR (travoprost)	Reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension.	iDose TR is a travoprost delivery system consisting of a travoprost releasing implant pre-loaded in a sterile, single-dose inserter. iDose TR is administered intracamerally through a small, clear corneal incision and is anchored into the sclera at the iridocorneal angle. iDose TR should not be readministered to an eye that received a prior iDose TR. See prescribing information for administration detail.

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Betaxolol (Betoptic®, Betoptic S®)	N/A	Hypersensitivity to betaxolol or any component of the formulation; sinus bradycardia; heart block greater than first-degree (except in patients with a functioning artificial pacemaker); cardiogenic shock; uncompensated cardiac failure.
Carteolol (Ocupress®)		Hypersensitivity to carteolol or any component of the formulation; sinus bradycardia; second- or third-degree atrioventricular block; cardiogenic shock; bronchial asthma or history of; severe chronic obstructive pulmonary disease (COPD); overt cardiac failure. Documentation of allergenic cross-reactivity for Ophthalmic Beta-Adrenergic Blocking Agents is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Levobunolol (Betagan®)		Hypersensitivity to levobunolol or any component of the formulation; bronchial asthma or history of bronchial asthma; severe COPD; sinus bradycardia; second- or third-degree atrioventricular block; overt heart failure; cardiogenic shock. Documentation of allergenic cross-reactivity for ophthalmic beta-adrenergic blocking agents is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Timolol (Timoptic®, Timoptic-XE®, Istalol®, Betimol®)		Hypersensitivity to timolol or any component of the formulation; bronchial asthma or history of bronchial asthma; severe chronic obstructive pulmonary disease (COPD); sinus bradycardia; second- or third-degree atrioventricular block; overt heart failure; cardiogenic shock. Documentation of allergenic cross-reactivity for Ophthalmic Beta-Adrenergic Blocking Agents is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.
Apraclonidine (Iopidine®)		Hypersensitivity to apraclonidine, clonidine, or any component of the formulation; concomitant use with MAO inhibitors.
Brimonidine (Alphagan®, Alphagan P®)		Hypersensitivity to brimonidine or any component of the formulation; neonates and infants <2 years; concomitant MAO inhibitor therapy.
Brinzolamide (Azopt®)		Hypersensitivity to brinzolamide or any component of the formulation.
Dorzolamide (Trusopt®)		Hypersensitivity to dorzolamide or any component of the formulation.
Acetazolamide (Diamox®, Diamox Sequels®)		Hypersensitivity to acetazolamide, sulfonamides, or any component of the formulation; marked hepatic disease or insufficiency; decreased sodium and/or potassium levels; adrenocortical insufficiency; cirrhosis; hyperchloremic acidosis; severe renal disease or dysfunction; long-term use in noncongestive angle-closure glaucoma
Methazolamide (Neptazane®)		Marked kidney or liver dysfunction; adrenal gland failure; cirrhosis; hyperchloremic acidosis; hyponatremia; hypokalemia; long-term treatment of angle-closure glaucoma.
Bimatoprost (Lumigan®)		Hypersensitivity to bimatoprost or any component of the formulation.
Latanoprost (Xalatan®, Xelpros®, Iyuzeh®)		Hypersensitivity to latanoprost, benzalkonium chloride, or any component of the formulation.
Travoprost (Travatan Z®)		N/A
Tafluprost (Zioptan®)		
latanoprostene bunod (Vyzulta®)		
Pilocarpine (Isopto Carpine®)		
Netarsudil (Rhopressa®)		

Medication	Boxed Warnings	Contraindications
Echothiophate iodide (Phospholine Iodide®)		Hypersensitivity to echothiophate or any component of the formulation; most cases of angle-closure glaucoma without iridectomy (due to possibility of increasing angle block); active uveal inflammation.
Brimonidine tartrate-timolol (Combigan®)		Reactive airway disease, including bronchial asthma; history of bronchial asthma; severe chronic obstructive pulmonary disease (COPD); sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, cardiogenic shock; known hypersensitivity to brimonidine/timolol or any component of the formulation; neonates, infants, and children younger than 2 years.
Brinzolamide-brimonidine (Simbrinza®)		Hypersensitivity to brinzolamide, brimonidine, or any component of the formulation; children <2 years of age.
Dorzolamide-timolol (Cosopt®)		Hypersensitivity to dorzolamide, timolol, or any component of the formulation; bronchial asthma or a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second- or third-degree atrioventricular block; overt cardiac failure; cardiogenic shock.
Rocklatan® (netarsudil-latanoprost)		N/A
Miochol-E® (Acetylcholine)		Hypersensitivity to acetylcholine chloride or any component of the formulation.
Miostat® (Carbachol)		Hypersensitivity to carbachol or any component of the formulation; acute iritis, acute inflammatory disease of the anterior chamber.
Durysta® (bimatoprost)		Active or suspected ocular or periocular infections, corneal endothelial cell dystrophy, prior corneal transplantation, or endothelial cell transplants, absent or ruptured posterior lens capsule, hypersensitivity to ingredients.
iDOSE® TR (travoprost)		Active or suspected ocular or periocular infections, corneal endothelial cell dystrophy, prior corneal transplantation, or endothelial cell transplants, hypersensitivity to ingredients.

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Betaxolol (Betoptic®, Betoptic S®)	Concerns related to adverse events: anaphylactic reactions Disease-related concerns: bronchospastic disease, cardiovascular insufficiency, diabetes, heart failure, myasthenia gravis, thyroid disease, vascular insufficiency Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Dosage form specific issues: bacterial keratitis, not to be monotherapy for angle-closure glaucoma, choroidal detachment Other warnings/precautions: systemic absorption
Carteolol (Ocupress®)	Concerns related to adverse events: anaphylactic reactions, choroidal detachment Disease-related concerns: diabetes, heart failure, myasthenia gravis, peripheral vascular disease and Raynaud disease, respiratory disease, thyroid disease Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Dosage form specific issues: systemic absorption, bacterial keratitis, not to be monotherapy for angle-closure glaucoma, may block systemic beta agonists during surgery
Levobunolol (Betagan®)	Concerns related to adverse events: anaphylactic reactions, choroidal detachment Disease-related concerns: cerebrovascular disease, diabetes, heart failure, myasthenia gravis, peripheral vascular disease and Raynaud disease, respiratory disease, thyroid disease Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Dosage form specific issues: metabisulfite (allergic reactions) Other warnings/precautions: systemic absorption, bacterial keratitis, not to be monotherapy for angle-closure glaucoma, may block systemic beta agonists during surgery
Timolol (Timoptic®, Timoptic-XE®, Istalol®, Betimol®)	Concerns related to adverse events: anaphylactic reactions, choroidal detachment Disease-related concerns: cerebrovascular disease, diabetes, heart failure, myasthenia gravis, peripheral vascular disease and Raynaud disease, respiratory disease, thyroid disease Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Other warnings/precautions: systemic absorption, bacterial keratitis, not to be monotherapy for angle-closure glaucoma, may block systemic beta agonists during surgery
Apraclonidine (Iopidine®)	Concerns related to adverse events: CNS effects, hypersensitivity Disease-related concerns: cardiovascular disease, hepatic impairment, renal impairment, vasovagal reactions Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Other warnings/precautions: appropriate use (topical only), tachyphylaxis
Brimonidine (Alphagan®, Alphagan P®)	Concerns related to adverse events: bacterial keratitis, CNS depression Disease-related concerns: cardiovascular disease, cerebrovascular insufficiency, depression, hepatic impairment, orthostatic hypotension, Raynaud phenomenon, renal impairment, thromboangiitis obliterans Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers, systemic absorption (higher risk for children)
Brinzolamide (Azopt®)	Concerns related to adverse events: ophthalmic effects (blurred vision), sulfonamide allergy Disease-related concerns: acute angle-closure glaucoma (not studied), corneal endothelium, renal impairment Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers
Dorzolamide (Trusopt®)	Concerns related to adverse events: bacterial keratitis, ocular effects, sulfonamide allergy, systemic absorption/effects Disease-related concerns: corneal endothelium, hepatic impairment, renal impairment Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers

Medication	Warnings/Precautions
	Other warnings/precautions: appropriate use in acute angle-closure glaucoma
Acetazolamide (Diamox®, Diamox Sequels®)	Concerns related to adverse events: CNS effects, sulfonamide allergy (likelihood of cross reaction is very low) Disease-related concerns: diabetes, hepatic impairment, respiratory acidosis Concurrent drug therapy issues: drug-drug interactions may exist Special populations: use with caution in elderly patients Other warnings/precautions: appropriate use, IM administration not recommended
Methazolamide (Neptazane®)	Concerns related to adverse events: CNS effects, electrolyte disturbance, sulfonamide allergy Disease-related concerns: diabetes, hepatic impairment, respiratory disease Concurrent drug therapy issues: high dose aspirin; may lead to death, coma, tachypnea, anorexia, and lethargy
Bimatoprost (Lumigan®)	Concerns related to adverse events: bacterial keratitis, ocular effects, ocular inflammation Disease-related concerns: caution in ocular disease Special populations: contact lens wearers
Latanoprost (Xalatan®, Xelpros®, Iyuzeh®)	Concerns related to adverse events: bacterial keratitis, ocular effects, ocular inflammation Disease-related concerns: herpetic keratitis, caution in ocular disease Special populations: contact lens wearers
Travoprost (Travatan Z®)	Concerns related to adverse events: bacterial keratitis, ocular effects Disease-related concerns: caution in ocular disease Special populations: contact lens wearers, pediatric patients
Tafluprost (Zioptan®)	Concerns related to adverse events: ocular effects Disease-related concerns: caution in ocular disease Special populations: pediatric patients
latanoprostene bunod (Vyzulta®)	Concerns related to adverse events: bacterial keratitis, ocular effects, ocular inflammation Disease-related concerns: caution in ocular disease Special populations: contact lens wearers
Pilocarpine (Isopto Carpine®)	Concerns related to adverse events: ophthalmic effects Disease-related concerns: asthma, cardiovascular disease, GI disease, hyperthyroidism, ocular inflammation, Parkinson disease, retinal disease, urinary tract obstruction Special populations: contact lens wearers, pediatric patients
Miochol-E® (Acetylcholine)	Disease-related concerns: can cause problems for patients with asthma, GI spasm, acute heart failure, hyperthyroidism, Parkinson's disease, peptic ulcer disease, and or urinary tract obstruction, myocardial dysfunction
Miostat® (Carbachol)	Disease-related concerns: asthma, corneal abrasion, gastrointestinal disease, heart failure, hyperthyroidism, Parkinson’s disease, urinary tract obstruction Concurrent drug therapy issues: general anesthesia Dosage form specific issues: may contain latex
Netarsudil (Rhopressa®)	Concerns related to adverse events: bacterial keratitis Special populations: contact lens wearers
Echothiophate iodide (Phospholine Iodide®)	Concerns related to adverse events: cardiac irregularities, cholinergic effects Disease-related concerns: asthma, cardiovascular disease, gastrointestinal disease, Parkinsonism, seizure disorder, vagotonia Concurrent drug therapy issues: drug-drug interactions may exist Other warnings/precautions: appropriate use, exposure to pesticides and insecticides, development of tolerance
Brimonidine tartrate-timolol (Combigan®)	Concerns related to adverse events: anaphylactic reactions, bacterial keratitis, CNS depression, hypersensitivity, ocular effects Disease-related concerns: angle-closure glaucoma, cardiovascular disease, cerebrovascular disease, depression, diabetes, hepatic impairment, myasthenia gravis, renal impairment, respiratory disease, thyroid disease, vascular insufficiency Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers, pediatric patients Other warnings/precautions: may block systemic beta agonists during surgery

Medication	Warnings/Precautions
Brinzolamide-brimonidine (Simbrinza®)	Concerns related to adverse events: acid-base disturbances, bacterial keratitis, CNS effects, sulfonamide allergy Disease-related concerns: Acute angle-closure glaucoma, cardiovascular disease, cerebrovascular insufficiency, corneal endothelium, depression, hepatic impairment, orthostatic hypotension, renal impairment, thromboangiitis obliterans, vascular insufficiency. Concurrent drug therapy issues: drug-drug interactions may exist Dosage form specific issues: may contain benzalkonium chloride
Dorzolamide-timolol (Cosopt®)	Concerns related to adverse events: anaphylactic reactions, bacterial keratitis, ocular effects, sulfonamide allergy, systemic effects Disease-related concerns: diabetes, heart failure, hepatic impairment, myasthenia gravis, narrow-angle glaucoma, peripheral vascular disease and Raynaud's disease, psychiatric disease, renal impairment, respiratory disease, thyroid disease Concurrent drug therapy issues: drug-drug interactions may exist Special populations: contact lens wearers Other warnings/precautions: surgery
Rocklatan® (netarsudil-latanoprost)	Concerns related to adverse events: bacterial keratitis, ocular effects, ocular inflammation Disease-related concerns: herpetic keratitis, ocular disease Special populations: contact lens wearers Other warnings/precautions: avoid use of 2 or more prostaglandin analogs or > once daily administration
Durysta® (bimatoprost)	Potential for corneal adverse reactions, caution in those with narrow iridocorneal angles or obstruction, possible macular edema, caution with active intraocular inflammation, may cause changes in iris pigmentation, monitor for endophthalmitis
iDOSE® TR (travoprost)	Caution in those with narrow iridocorneal angles or abnormalities, monitor for devise dislocation, possible macular edema, caution with active intraocular inflammation, may cause changes in iris pigmentation, monitor for endophthalmitis, implant is MR Conditional

PRACTICE GUIDELINES

**Note: Guidelines from the American Optometric Association were not included with this review due to being greater than 5 years since last update and currently undergoing revision.*

American Academy of Ophthalmology – 2020

Gedde SJ, Vinod K, Wright MM, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern®. *Ophthalmology*. 2021;128(1):P71-P150. doi:10.1016/j.ophtha.2020.10.022.

Current AAO guidelines do not state preference for any particular class of agents over another for open-angle glaucoma treatment. Prostaglandin analogs are mentioned as most frequently prescribed and typically the initial choice of therapy in most situations due to their efficacy, tolerability/safety, and convenient once-daily dosing. Topical beta-blockers are also highlighted as commonly prescribed, but may carry risk of pulmonary adverse effects in patients with obstructive airway disease. Agents should be selected based on patient-specific factors (amount of IOP lowering required, contraindications, cost, side effects, etc.) and can be switched or used in combination to achieve IOP in the target range. Fixed combination therapy may be helpful for patient adherence when multiple agents are required.

Highlighted Findings and Recommendations for Care

- Established risk factors for primary open-angle glaucoma (POAG) include older age, African race or Latino/Hispanic ethnicity, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, myopia, and thin central cornea.
- Primary open-angle glaucoma patients often have untreated IOP consistently within the normal range (i.e., normal tension glaucoma). Lowering pressure in these patients is beneficial.
- Characteristic clinical features of POAG include an open angle on gonioscopy, and glaucomatous optic nerve head (ONH) and retinal nerve fiber layer (RNFL)/macula imaging changes that are usually associated with typical glaucomatous visual field defects.
- Computer-based imaging and stereoscopic photography provide different and complementary information about optic nerve status.
- Adjusting computerized visual field programs (24 degrees, 30 degrees, 10 degrees) and stimulus size (III, V) can aid in detecting and monitoring progressive visual field loss.
- Clinical trials have shown that lowering IOP reduces the risk of developing POAG and slows the progression of POAG. Effective medical, laser, and incisional surgical approaches exist for lowering IOP.
- A reasonable initial treatment goal in a POAG patient is to reduce the IOP 20% or 30% below baseline and to adjust up or down as indicated by disease course and severity.

Gedde SJ, Chen PP, Muir KW, et al. Primary Angle-Closure Disease Preferred Practice Pattern®. *Ophthalmology*. 2021;128(1):P30-P70. doi:10.1016/j.ophtha.2020.10.021.

As with treatment recommendations regarding topical medications for open-angle glaucoma management, this guideline does not specifically suggest a hierarchy of agents to be used in angle closure glaucoma. Interventional surgical therapies are standard of care, with pharmacological treatments used for immediate reduction of IOP/alleviating symptoms in acute angle closure crisis, or to manage chronic IOP elevation after surgical interventions which occurs in some patients. Chronic angle-closure glaucoma patients with continued elevation of IOP after surgery are managed similarly to those with open-angle glaucoma.

Highlighted Findings and Recommendations for Care

- Understanding the current disease definition is important in the management of the primary angle-closure disease (PACD) spectrum. Modern classification includes:
    - Primary angle-closure suspect (PACS): >180 degrees iridotrabecular contact (ITC), normal intraocular pressure (IOP), and no optic nerve damage
    - Primary angle-closure (PAC): >180 degrees ITC with peripheral anterior synechiae (PAS) or elevated IOP but no optic neuropathy
    - Primary angle-closure glaucoma (PACG): >180 degrees ITC with PAS, elevated IOP, and optic neuropathy
    - Acute angle-closure crisis (AACC): occluded angle with symptomatic high IOP

    - Plateau iris configuration: narrow angle due to an anteriorly positioned ciliary body, with deep central anterior chamber
    - Plateau iris syndrome: narrow angle due to an anteriorly positioned ciliary body, with deep central anterior chamber, and any ITC persisting after patent peripheral iridotomy
- Common risk factors for PACD include Asian descent, hyperopia, older age, female gender, short axial length, and thick and anteriorly positioned crystalline lens.
- Dark-room dynamic gonioscopy should be performed to diagnose PACD and to verify improvement in angle configuration following treatment. Ultrasound biomicroscopy (UBM) and anterior segment optical coherence tomography (AS-OCT) can also aid in the diagnosis of angle closure, but only UBM and dynamic gonioscopy can identify the etiology of plateau iris.
- The clinical signs and symptoms of AACC include pressure-induced corneal edema (experienced as blurred vision and occasionally as halos around lights), a mid-dilated pupil, vascular congestion (i.e., conjunctival and episcleral), eye pain, headache, and nausea/vomiting.
- Patients experiencing AACC should receive medical treatment, including aqueous suppressants, parasympathomimetics, and osmotic agents, if necessary, to lower the IOP acutely and relieve symptoms. This should be followed by laser iridotomy or iridectomy. After addressing the episode of AACC, it is important to perform laser iridotomy in the fellow eye when indicated.
- Lens extraction is an effective treatment for some patients with PAC and PACG.

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Li T, Lindsley K, Rouse B, et al. Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis. Ophthalmology. 2016 Jan;123(1):129-40. doi: 10.1016/j.ophtha.2015.09.005. Epub 2015 Oct 31.	This systematic review/meta-analysis included randomized controlled trials of single-agent ophthalmic medications (from beta-blockers, prostaglandin analogs, carbonic anhydrase inhibitors, or alpha-2 adrenergic agonists) for POAG vs placebo/no treatment or another single active topical medical treatment. 114 RCTs were included, involving 20,275 subjects data. Bayesian network meta-analysis was performed.	• To compare effectiveness of first-line agents for POAG and rank these treatments in terms of reduction of IOP.
Results: The mean reductions (95% credible intervals) in IOP in mmHg at 3 months, ordered from the most to least effective drugs were: bimatoprost 5.61 (4.94; 6.29), latanoprost 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.7 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), betaxolol 2.24 (1.59; 2.88), and unoprostone 1.91 (1.15; 2.67). **Conclusion**: The authors concluded the prostaglandin analogs bimatoprost, latanoprost and travoprost were the most effective at lowering IOP. Prostaglandin analogs were the most efficacious class of those studied. Of note the median length of follow up in the trials was very short (3 months) and glaucoma is unfortunately a disease where progression is gradual and long term. All drugs were effective compared to placebo. Patient specific considerations should be given when deciding drug therapy.		
Citation	**Design**	**Endpoints**
Budengeri P, Cheng JW, Cai JP, Wei RL. Efficacy and tolerability of fixed combination of brimonidine 0.2%/timolol 0.5% compared with fixed combination of dorzolamide 2%/timolol 0.5% in the treatment of patients with elevated intraocular pressure: a meta-analysis of randomized controlled trials. J Ocul Pharmacol Ther. 2013 Jun;29(5):474-9. doi: 10.1089/jop.2012.0134. Epub 2013 Feb 4.	This was a meta-analysis examined 7 randomized controlled trials (582 patients) with elevated IOP being treated with fixed-dose combination brimonidine 0.2%/timolol 0.5% (FCBT) or dorzolamide 2%/timolol 0.5% (FCDT).	• Comparative efficacy and tolerability of FCBT and FCDT were examined in patients treated for elevated IOP. • Efficacy measures used were IOP reduction (IOPR) (diurnal mean IOPR, peak IOPR); tolerability was measured with adverse events.
Results: With a weighted mean difference (WMD) of IOPR in diurnal mean of 0.44 mmHg (95% CI, 0.00-0.88), the FCBT was as effective as FCDT in lowering IOP in patients with elevated IOP (P=0.05). The WMD of IOPR at peak was 0.65 mmHg (95% CI, -0.06 to 1.35) (P=0.76), and there was no significant difference between FCBT and FCDT. FCBT caused burning/stinging in less patients than FCDT [pooled relative risk: 0.45 (95% CI, 0.29-0.70)]. **Conclusion**: The authors concluded both products effectively lower elevated IOP in patients with elevated IOP, and the brimonidine FDC is not inferior to the dorzolamide FDC. The brimonidine FDC caused less ocular discomfort.		

Citation	Design	Endpoints
Lin L, Zhao YJ, Chew PT, et al. Comparative efficacy and tolerability of topical prostaglandin analogues for primary open-angle glaucoma and ocular hypertension. Ann Pharmacother. 2014 Dec;48(12):1585-93. doi: 10.1177/1060028014548569. Epub 2014 Sep 2.	This network meta-analysis reviewed 32 randomized controlled trials for bimatoprost, latanoprost, tafluprost and travoprost. Trials compared prostaglandin analogs to each other or to timolol.	• Review efficacy and tolerability of prostaglandins in POAG/ocular hypertension for first-line monotherapy for IOP lowering (adults).
Results: Using timolol as reference, the relative risks of achieving treatment success, (proportion of patients achieving at least 30% reduction in IOP), with 95% CIs, were: bimatoprost, 1.59 (1.28-1.98); latanoprost, 1.32 (1.00-1.74); travoprost, 1.33 (1.03-1.72); and tafluprost, 1.10 (0.85-1.42). Mean IOP reductions after 1 month: 1.98 (1.50-2.47), 1.01 (0.55-1.46), 1.08 (0.59-1.57), and 0.46 (-0.41 to 1.33) mm Hg, respectively, and the results were sustained at 3 months. Bimatoprost was correlated with the highest risk of developing hyperemia, and the lowest risk was with latanoprost, with RRs (95% CI) of 4.66 (3.49-6.23) and 2.30 (1.76-3.00), respectively. **Conclusion**: The authors concluded bimatoprost lowers IOP the most, and latanoprost was the most tolerable.		
Citation	**Design**	**Endpoints**
Serle JB, Katz LJ, McLaurin E, et al. Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). Am J Ophthalmol. 2018 Feb;186:116-127. doi: 10.1016/j.ajo.2017.11.019. Epub 2017 Dec 1.	These Phase III clinical trials were pivotal in the approval of netarsudil by the FDA. These were double-masked, randomized non-inferiority clinical trials. Patients went through a washout period, then randomized to netarsudil 0.02% once daily, timolol 0.5% twice a day, and (ROCKET-2 only) netarsudil 0.02% twice a day. N=1167 (between the two studies); mean age in the mid-60s, predominantly female, and ¾ white, ¼ African American across the study groups.	• Efficacy and safety of netarsudil 0.02% ophthalmic solution in open-angle glaucoma/ocular hypertension patients. Primary efficacy outcome was mean intraocular pressure at week 2, 4 and month 3 visit.
Results: Once-daily dosing of netarsudil produced clinically and statistically significant reductions from baseline intraocular pressure ($P < .001$), and was non-inferior to timolol in the per-protocol population with maximum baseline IOP < 25 mm Hg in both studies (ROCKET-2, primary outcome measure and population, ROCKET-1, post hoc outcome measure). Netarsudil twice daily dosing in ROCKET-2 was also non-inferior to timolol. The most frequent adverse event was conjunctival hyperemia, the incidence of which ranged from 50% (126/251, ROCKET-2) to 53% (108/203, ROCKET-1) for netarsudil q.d., 59% (149/253, ROCKET-2) for netarsudil b.i.d., and 8% (17/208, ROCKET-1) to 11% (27/251, ROCKET-2) for timolol ($P < .0001$ for netarsudil vs timolol).[11] **Conclusion**: Netarsudil proved non-inferiority to timolol only in lower IOP groups (< 25 mm Hg) dosed once daily. Twice daily dosing demonstrated non-inferiority to timolol in ROCKET-2 for efficacy, but had much higher rates of conjunctival hyperemia than the once daily dosing regimen, and also was much more frequent than the active comparator timolol. The primary endpoint was not met in ROCKET-1.		
Citation	**Design**	**Endpoints**
Efficacy and Safety of Bimatoprost Sustained-Release (SR) in Patients With Open-angle Glaucoma or	These Phase III clinical trials were pivotal in the approval of Durysta by the FDA. These multicenter, randomized, parallel-group, controlled 20-month (including 8-month extended follow-up) studies compared Durysta implant administered on day 1, week	• Change in baseline IOP in the study eye at 12 weeks (noninferiority to timolol).

Ocular Hypertension. Durysta prescribing information NCT: 02247804 NCT: 02250651	16, and week 20, to twice daily topical timolol 0.5% drops in patients with open angle glaucoma or ocular hypertension. Subjects with a history of glaucoma surgery or recent history of any eye surgery were excluded. These were non-inferiority trials. N=594 subjects in trial 1 and 528 subjects in trial 2	
Results: In both trials, Bimatoprost SR reduced IOP by approximately 30 percent over the 12-week primary efficacy period, meeting the predefined criteria for non-inferiority to the study comparator, timolol. The most common ocular adverse reaction observed in two randomized, active-controlled clinical trials with Durysta in patients with OAG or OHT was conjunctival hyperemia, which was reported in 27% of patients. Other common ocular adverse reactions reported in 5-10% of patients were foreign body sensation, eye pain, photophobia, conjunctival hemorrhage, dry eye, eye irritation, intraocular pressure increased, corneal endothelial cell loss, vision blurred, and iritis. The most common non-ocular adverse reaction was headache, which was observed in 5% of patients. **Conclusion**: Durysta implant met non-inferiority criteria compared to topical timolol drops and was well tolerated. Interestingly, Durysta was only approved by the FDA for a one-time administration per eye, whereas the implant was designed and tested in trials to be administered every 12 weeks. Package insert warns the presence of Durysta implants has been associated with corneal adverse reactions and increased risk of corneal endothelial cell loss. Therefore, Durysta should be limited to a single implant per eye without retreatment. This will likely be a disadvantage for this product considering the lifelong therapy patients will need.		
Citation	**Design**	**Endpoints**
Prospective, Randomized Phase III Study Comparing Two Models of a Travoprost Intraocular Implant to Timolol Maleate Ophthalmic Solution, 0.5%. iDose TR prescribing information NCT: 03519386 NCT: 03868124	These Phase III clinical trials were pivotal in the approval of iDose TR by the FDA. These multicenter, 12-month, randomized, parallel-group, double-masked, controlled clinical trials compared iDose TR was to twice-daily topical administration of timolol maleate ophthalmic solution, 0.5% in patients with open angle glaucoma or ocular hypertension. Subjects with active corneal inflammation or edema, or retinal disorders not associated with glaucoma were excluded. These were non-inferiority trials. N=590 subjects in trial 1 and 560 subjects in trial 2	• Non-inferiority comparison to topical timolol 0.5% BID over the first 3 months, defined as time-matched diurnal IOP measurements at 8 a.m. and 10 a.m. at Day 10, Week 6 and Month III.
Results: In both trials, iDose TR demonstrated non-inferiority to timolol ophthalmic solution in IOP reduction during the first 3 months. Subsequently, iDose TR did not demonstrate non-inferiority over the next 9 months. In the first 3 months following administration, iDose TR demonstrated an IOP change from baseline of -6.6 to -8.4 mmHg in the study eye of patients with a mean baseline IOP of 24 mmHg. The most commonly reported ocular adverse reactions (2% to 6%) were increases in intraocular pressure, iritis, dry eye, visual field defects, eye pain, ocular hyperaemia, and reduced visual acuity. Ocular adverse reactions reported in less than 2% of patients were conjunctival hemorrhage, photophobia, punctate keratitis, blepharitis, eye irritation, corneal abrasion, device dislocation, vitreous detachment, and foreign body sensation in eyes. **Conclusion**: iDose TR implant met non-inferiority criteria compared to topical timolol drops and was well tolerated.		

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (04-01-2024 to 06-30-2024)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Beta Adrenergic Blockers								
Betaxolol (Betoptic®) 0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Betoptic S® (betaxolol) 0.25% ophthalmic drops suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Carteolol (Ocupress®) 1% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Levobunolol (Betagan®) 0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Timolol (Timoptic®) 0.25%, 0.5% ophthalmic drops	21	14	$302.83	$14.42	0	0 (0%)	F	No change
Timolol (Timoptic-XE®) 0.25%, 0.5% ophthalmic gel solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
timolol (Timoptic® Ocudose) 0.25%, 0.5% ophthalmic drops in droperette	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Timolol (Istalol®) 0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Betimol® (timolol) 0.25%, 0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Alpha-2 Adrenergic Agonists								
Iopidine® (apraclonidine) 1% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Apraclonidine (Iopidine®) 0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	F-PA	**->NF**
Brimonidine (Alphagan P®) 0.15% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
brimonidine (Alphagan P®) 0.1% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Brimonidine (Alphagan®) 0.2% ophthalmic drops	30	12	$177.91	$5.93	0	0 (0%)	F	No change

Carbonic Anhydrase Inhibitors								
Brinzolamide (Azopt®) 1% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dorzolamide (Trusopt®) 2% ophthalmic drops	5	3	$96.60	$19.32	0	0 (0%)	F	No change
Acetazolamide (Diamox Sequels®) 500 mg ER cap	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Acetazolamide (Diamox®) 125, 250 mg tab	1	1	$3.05	$3.05	0	0 (0%)	F	No change
Methazolamide (Neptazane®) 25, 50 mg tab	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Prostaglandin Analogues								
Travoprost (Travatan Z®) 0.004% ophthalmic drops	4	2	$319.92	$79.98	0	0 (0%)	F-ST (Requires prior use of latanoprost eye drops)	No change
iDose® TR (travoprost) intracameral implant	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Bimatoprost (Lumigan®) 0.03% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Lumigan® (bimatoprost) 0.01% ophthalmic drops	3	1	$1,470.63	$490.21	1	0 (0%)	NF	No change
Durysta® (bimatoprost) 10 mcg implant	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Latanoprost (Xalatan®) 0.005% ophthalmic drops	120	58	$1,728.82	$14.41	0	0 (0%)	F	No change
Xelpros® (latanoprost) 0.005% ophthalmic drops emulsion	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Iyuzeh® (latanoprost) 0.005% eye drop	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
tafluprost (Zioptan®) 0.0015% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Vyzulta® (latanoprostene bunod) 0.02% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Cholinergic Agonists (Miotics)								
Pilocarpine (Isopto Carpine®) 1%, 2%, 4% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	F	No change

Miochol-E® (Acetylcholine) 1% kit	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Miostat® (Carbachol) 0.01% inj	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Rho Kinase Inhibitors								
Rhopressa® (netarsudil) 0.02% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change; new MRG criteria
Acetylcholinesterase Inhibitors								
Phospholine Iodide® (echothiophate iodide) 0.13% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Combination Products								
brimonidine tartrate-timolol (Combigan®) 0.2%-0.5% ophthalmic drops	1	1	$117.63	$117.63	0	0 (0%)	NF	No change
Simbrinza® (brinzolamide-brimonidine) 1%-0.2% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dorzolamide-timolol (Cosopt®) 2%-0.5% ophthalmic drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dorzolamide-timolol (Cosopt®) 22.3mg-6.8mg/1 mL ophthalmic drops	10	7	$236.81	$23.68	0	0 (0%)	F	No change
Rocklatan® (netarsudil-latanoprost) 0.02%-0.005% ophthalmic drops	1	1	$338.22	$338.22	1	1 (100%)	NF	No change; new MRG criteria
TOTAL	**196**	**100**	**$4,792.42**	**$24.45**	**2**	**1 (50%)**		

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

PRIOR AUTHORIZATION CRITERIA

New MRG:

Rho Kinase Inhibitors	
Therapeutic Classes (AHFS)	Rho Kinase Inhibitors
Medications	Rhopressa (netarsudil) Rocklatan (netarsudil/latanoprost)
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 ≥ 18 years old
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval:** 12 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:**
	• Diagnosis of ocular hypertension or open-angle glaucoma
	• Documented trial and failure of a prostaglandin inhibitor or beta-adrenergic antagonist
	• Member has not had:
	  ○ Previous glaucoma intraocular surgery or glaucoma laser procedure in the affected eye; OR
	  ○ Ocular surgery or laser treatment within three months prior to initiation
	• Member does not currently have any of the following:
	  ○ Ocular infection
	  ○ Inflammation
	  ○ Blepharitis
	  ○ Conjunctivitis
	  ○ Ocular disease
	
	Re-Authorization:
	• Member must continue to meet above criteria
	• Member has demonstrated efficacy (e.g. reduction in intraocular pressure)

Criteria Statement	Rhopressa and Rocklatan are reserved for members who have a diagnosis of ocular hypertension or open-angle glaucoma and have tried and failed a prostaglandin inhibitor or beta-adrenergic antagonist.
Last P&T Review Date	9/2024

REFERENCES

1. National Eye Institute. Facts about glaucoma. National Institutes of Health. Available at: https://nei.nih.gov/health/glaucoma/glaucoma_facts. Accessed on April 9, 2019.
2. Biomedtracker. Cambridge, MA: Informa Business Intelligence, Inc. https://www.biomedtracker.com/. Accessed on February 1, 2021.
3. Jacobs DS. Open-angle glaucoma: Treatment. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on March 28, 2024.
4. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on March 28, 2024.
5. "DailyMed." DailyMed. N.p., n.d. Web. Available at https://dailymed.nlm.nih.gov/dailymed/. Accessed on March 28, 2024.
6. Micromedex® (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: http://www.micromedexsolutions.com/. Accessed on July 17, 2019.
7. Li T, Lindsley K, Rouse B, et al. Comparative Effectiveness of First-Line Medications for Primary Open-Angle Glaucoma: A Systematic Review and Network Meta-analysis. Ophthalmology. 2016 Jan;123(1):129-40. doi: 10.1016/j.ophtha.2015.09.005. Epub 2015 Oct 31. Accessed on April 15, 2019.
8. Lin L, Zhao YJ, Chet PT, et al. Comparative efficacy and tolerability of topical prostaglandin analogues for primary open-angle glaucoma and ocular hypertension. Ann Pharmacother. 2014 Dec;48(12):1585-93. doi: 10.1177/1060028014548569. Epub 2014 Sep 2. Accessed on April 15, 2019.
9. Budengeri P, Cheng JW, Cai JP, Wei RL. Efficacy and tolerability of fixed combination of brimonidine 0.2%/timolol 0.5% compared with fixed combination of dorzolamide 2%/timolol 0.5% in the treatment of patients with elevated intraocular pressure: a meta-analysis of randomized controlled trials. J Ocul Pharmacol Ther. 2013 Jun;29(5):474-9. doi: 10.1089/jop.2012.0134. Epub 2013 Feb 4. Accessed on April 16, 2019.
10. Serle JB, Katz LJ, McLaurin E, et al. Two Phase 3 Clinical Trials Comparing the Safety and Efficacy of Netarsudil to Timolol in Patients With Elevated Intraocular Pressure: Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2). Am J Ophthalmol. 2018 Feb;186:116-127. doi: 10.1016/j.ajo.2017.11.019. Epub 2017 Dec 1. Accessed on April 16, 2019.
11. Lexicomp Online. Hudson, OH: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on February 2, 2021.
12. Gedde SJ, Vinod K, Wright MM, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern®. Ophthalmology. 2021;128(1):P71-P150. doi:10.1016/j.ophtha.2020.10.022.
13. Gedde SJ, Chen PP, Muir KW, et al. Primary Angle-Closure Disease Preferred Practice Pattern®. Ophthalmology. 2021;128(1):P30-P70. doi:10.1016/j.ophtha.2020.10.021.

Hepatitis B

Executive Summary

CLASS OVERVIEW

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV), a double-stranded DNA virus belonging to the family of hepadnaviruses. HBV infection is transmitted by sexual contact, injection drug use, infected mothers to newborn infants, contact with blood or open sores, needle sticks, and other sharing of items such as toothbrushes or razors. Although initiatives for universal HBV infection prevention through vaccination have been successful, HBV continues to generate significant disease burden with more than 296 million chronic carriers globally as of 2019. In the United States, an estimated 880,000 to 1.89 million people are chronically infected with HBV, with men having a slightly increased risk. Patients infected with HBV may be asymptomatic, develop nonspecific symptoms such as fatigue and anorexia, or experience acute symptoms such as jaundice and right upper quadrant discomfort. While acute HBV can be cleared, some patients may develop a chronic infection. Chronic hepatitis B (CHB), if left unmanaged, can result in complications such as necroinflammatory liver damage and hepatocellular carcinoma. This review covers all oral and injectable medications indicated and approved for the treatment of CHB. This includes Baraclude® (entecavir) oral tablet and solution, Epivir® HBV (lamivudine) oral tablet, Hepsera® (adefovir), Viread® (tenofovir disoproxil fumarate), and the newest oral medication, Vemlidy® (tenofovir alafenamide), as well as injectable Pegasys® (peginterferon alfa-2a).

UTILIZATION FINDINGS

There were 101 claims for 49 members, for a total cost of $86,350.36 and an average cost per claim of $854.95. The most highly utilized medication was Vemlidy 25 mg tablet, with 51 claims, followed by Entecavir 0.5 and 1 mg tablet with 35 claims. There were 15 prior authorizations with 11 approvals (73%).

RECOMMENDATIONS

- Change from F to F-PA based on no utilization, cost-effective and guideline recommended alternatives on formulary, and to reflect MRG criteria status
    - Adefovir (Hepsera®) 10 mg oral tablet
    - Lamivudine (Epivir® HBV) 100 mg oral tablet

CLINICAL SUMMARY

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV), a double-stranded DNA virus belonging to the family of hepadnaviruses. HBV infection is transmitted by sexual contact, injection drug use, infected mothers to newborn infants, contact with blood or open sores, needle sticks, and other sharing of items such as toothbrushes or razors. Although initiatives for universal HBV infection prevention through vaccination have been successful, HBV continues to generate significant disease burden with more than 296 million chronic carriers globally as of 2019. In the United States, an estimated 880,000 to 1.89 million people are chronically infected with HBV, with men having a slightly increased risk. Patients infected with HBV may be asymptomatic, develop nonspecific symptoms such as fatigue and anorexia, or experience acute symptoms such as jaundice and right upper quadrant discomfort. While acute HBV can be cleared, some patients may develop a chronic infection. Chronic hepatitis B (CHB), if left unmanaged, can result in complications such as necroinflammatory liver damage and hepatocellular carcinoma. However, with antiviral treatment, HBV can be well-managed.

Different stages of HBV infection are characterized by the presence of HBV-specific antibodies or antigens. Hepatitis B surface antigen (HBsAg) is detected within 1 to 9 weeks of a new acute infection. A majority of patients will have detectable levels after one month from exposure to HBV, indicating that the patient is infectious. Fifteen weeks from the first symptoms, about 50% of those infected will test negative for HBsAg and HBV DNA. Hepatitis B surface antibody (HBsAb) becomes detectable after HBsAg disappears in patients who recover from the virus and avoid a chronic infection. Generally, the presence of serum HBsAb indicates recovery and immunity from HBV. The hepatitis B core antibody (HBcAb) remains in the blood indefinitely, regardless of acute or chronic infection status. Similarly, IgG anti-HBc will also remain in the blood indefinitely. Hepatitis B e-antigen (HBeAg) is generally detectable in patients with a new acute infection and is associated with higher HBV DNA levels. Along with HBeAg, IgM anti-HBc also indicates a new acute infection. In particular, IgM anti-HBc can indicate an acute exacerbation in a chronically infected patient. Table 1 summarizes key HBV serology information.

Table 1: HBV Serology and Interpretation for HBV Infection Serology

Serologic Marker	Abbreviation	Interpretation
Hepatitis B surface antigen	HBsAg	HBsAg is detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious.
Hepatitis B surface antibody	HBsAb	As part of the normal immune response to infection, the body produces antibodies to HBsAg. The presence of anti-HBs generally indicates recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
Hepatitis B core antibody	HBcAb	HBcAb appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
Hepatitis B e antigen	HBeAg	HBeAg indicates that the virus is replicating and the patient has high levels of HBV.
IgM antibody to hepatitis B core antigen	IgM HBcAb	IgM HBcAb indicates recent infection with HBV. Its presence indicates acute infection.

Adapted from Mast EE et al. CDC Morbidity and Mortality Weekly Report. 2005; 54(RR-16):1-31.

CHB is defined as having HBsAg ≥6 months and is classified in four stages: immune tolerance, immune active/clearance, inactive carrier, and reactivation. In children and less commonly in adults, CHB begins with an immune-tolerant phase, high-level viremia, and minimal liver inflammation. As the virus interacts with the host immune system and viral co-infections, CHB progresses to an immune active/clearance phase with active liver disease and viral replication followed by an inactive carrier phase with low viral replication and minimal liver inflammation. In patients with inactive or resolved hepatitis B or in the setting of immunosuppression, reactivation may occur spontaneously, and manifests as increases in

serum hepatitis B DNA and HBeAg. In order to prevent potentially fatal hepatitis and liver failure due to hepatitis B reactivation, hepatitis B serology should be identified prior to beginning immunosuppressive agents or chemotherapy, and preemptive antiviral therapy may be warranted. The specific criteria and laboratory characteristics for the different classifications of CHB are summarized in Table 2.

Table 2: Chronic Hepatitis B (CHB) Immune Stages: Laboratory Characteristics					
	HBsAg	**HBeAg**	**HBcAg**	**HBV DNA**	**ALT**
Immune-tolerant CHB	+	+	+	+++	-
Immune-active CHB	+	+/-	+	+++	+
Inactive CHB	+	-	+	+/-	-

Adapted from: McMahon BJ et al. The Medscape Journal of Medicine. 2008; 10(4):91; Table 1

The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend pegylated-interferon (Peg-IFN)-alfa-2a or Peg-IFN-alfa-2b, entecavir (ETV, Baraclude®), or tenofovir disoproxil fumarate (TDF, Viread®) or tenofovir alafenamide (TAF, Vemlidy®) as preferred initial therapy for adults with immune-active CHB to decrease the risk of liver-related complications. Tenofovir alafenamide (TAF, Vemlidy®) received a new indication in 03/2024 for treatment of chronic hepatitis B virus infection in adults and pediatric patients ≥6 years of age and weighing ≥25 kg with compensated liver disease. However, no current guidelines reflect its use in pediatric populations. The World Health Organization offers similar recommendations for the nucleot(s)ide analogs (NAs; e.g. ETV, TDF/TAF) but excludes immunomodulators (e.g. Peg-IFN) as they have fallen out of favor in clinical practice due to their extensive adverse effect profiles. Peg-IFN-alfa-2b has been permanently discontinued and therefore, Peg-IFN-alfa-2a is the only interferon product indicated for CHB that is readily available. Head-to-head comparisons of antiviral therapies fail to show superiority of one therapy over another in achieving risk reduction in liver-related complications. However, in recommending Peg-IFN, TDF/TAF, and ETV as preferred therapies, the most important factor to consider is the lack of resistance with long-term use. Aside from antiviral resistance, patient-specific factors that must be considered when choosing between Peg-IFN, ETV, and TDF/TAF including the:

- Desire for finite therapy
- Anticipated tolerability of treatment side effects
- Comorbidities: Peg-IFN is contraindicated in persons with autoimmune disease, uncontrolled psychiatric disease, cytopenias, severe cardiac disease, uncontrolled seizures, and decompensated cirrhosis.
- Previous history of lamivudine resistance (entecavir is not preferred in this setting).
- Family planning: A finite therapy with Peg-IFN pre-pregnancy or use of oral antiviral that is safe in pregnancy is best.
- HBV genotype: A and B genotypes are more likely to achieve HBeAg and HBsAg loss with Peg-IFN than non-A/B genotypes.
- Medication costs.

TAF (Vemlidy®), the novel prodrug of TDF (Viread®), was added to the list of preferred agents in the most recent updates of all three practice guidelines. This drug was noted for its lower incidence of bone and renal toxicity compared to TDF, but is not preferred over TDF. Both drugs are currently priced similarly, however, the highest dose of TDF (300 mg) is now available generically at significantly reduced costs. Lamivudine (LAM, Epivir® HBV) and adefovir (ADV, Hepsera®) are also available generically but are non-preferred NAs. The duration of therapy for NA-based therapy is variable and influenced by HBeAg status, duration of HBV DNA suppression, and the presence of cirrhosis/decompensation. All NAs require dose adjustment in persons with creatinine clearance <50 mL/min. Clinical studies indicate that patients taking TAF have better renal laboratory tests and less bone mineral density decreases when compared to TDF and that switching from TDF to TAF preserves efficacy while maintaining these renal and bone benefits.

INDICATIONS, DOSING and ADMINISTRATION*

Medication	Indications	Dosing/Administration
	Oral Agents	
Tenofovir disoproxil fumarate (Viread®)	• Chronic hepatitis B in adults and pediatric patients 12 years of age and older	• Chronic hepatitis B: 300 mg once daily Treatment duration (AASLD practice guidelines): • Patients not achieving <2 log decrease in serum HBV DNA after at least 6 months of therapy should either receive additional treatment or be switched to an alternative therapy. • Hepatitis Be antigen (HBeAg) positive chronic hepatitis: Treat ≥1 year until HBeAg seroconversion and undetectable serum HBV DNA; continue therapy for ≥6 months after HBeAg seroconversion • HBeAg negative chronic hepatitis: Treat >1 year until hepatitis B surface antigen (HBsAg) clearance • Decompensated liver disease: Lifelong treatment is recommended
Vemlidy® (tenofovir alafenamide fumarate)	• Chronic hepatitis B virus infection in adults and pediatric patients ≥6 years of age and weighing ≥25 kg with compensated liver disease	• Chronic hepatitis B: Oral: 25 mg once daily
Adefovir (Hepsera®)	• Chronic hepatitis B (adults and children ≥12 yo) with evidence of active viral replication (based on persistent elevation of ALT/AST or histologic evidence), including patients with lamivudine-resistant hepatitis B	• Chronic hepatitis B: Oral: 10 mg once daily Treatment duration (AASLD practice guidelines): • Hepatitis Be antigen (HBeAg) positive chronic hepatitis: Treat ≥1 year until HBeAg seroconversion and undetectable serum HBV DNA; continue therapy for ≥6 months after HBeAg seroconversion • HBeAg negative chronic hepatitis: Treat >1 year until hepatitis B surface antigen (HBsAg) clearance • Patients not achieving a <2 log decrease in serum HBV DNA after at least 6 months of therapy should either receive additional treatment or be switched to an alternative therapy.
Entecavir (Baraclude®)	• Chronic hepatitis B virus (HBV) infection in adults and pediatric patients 2 years and older with evidence of active viral replication and either evidence of persistent transaminase elevations or histologically-active disease. • HBV reinfection prophylaxis, post liver transplant (off-label) • HIV/HBV coinfection (off-label) • Note: In adults, indication is based on data in patients with compensated and	• Chronic hepatitis B virus (HBV) infection, treatment: Oral: ○ Nucleoside treatment naive: 0.5 mg once daily ○ Lamivudine-refractory or -resistant viremia (or known lamivudine- or telbivudine-resistant mutations): 1 mg once daily ○ Decompensated liver disease: 1 mg once daily

Medication	Indications	Dosing/Administration
	decompensated liver disease; in children, indication is based on data in patients with compensated liver disease.	Treatment duration (AASLD Practice Guidelines): • Hepatitis Be antigen (HBeAg) positive chronic hepatitis: Treat ≥1 year until HBeAg seroconversion and undetectable serum HBV DNA; continue therapy for ≥6 months after HBeAg seroconversion • HBeAg negative chronic hepatitis: Treat >1 year until hepatitis B surface antigen (HBsAg) clearance • Decompensated liver disease: Lifelong treatment is recommended. • Patients not achieving a primary response (<2 log decrease in serum HBV DNA) after at least 6 months of therapy should either receive additional treatment or be switched to an alternative therapy.
Lamivudine (Epivir® HBV) tablet	• Chronic hepatitis B associated with evidence of hepatitis B viral replication and active liver inflammation. • Limitations of use: Use only when an alternative antiviral agent with a higher genetic barrier to resistance is not available or appropriate; has not been evaluated in patients with HBV-HIV-1 coinfection, hepatitis C virus or hepatitis delta virus; has also not been evaluated in patients with chronic HBV infection with decompensated liver disease or in liver transplant recipients. • Not a preferred agent due to high rates of resistance.	• Chronic hepatitis B: Oral: 100 mg once daily Treatment duration (AASLD practice guidelines): • Hepatitis Be antigen (HBeAg) positive chronic hepatitis: Treat ≥1 year until HBeAg seroconversion and undetectable serum HBV DNA; continue therapy for ≥6 months after HBeAg seroconversion • HBeAg negative chronic hepatitis: Treat >1 year until hepatitis B surface antigen (HBsAg) clearance • Patients not achieving <2 log decrease in serum HBV DNA after at least 6 months of therapy should either receive additional treatment or be switched to an alternative therapy
Injectable Agents		
Pegasys® (peginterferon alfa-2a) 180 mcg/0.5 mL SQ syringe, solution	• Adult Patients: Adults with HBeAg-positive and HBeAgnegative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation • Pediatric Patients: Non-cirrhotic pediatric patients 3 years of age and older with HBeAg-positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase (ALT)	• Chronic hepatitis B: SubQ: 180 mcg once weekly for 48 weeks.

*****Non-HBV indications for these agents and pediatric dosing are not included in this chart.

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Oral Agents		
Tenofovir disoproxil fumarate (Viread®) Vemlidy® (tenofovir alafenamide fumarate)	• Severe acute exacerbations of hepatitis B have been reported in patients who discontinue therapy	None
Adefovir (Hepsera®)	• Severe acute exacerbations of hepatitis B have been reported in patients who discontinue therapy • Therapy with entecavir is not recommended for HIV/HBV coinfected patients who are not also receiving antiretroviral therapy. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported • Long term administration may result in nephrotoxicity in patents at risk of or with underlying renal dysfunction	
Entecavir (Baraclude®) Lamivudine (Epivir® HBV) tablet	• Severe acute exacerbations of hepatitis B have been reported in patients who discontinue therapy • Therapy with entecavir is not recommended for HIV/HBV coinfected patients who are not also receiving antiretroviral therapy. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported	
Injectable Agents		
Pegasys® (peginterferon alfa-2a) SQ syringe, solution	• Risk of serious disorders: Peginterferon alfa-2a may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all, cases, these disorders resolve after stopping peginterferon alfa-2a therapy.	• Hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis, Stevens-Johnson syndrome) to peginterferon alfa-2a, other alfa interferons, or any component of the formulation; autoimmune hepatitis; hepatic decompensation in cirrhotic patients (Child-Pugh score >6, class B and C) before treatment; hepatic decompensation with Child-Pugh score ≥6 in cirrhotic CHC coinfected with HIV before treatment; neonates and infants (due to benzyl alcohol component) • Combination therapy with peginterferon alfa-2a and ribavirin is also contraindicated in pregnancy; men whose female partners are pregnant; patients with

Medication	Boxed Warnings	Contraindications
		hemoglobinopathies (ie, thalassemia major, sickle cell disease); coadministration with didanosine

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Oral Agents	
Tenofovir disoproxil fumarate (Viread®)	**Concerns related to adverse effects:** • Decrease bone mineral density, immune reconstitution syndrome, lactic acidosis/hepatomegaly, osteomalacia, renal dysfunction, renal toxicity **Disease related concerns:** • Use caution in patients with hepatic impairment, there is limited data supporting treatment of chronic hepatitis B in patients with decompensated liver disease, dosage adjustment is required in renal impairment CrCl < 50 mL/min, IDSA guidelines recommend avoiding tenofovir in HIV patients with preexisting kidney disease and not on hemodialysis when other options exist. **Concerns related to concurrent drug therapy**: • Do not use in combination with other adefovir or other tenofovir containing products.
Vemlidy® (tenofovir alafenamide fumarate)	**Concerns related to adverse effects:** • Lactic acidosis/hepatomegaly **Disease related concerns:** • Use is not recommended in patients with Child Pugh class B or C hepatic impairment, should not be used as a single treatment for HIV-1 due to risk of developing resistance, use is not recommended in CrCl < 15 mL/min, acute renal failure, Fanconi syndrome, or renal toxicity have been reported
Adefovir (Hepsera®)	**Concerns related to concurrent drug therapy:** • Do not use concurrently with any product containing tenofovir
Entecavir (Baraclude®)	**Concerns related to adverse effects:** • See boxed warnings **Disease related concerns:** • Observe patients with hepatic impairment for increased adverse reactions, use caution in patients with renal impairment, dosage adjusted recommended for CrCl < 50 mL/min
Lamivudine (Epivir® HBV) tablet	**Concerns related to adverse effects:** • May cause fat redistribution, patients may develop immune reconstitution syndrome, discontinue treatment if signs/symptoms of pancreatitis occur **Disease related concerns:** • Use caution in patients with renal impairment, dosage reduction is recommended, patients treated with lamivudine-HBV with YMDD-mutant HBV showed diminished treatment response
Injectable Agents	
Pegasys® (peginterferon alfa-2a) SQ syringe, solution	**Concerns related to adverse effects:** • Bone marrow suppression, CNS depression, dermatologic effects, gastrointestinal effects, hepatic effects, hypersensitivity reactions, neuropsychiatric disorders: [US Boxed Warning], ophthalmic effects (decreased or loss of vision and retinopathy, including macular edema, optic neuritis, papilledema, retinal hemorrhages, retinal detachment (serous), cotton wool spots, and retinal artery or vein thrombosis), pancreatitis, pulmonary effects **Disease-related concerns:**

Medication	Warnings/Precautions
	• Autoimmune disease: [US Boxed Warning], cardiovascular disease, diabetes, hepatitis B flares, infectious disorders: [US Boxed Warning], ischemic disorders: [US Boxed Warning], renal impairment, seizure disorders, thyroid disorders **Special populations:** • Use with caution in the elderly; certain adverse effects (eg, neuropsychiatric, cardiac, flu-like reactions) may be more severe. • Growth velocity (height and weight) was decreased in children with or without combination treatment with ribavirin, during the length of treatment **Other warnings/precautions:** • Appropriate use: Hepatitis B: Hepatitis B genotypes A and B are more likely to achieve HBeAg and HBsAg loss with peg-interferon than non-A/B genotypes. For patients with hepatitis B coinfected with hepatitis delta virus, pegylated interferon is the only effective therapy.

PRACTICE GUIDELINES

Update to AASLD Hepatitis B Guidelines (2018)

Terrault NA, Bzowej NH, Chang KM, et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B. Hepatology. 2018; 67(4): 1560-1599.

In the 2018 hepatitis B guidance, AASLD added evidence pertaining to tenofovir alafenamide (TAF)'s place in therapy. However, there were no clinically significant changes in hepatitis B treatment recommendations. The following is a summary of major points from the 2018 AASLD hepatitis B update:

- TAF was added to the list of preferred antivirals (tenofovir disoproxil fumarate [TDF], entecavir [ETV], PEG-interferon [IFN]-alfa-2a, and IFN-alfa-2b) because it was noted for its high barrier to resistance, and decreased bone and renal toxicity compared to TDF. However, it is not preferred over TDF or any other preferred agent. Further, TAF is not recommended in pregnancy or children due to insufficient data.
- Lamivudine (LAM) and adefovir (ADV) are treatment options, but are not preferred.
- In certain scenarios, the AASLD recommends against antiviral therapy: in immune-tolerant CHB; for prevention of HBV perinatal transmission when HBV DNA ≤ 200,000 IU/mL in pregnant women; and in HBeAg-positive children with normal ALT levels.
- AASLD recommends antiviral therapy indefinitely for patients with decompensated cirrhosis. Patients who seroconvert can consider treatment discontinuation while immune-active patients should remain on treatment indefinitely. Upon treatment failure, the guidelines suggest switching, not adding on, within the preferred agents.

European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on the Management of Hepatitis B Virus Infection (2017)

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology. 2017; 67(2): 370-398.

- The preferred treatment options are identical to the AASLD preferred treatment options: ETV, TDF, or TAF, which all have a high barrier to resistance. PEG-IFN can be considered in mild-to-moderate CHB but must be avoided in acute hepatitis B infections. Upon treatment failure, the guidelines suggest switching, not adding on, within the preferred agents. Combination therapies are not generally recommended.

AASLD Hepatitis B Guidelines (2016)

Terrault NA, Bzowej NH, Chang KM, et al. AASLD Guidelines for Treatment of Chronic Hepatitis B. Hepatology. 2016; 63(1): 261-83.

Treatment of Persons with Immune-Active CHB

- Recommends antiviral therapy for adults with immune-active CHB (HBeAg negative or positive) to decrease the risk of liver-related complications (Level 1)
- Recommends PEG-IFN-alfa-2a, IFN-alfa-2b, ETV, or tenofovir (TDF or TAF) as preferred initial therapy for adults with immune-active CHB (Level 1)

Treatment of immune-tolerant adults with hepatitis B

- The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB (Level 1).
- Suggests that ALT levels be tested at least every 6 months for adults with immune tolerant CHB to monitor for potential transition to immune-active or immune-inactive CHB (Level 2)
- Suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis (Level 2)

Treatment of HBeAg-positive, immune-active persons with chronic hepatitis who seroconvert to anti-HBe on NA therapy

- Suggests that HBeAg-positive adults without cirrhosis but with CHB who seroconvert to anti-HBe on therapy discontinue NAs after a period of treatment consolidation (Level 2)

- Suggests indefinite antiviral therapy for HBeAg-positive adults with cirrhosis and CHB who seroconvert to anti-HBe on NA therapy, based on concerns for potential clinical decompensation and death, unless there is a strong competing rationale for treatment discontinuation (Level 2)

Duration of treatment in persons with HBeAg-negative, immune-active CHB

- Suggests indefinite antiviral therapy for adults with HBeAg-negative, immune-active CHB unless there is a compelling rationale for treatment discontinuation (Level 2)

Renal and bone disease in persons on NA therapy

- Suggests no preference between ETV or TDF regarding potential long-term risks of renal and bone complications (Level 2)

Management of persons with persistent low-level viremia on NA therapy

- Suggests that persons with persistent low-level viremia (<2,000 IU/mL) on ETV or TDF monotherapy continue monotherapy, regardless of ALT (Level 2)
- Suggests 1 of 2 strategies in persons with virological breakthrough on ETV or TDF monotherapy: either switch to another antiviral monotherapy with a high barrier to resistance or add a second antiviral drug that lacks cross-resistance (Level 2)

Management of adults with cirrhosis and low-level viremia

- Suggests that adults with compensated cirrhosis and low-level viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level (Level 2)
- Recommends that HBsAg-positive adults with decompensated cirrhosis be treated with antiviral therapy indefinitely regardless of HBV DNA level, HBeAg status, or ALT level to decrease risk of worsening liver-related complications (Level 1)

Management of chronic hepatitis b in pregnancy

- Suggests antiviral therapy to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with an HBV DNA level >200,000 IU/mL (Level 2)
- Recommends against the use of antiviral therapy to reduce the risk of perinatal transmission of HBV in HBsAg-positive pregnant women with an HBV-DNA level ≤ 200,000 IU/mL (Level 1)

Treatment of CHB in children

- Suggests antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with both elevated ALT and measurable HBV-DNA levels, with the goal of achieving sustained HBeAg seroconversion (Level 2)
- Recommends against the use of antiviral therapy in HBeAg-positive children (ages 2 to <18 years) with persistently normal ALT, regardless of HBV-DNA level (Level 1)

AASLD Levels of Evidence

Level of Evidence	Description
Level 1	"We recommend"; Most patients should receive the recommended course of action; The recommendation can be adopted as policy in most situations
Level 2	"We suggest"; Different choices will be appropriate for different patients; The recommendation is likely to require debate and involvement of stakeholders

WHO Hepatitis B Guidelines (2015)

Abraham P, Aghokeng A, Andrieux-Meyer I, et al. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization. 2015; 1-166.

Recommendations: First-line antiviral therapies for chronic hepatitis B

- In all adults, adolescents and children aged 12 years or older in whom antiviral therapy is indicated, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (TDF/TAF or ETV) are recommended. Entecavir is recommended in children aged 2–11 years. (Strong recommendation, moderate quality of evidence)
- NAs with a low barrier to resistance (LAM, adefovir or telbivudine) can lead to drug resistance and are not recommended. (Strong recommendation, moderate quality of evidence)

Recommendations: Second-line antiviral therapies for management of treatment failure

- In persons with confirmed or suspected antiviral resistance (i.e. history of prior exposure or primary non-response) to lamivudine, ETV, adefovir or telbivudine, a switch to TDF/TAF is recommended. (Strong recommendation, low quality of evidence)
    - Treatment adherence should be reinforced
    - For adefovir resistance, a switch to either TDF/TAF or ETV can be considered
    - To date, there has been no reported resistance with TDF/TAF. If there is primary non-response, then treatment adherence should be reinforced and monitored. At present, there is therefore no indication to switch to an alternative drug regimen

Recommendations: When to stop treatment

- Lifelong NA therapy: All persons with cirrhosis based on clinical evidence (or APRI score >2 in adults) require lifelong treatment with NAs, and should not discontinue antiviral therapy because of the risk of reactivation, which can cause severe acute-on-chronic liver injury. (Strong recommendation, low quality of evidence)
- Discontinuation: Discontinuation of NA therapy may be considered exceptionally in:
    - persons without clinical evidence of cirrhosis (or based on APRI score ≤2 in adults);
    - and who can be followed carefully long term for reactivation;
    - and if there is evidence of HBeAg loss and seroconversion to anti-HBe (in persons initially HBeAg-positive) and after completion of at least one additional year of treatment;
    - and in association with persistently normal ALT levels and persistently undetectable HBV DNA levels (where testing is available).
        - Where HBV DNA testing is not available: Discontinuation of NA therapy may be considered in persons who have evidence of persistent HBsAg loss and after completion of at least one additional year of treatment, regardless of prior HBeAg status. (Conditional recommendation, low quality of evidence)
- Retreatment: Relapse may occur after stopping therapy with NAs. Retreatment is recommended if there are consistent signs of reactivation (HBsAg or HBeAg becomes positive, ALT levels increase, or HBV DNA becomes detectable again) (where HBV DNA testing is available) (Strong recommendation, low quality of evidence)

WHO Level of Evidence

Level of Evidence	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the effect.
Low	Further research is very likely to have an estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Biomedtracker. A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Switching From Tenofovir Disoproxil Fumarate 300 mg QD to Tenofovir Alafenamide 25mg QD in Subjects With Chronic Hepatitis B Who Are Virologically Suppressed (NCT02979613). Informa Business Intelligence Inc. https://www.biomedtracker.com	Randomized, double-blind, parallel assignment, phase III trial enrolled 488 participants with chronic hepatitis B (CHB) who were assigned to receive tenofovir alafenamide (TAF) 25 mg (n=233) or tenofovir disoproxil fumarate (TDF) 300 mg daily (n=232) for 48 weeks and then switched to the other therapy for 48 more weeks. Inclusion criteria: Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures; Adult male and non-pregnant, non-lactating females; Documented evidence of chronic HBV infection previously; Maintained on TDF 300 mg QD for at least 48 weeks, and as monotherapy for chronic hepatitis B for at least 24 weeks with viral suppression (HBV DNA < LLOQ) for a minimum of 12 weeks prior to screening; Adequate renal function; Normal ECG	• Primary endpoints: Proportion of Participants with hepatitis B virus (HBV) DNA ≥ 20 IU/mL at Week 24, as Determined by the Modified US FDA-Defined Snapshot Algorithm (virologic suppression) • Secondary endpoints: Alanine aminotransferase (ALT) normalization; bone and renal safety parameters
Results: Virologically suppressed patients who were switched from TDF to TAF displayed non-inferior rates of viral suppression (96.3% in both arms) after 48 weeks of treatment compared to patients who remained on TDF; TAF demonstrated significant improvements in renal and bone safety parameters compared to TDF, with TAF-treated patients displaying mean changes of +0.66g/cm^2 and +1.74g/cm^2 in hip and spine bone mineral density, respectively, versus declines of -0.51g/cm^2 and -0.11g/cm^2 in TDF-treated patients; TAF-treated patients displayed a small median recovery in estimated glomerular filtration rate (+0.99 mL/min) after 48 weeks of treatment, versus continued declines in TDF-treated patients (-2.74 mL/min); rates of ALT normalization were increased in both groups. **Conclusion**: TAF was non-inferior to TDF in the treatment of patients with CHB, having comparable viral suppression and increases in ALT normalization. However, TAF had significant improvements in bone and renal safety parameters when compared to TDF.		
Citation	**Design**	**Endpoints**
Han Y, Zeng A, Liao H, et al. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis. International Immunopharmacology. 2017; 42: 168-175. DOI: 10.1016/j.intimp.2016.11.022	Meta-analysis assessing the efficacy and safety between tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in the treatment of chronic hepatitis B (CHB) and HBV related cirrhosis. PubMed, the Cochrane Library, Nature, CNKI and WanFang data were searched for the keywords “tenofovir,” “entecavir,” “chronic hepatitis B,” or “CHB”.	• Primary endpoints: Differences in undetectable HBV-DNA, ALT normalization; eGFR levels; and hypophosphatemia incidence.
Results: There was a significant difference of ALT normalization in the short-term period of 3 months (RR=1.43, 95%CI: 1.06-1.94, P<0.017) and 6 months (RR=0.89, 95%CI: 0.81-0.97, P<0.017), and significant difference of undetectable HBV-DNA only in 3 month follow-up period (RR=1.59, 95%CI: 1.04-2.42, P<0.017) between TDF and ETV, but no significant difference in the long-term period. There was a significant difference between TDF and ETV in eGFR level (RR=1.601, 95%CI: 1.035-2.478, P=0.0034) and hypophosphatemia incidence (RR=4.008, 95%CI: 1.485-10.820, P=0.006). **Conclusion:** TDF had better efficacy than ETV in the short-term (3 months) but this normalized and viral suppression and liver function improvement, including HBV-related liver cirrhosis, was similar after 6 months. TDF and ETV may influence renal function but TDF may increase the risk of renal damage and hypophosphatemia.		

Citation	Design	Endpoints
Jun DW, Ahn SB, Kim TY, et al. Efficacy of Pegylated Interferon Monotherapy versus Sequential Therapy of Entecavir and Pegylated Interferon in Hepatitis B e Antigen-Positive Hepatitis B Patients: A Randomized, Multicenter, Phase IIIb Open-Label Study (POTENT Study). Chinese Medical Journal. 2018; 131(14): 1645-1651.	Randomized, multicenter, open-label, phase IIIb study evaluating the efficacy of pegylated interferon (Peg-IFN) monotherapy versus sequential therapy of entecavir (ETV) and pegylated interferon in 162 hepatitis B e-antigen (HBeAg)-positive HBV patients (POTENT study). HBeAg-positive patients received Peg-IFN (mono-treatment group, n=81) for 48 weeks or ETV for 12 weeks with a 48 week course of Peg-IFN starting at week 5 of ETV therapy (sequential treatment group, n=81). Inclusion criteria: Chronic HBV (HBeAg-positive); Elevated ALT (>2x upper limit of normal)	• Primary endpoint: HBeAg seroconversion at week 24 • Secondary endpoints: HBeAg seroclearance at week 24; HBV DNA levels at week 24
Results: HBeAg seroconversion rate in PEG-IFN vs. ETV then PEG-IFN (18.2% vs 18.2%; p = 1.000); HBeAg seroclearance rate in PEG-IFN vs. ETV then PEG-IFN (19.7% vs 19.7%; p = 1.000); HBV DNA levels in PEG-IFN vs. ETV then PEG-IFN (28.8% vs 28.8%; p = 1.000); Adverse event profiles were similar between the two arms, although the PEG-IFN monotherapy arm had a slightly more hepatotoxicity. **Conclusion**: There were no differences in the HBeAg seroconversion and seroclearance rate, and HBV DNA levels. Slightly more hepatotoxicity was observed in the PEG-IFN monotherapy arm but overall, the safety profiles between the two regimens were similar. The increased risk of hepatotoxicity may be associated with the longer duration of PEG-IFN therapy but this is unclear given the limited sample size.		
Citation	**Design**	**Endpoints**
Su YC, Lin PC, Yu HC et al. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. European Journal of Clinical Pharmacology. 2018; 74(9): 1111-1119.	Systematic review and meta-analysis comparing the efficacy of antiviral prophylaxis versus that of non-prophylaxis in resolved HBV-infected patients undergoing chemotherapy or immunotherapy. Pubmed, the Cochrane library, and clinicaltrials.gov were searched and included studies evaluating patients with resolved HBV who received chemotherapy or immunosuppressive therapy and adults using LAM, ETV, telbivudine (TBV), and TDF. A total of 13 studies of 1,210 patients were included.	• Primary endpoint: Relative risk of HBV reactivation • Secondary endpoints: Hepatitis rates; liver failure rates
Results: Risk of HBV reactivation in antiviral prophylaxis vs placebo: RR = 0.47 (95% CI: [0.13, 1.69]); Hepatitis rates in antiviral prophylaxis vs placebo: RR = 1.19 (95% CI: [0.4, 3.57]); Liver failure rates in antiviral prophylaxis vs placebo: RR = 2.74 (95% CI: [0.26, 29.05]); There were no differences in safety between the two groups. Adverse events included disease- or immunosuppression-related complications. **Conclusion**: This meta-analysis did not demonstrate a clear difference in risk of HBV reactivation, hepatitis rates, or liver failure rates. Clinicians may consider prophylaxis given comparable safety profiles between the prophylaxis and placebo groups.		
Citation	**Design**	**Endpoints**
Wu J, Yin F, Zhou X et al. Efficacy of nucleoside analogues for hepatitis B virus-related liver failure: A network meta-analysis. Acta Pharmaceutica. 2018; 68(1): 19-30.	Meta-analysis to compare the efficacy of nucleos(t)ide analogs (NAs) in the treatment of HBV-related liver failure. A total of 1,660 patients from 12 studies about the efficacy of LAM (n=563), ETV (n=520), TBV (n=105), and TDF (n=14) in HBV-related liver failure or comparing several NAs with regards to mortality, survival, HBV DNA, or model for end-stage liver disease (MELD) score were included (non-NA, n=458).	Primary endpoints: Mortality; Three-month survival rate; HBV DNA levels; MELD score reduction

Results: Mortality of the TDF group was found to be the lowest. However, there were no significant differences compared to the ETV group (OR: 0.39; 95% CI [0.02, 5.02]), LAM group (OR: 0.43; 95% CI [0.03, 5.17]), TBV group (OR: 0.75; 95% CI [0.03, 15.74]) and non-NAs group (OR: 0.11; 95% CI [0.01, 1.13]); The three month survival rate of the TDF group was the highest and the difference was significant compared to the non-NAs group (OR: 8.30; 95% CI [1.31, 69.38]). However, the differences compared with the other NAs, including the ETV group (OR: 3.94; 95 % CI [0.57–33.21]), LAM group (OR: 3.09; 95% CI [0.46, 25.94]), and TBV group (OR: 4.18; 95% CI, [0.51, 39.41]) were not significant; The HBV DNA in the ETV group was lowest and the mean difference (MD) was significant compared to the non-NAs group (MD: -2.66, 95% CI [-5.19, -0.16]). However, there were no significant differences between the ETV group and the other two NA groups, including the LAM group (MD: -0.33; 95% CI [-1.91, 1.25]) and TBV group (MD: -0.25; 95% CI [-4.73 to 4.08]); The TDF group had the lowest MELD score. There was also a significant difference between the TDF group and the non-NAs group (MD: -7.85, 95% CI [-13.27, -2.20]) while the differences between the TDF group and the other NA groups, including ETV group (MD: -3.79; 95% CI [-10.08, 2.80]), LAM group (MD: -4.47; 95% CI [-10.93, 2.25) and TBV group (MD: -2.59; 95% CI: [-10.48, 5.61]), were not significant; No new safety signals were detected.
Conclusion: TDF demonstrated the lowest mortality rate, highest survival rate, and largest MELD score reduction compared to other NAs, and ETV the largest in HBV DNA level reductions. However, the TDF group only had a sample size of 14 subjects. All of the reviewed NAs were shown to be clinically comparable and no new safety signals were detected.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (04-01-2024 to 06-30-2024)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
Oral Agents								
Tenofovir disoproxil fumarate (Viread®) 300 mg oral tablet	15	12	$622.09	$41.47	0	0 (0%)	F	No change
Viread® (tenofovir disoproxil fumarate) 150, 200, 250 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Viread® (tenofovir disoproxil fumarate) 40 mg/gram oral powder	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Vemlidy® (tenofovir alafenamide) 25 mg oral tablet	51	21	$76,717.38	$1,504.26	10	7 (70%)	F-PA	No change
Adefovir (Hepsera®) 10 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F	→ **F-PA**
Entecavir (Baraclude®) 0.5, 1 mg oral tablet	35	16	$9,010.89	$257.45	5	4 (80%)	F	No change
Baraclude® (entecavir) 0.05 mg/mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Lamivudine (Epivir® HBV) 100 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F	→ **F-PA**
Injectable Agents								
Pegasys® (peginterferon alfa-2a) 180 mcg/0.5 mL SQ syringe	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Pegasys® (peginterferon alfa-2a) 180 mcg/0.5 mL SQ solution	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
TOTAL	**101**	**49**	**$86,350.36**	**$854.95**	**15**	**11 (73%)**		

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

PRIOR AUTHORIZATION CRITERIA

Recommendation: No change

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. 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 Decompensated Cirrhosis:**
  Presence of 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
  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.

***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.
Criteria Statement	N/A
Last P&T Review Date	~~6/2024~~9/2024

REFERENCES

1. Centers for Disease Control and Prevention. Hepatitis B Information. https://www.cdc.gov/hepatitis/hbv/index.htm. Accessed May 11, 2022.
2. Lok AS. Hepatitis B virus: Overview of management. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
3. Lok AS. Hepatitis B virus: Clinical manifestations and natural history. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
4. Lok AS. Hepatitis B virus: Screening and diagnosis. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
5. Teo EK, Lok AS. Epidemiology, transmission, and prevention of hepatitis B virus infection. Kaplan SL, Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
6. Lok AS. Combination therapy for chronic hepatitis B virus infection. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
7. Lok AS. Standard and pegylated interferon for chronic hepatitis B virus infection. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
8. Lok AS. Entecavir in the treatment of chronic hepatitis B virus infection. Esteban R, Mitty J, eds. UpToDate. Waltham, Mass.: UpToDate; 2022. www.uptodate.com. Accessed May 11, 2022.
9. Viread® [package insert]. Foster City, CA: Gilead Sciences, Inc.; April 2019.
10. Vemlidy® [package insert]. Foster City, CA: Gilead Sciences, Inc.; February 2019.
11. Baraclude® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; December 2018.
12. Epivir® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; May 2019.
13. Hepsera® [package insert]. Foster City, CA: Gilead Sciences, Inc.; November 2012.
14. Pegasys® [package insert]. South San Francisco, CA: Genentech USA, Inc.; October 2017
15. Mast EE, Margolis HS, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. CDC Morbidity and Mortality Weekly Report. 2005; 54 (RR-16):1-31.
16. Mcmahon BJ. Natural history of chronic hepatitis B - clinical implications. Medscape Journal of Medicine. 2008;10(4):91.
17. Terrault NA, Bzowej NH, Chang KM, et al. AASLD Guidelines for Treatment of Chronic Hepatitis B; Hepatology. 2016; 63 (1):261-83.
18. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. Journal of Hepatology. 2017; 67(2): 370-398.
19. Terrault NA, Bzowej NH, Chang KM, et al. AASLD Guidelines for Treatment of Chronic Hepatitis B. Hepatology. 2016; 63(1): 261-83.
20. Abraham P, Aghokeng A, Andrieux-Meyer I, et al. Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. World Health Organization. 2015; 1-166.
21. ClinicalTrials.gov: National Library of Medicine (US). Identifier NCT0194034. A Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD Versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B 1 Available at: https://clinicaltrials.gov/ct2/show/study/NCT01940341?sect=Xa98756
22. Biomedtracker. A Phase 3, Randomized, Double-Blind Study to Evaluate the Efficacy and Safety of Switching From Tenofovir Disoproxil Fumarate 300 mg QD to Tenofovir Alafenamide 25mg QD in Subjects With Chronic Hepatitis B Who Are Virologically Suppressed (NCT02979613). Informa Business Intelligence Inc. https://www.biomedtracker.com
23. Han Y, Zeng A, Liao H, et al. The efficacy and safety comparison between tenofovir and entecavir in treatment of chronic hepatitis B and HBV related cirrhosis: A systematic review and Meta-analysis. International Immunopharmacology. 2017; 42: 168-175. DOI: 10.1016/j.intimp.2016.11.022
24. Jun DW, Ahn SB, Kim TY, et al. Efficacy of Pegylated Interferon Monotherapy versus Sequential Therapy of Entecavir and Pegylated Interferon in Hepatitis B e Antigen-Positive Hepatitis B Patients: A Randomized, Multicenter, Phase IIIb Open-Label Study (POTENT Study). Chinese Medical Journal. 2018; 131(14): 1645-1651.
25. Su YC, Lin PC, Yu HC et al. Antiviral prophylaxis during chemotherapy or immunosuppressive drug therapy to prevent HBV reactivation in patients with resolved HBV infection: a systematic review and meta-analysis. European Journal of Clinical Pharmacology. 2018; 74(9): 1111-1119.
26. Wu J, Yin F, Zhou X et al. Efficacy of nucleoside analogues for hepatitis B virus-related liver failure: A network meta-analysis. Acta Pharmaceutica. 2018; 68(1): 19-30.

Alameda MRGs for review Q3 2024 P&T

Recommendation:

- Add adalimumab-aaty and Simlandi to the step 1: preferred drug list to allow for additional cost-effective agents and a new dosage form of 80mg/0.8ml of a biosimilar adalimumab-aaty
- Add Tyenne (tocilizumab-aazg) and Tofidence (tocilizumab-bavi) to the step 2: preferred (PA required) list and move Actemra (tocilizumab) to the step 3 non-preferred list (PA required) as the biosimilar products are more cost effective
- Add new products: Zymfentra (infliximab), Bimzelx (bimekizumab), and Omvoh (mirikizumab) to the step 3: non-preferred drug list
- Remove the criteria for requests for 80mg/0.8mL dose presentations of Humira or non-preferred biosimilar adalimumab agents, requiring a trial of 40mg dose preparation now that adalimumab-aaty is a step 1 preferred agent and available in an 80mg dosage form
- Actemra Utilization—2 members with $65,588.42 plan cost (utilization timeframe: 7/1/2023-6/30/2024)

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) ~~Actemra (tocilizumab)~~ Tyenne (tocilizumab-aazg) Tofidence (tocilizumab-bavi) Olumiant (baricitinib) Entyvio (vedolizumab) Step 3: Non-Preferred (PA required) Humira (adalimumab) Stelara (ustekinumab) Skyrizi (risankizumab) Actemra (tocilizumab) Arcalyst (rilonacept) Ilaris (canakinumab) Tremfya (guselkumab)

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	Remicade (infliximab) Cosentyx (secukinumab) Zeposia (ozanimod) Taltz (ixekizumab) Tysabri (natalizumab) Cimzia (certolizumab) Rinvoq (upadacitinib) 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) 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), 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:~~ ~~○ Documentation that member has tried 40mg dose presentations to achieve desired dose, or a medical reason must be provided why this cannot be used.~~ • 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	~~9/2023~~9/2024

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Recommendation:

- Change naming convention to reflect generic availability of Mozobil
- Add new product Aphexda which shares the same indication as plerixafor and update criteria accordingly
- Update criteria for pegfilgrastim formulations for acute hematopoietic radiation injury syndrome to approve Neulasta without prior use of a biosimilar since 3 of the pegfilgrastim biosimilars now also have this indication (Ziextenzo, Udenyca and Stimufend)
- Change preferred agent to Fulphila as it is most cost effective product
- Add Udenyca Onbody solution prefilled subcutaneous syringe 6mg/0.6mL to formulary with PA for consistency with other on formulary formulations of Udenyca

White Blood Cell Stimulators		
Therapeutic Classes (AHFS)	Hematopoietic agents	
Medications	Formulary, PA required ~~Mozobil (~~plerixafor~~)~~ (Mozobil) Leukine (sargramostim) Ziextenzo (pegfilgrastim-bmez) ~~– PREFERRED AGENT~~ Fulphila (pegfilgrastim-jmdb) –PREFERRED AGENT Udenyca (pegfilgrastim-cbqv) Stimufend (pegfilgrastim-fpgk) Fylnetra (pegfilgrastim-pbbk) Nivestym (filgrastim-aafi) – PREFERRED AGENT Zarxio (filgrastim-sndz) Releuko (filgrastim-ayow) Non-formulary Nyvepria (pegfilgrastim-apgf) Neulasta (pegfilgrastim) Neulasta (pegfilgrastim) Onpro Neupogen (filgrastim) Granix (filgrastim-aafi) Rolvedon (eflapegrastim-xnst) Aphexda (motixafortide) 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 a hematologist/oncologist.	
Coverage Duration	**Initial Approval**	12 weeks or as recommended per FDA approved indications and/or as defined by the medical compendium as defined above and/or per the NCCN or ASCO standard of care guidelines

	Later Approval	If conditions are not met, the request will be sent to a clinical reviewer. For all indications except chronic neutropenia: 12 weeks. For chronic neutropenia: 24 weeks. If all of the criteria are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	For approval: • Drug is being used for an FDA-approved indication at an FDA approved dose. AND • If the request is for Leukine: Documentation is submitted of the patient's current diagnosis, current bodyweight, body surface area and absolute neutrophil count (within 30 days of the request). • If the request is for a pegfilgrastim formulation or Rolvedon: ○ The patient has a documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of the preferred agent: ~~Ziextenzo~~ Fulphila and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using ~~Ziextenzo~~ Fulphila to treat their medical condition. ○ If the request is for acute hematopoietic radiation injury syndrome, the patient has documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of a biosimilar such as Ziextenzo, Udenyca or Stimufend, and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using a biosimilar indicated for acute hematopoietic radiation injury syndrome. ~~Neulasta can be approved without prior use of Ziextenzo or medical reason for not using Ziextenzo.~~ • If the request is for a filgrastim formulation: ○ The patient has a documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of the preferred agent: Nivestym and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using Nivestym. ○ If the request is for acute hematopoietic radiation injury syndrome, Neupogen can be approved without prior use of Nivestym or medical reason for not using Nivestym. • If the request is for ~~Mozobil~~plerixafor or Aphexda: ○ Documentation is submitted of the patient's current diagnosis, current body weight, and that the patient is using ~~Mozobil~~product in combination with a granulocyte-colony stimulating factor (G-CSF) agent (i.e. Zarxio or Fulphila) ○ If the request is for Aphexda, the patient has a documented ~~treatment~~ failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of plerixafor and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using plerixafor.
Criteria Statement	Neupogen, Zarxio, Releuko, and Granix are reserved for members who have used (or cannot/should not use) Nivestym. Neulasta, Ziextenzo, ~~Fulphila,~~ Nyvepria, Stimufend, Fylnetra, Rolvedon, and Udenyca are reserved for members who have used (or cannot/should not use) ~~Ziextenzo~~ Fulphila. ~~Mozobil~~Plerixafor is reserved for members who are using ~~Mozobil~~plerixafor in combination with a granulocyte-colony stimulating factor (G-CSF) agent (i.e. Zarxio or Fulphila).

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	Aphexda is reserved for members who have used (or cannot/should not use) plerixafor in combination with a G-CSF agent.
Last P&T Review Date	~~9/2023~~9/2024

Recommendation:

- Add new indication for Linzess for functional constipation in pediatric patients 6-17 years old, update age restriction section

Constipation agents	
Therapeutic Classes (AHFS)	N/A
Medications	Formulary, Prior Authorization Required Linzess (linaclotide) capsule lubiprostone (Amitiza) Movantik (naloxegol) Relistor (methylnaltrexone) Symproic (naldemedine) Motegrity (prucalopride) Trulance (plecanatide) Ibsrela (tenapanor)
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"**
Age Restrictions	Patient must be ≥ 18 years of age Linzess: functional constipation in pediatric patients 6 to 17 years old
Prescriber Restrictions	None
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	**INITIAL AUTHORIZATION for irritable bowel syndrome with constipation predominate (IBS-C):** • The patient has a clinical diagnosis of irritable bowel syndrome constipation predominate (IBS-C) • Medication is prescribed at an FDA approved dosage • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to a soluble fiber (e.g. psyllium) within the last 90 days • If the above criteria are met, for requests for Linzess, Trulance, or lubiprostone (Amitiza): approve. **OR** • For requests for other formulary, prior authorization required medications, the above criteria must be met, AND documentation of trial and failure, contraindication, or intolerance of Linzess, Trulance, or lubiprostone (Amitiza) within the last 90 days is required. **INITIAL AUTHORIZATION for chronic idiopathic constipation (CIC):** • The patient has a clinical diagnosis of chronic idiopathic constipation (CIC) • Medication is prescribed at an FDA approved dosage

	• Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to use a soluble fiber (e.g. psyllium) within the last 90 days • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance, to at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days • If the above criteria are met, for requests for Linzess, Trulance, Motegrity, or lubiprostone (Amitiza): approve. **OR** • For requests for other formulary, prior authorization required medications, the above criteria must be met, AND documentation of trial and failure, contraindication, or intolerance to Linzess, Trulance, Motegrity, or lubiprostone (Amitiza) within the last 90 days is required **INITIAL AUTHORIZATION FOR DIAGNOSIS OPIOID-INDUCED CONSTIPATION (OIC) with chronic non-cancer pain:** • The patient has a clinical diagnosis of opioid-induced constipation with chronic non-cancer pain • Medication is being prescribed at an FDA approved dosage • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days • If the above criteria are met, for requests for Movantik, Symproic, or lubiprostone (Amitiza): approve **OR** • For requests for other formulary, prior authorization required medications, the above criteria must be met, AND documentation of trial and failure, contraindication, or intolerance to Movantik, Symproic, or lubiprostone (Amitiza) within the last 90 days is required **INITIAL AUTHORIZATION FOR DIAGNOSIS OPIOID-INDUCED CONSTIPATION (OIC) with advanced illness:** • The patient has a clinical diagnosis of opioid-induced constipation with advanced illness • Medication is being prescribed at an FDA approved dosage • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days • If the above criteria are met, for requests for Relistor injectable (e.g. vial or syringe) approve. **OR** • For requests for other formulary, prior authorization required medications, the above criteria must be met, AND documentation of trial and failure, contraindication, or intolerance to Relistor injectable (e.g. vial or syringe) within the last 90 days is required **INITIAL AUTHORIZATION FOR functional constipation in pediatric patients (Linzess only):** • The patient has a clinical diagnosis of functional constipation (FC) • Medication is being prescribed at an FDA approved dosage • Documentation (by either attestation or claims data) of trial and failure, contraindication, or intolerance to at least 2 laxatives (example:

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	polyethylene glycol, lactulose, milk of magnesia, docusate sodium, senna) within the last 90 days **PA CRITERIA FOR REAUTHORIZATION (IBS-C, CIC, opioid-induced constipation, FC):** • Documentation of continued clinical benefit from treatment. • Medication is being prescribed at an FDA approved dosage
Criteria Statement	For the diagnosis of irritable bowel syndrome with constipation, lubiprostone (Amitiza), Linzess, and Trulance are reserved for members who have used (or cannot/should not use) a soluble fiber (example: psyllium) within the last 90 days. Ibsrela is reserved for members who have also used lubiprostone (Amitiza), Linzess, or Trulance within the last 90 days. For the diagnosis of chronic idiopathic constipation, lubiprostone (Amitiza), Linzess, Motegrity, and Trulance are reserved for members who have used (or cannot/should not use) a soluble fiber (example: psyllium) AND at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days. For the diagnosis of opioid-inducted constipation with chronic non-cancer pain, lubiprostone (Amitiza), Symproic, and Movantik are reserved for members who have used (or cannot/should not use) at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days. Relistor is reserved for members who have also used lubiprostone (Amitiza), Symproic, or Movantik within the last 90 days. For the diagnosis of opioid-inducted constipation with advanced illness, Relistor injectable is reserved for members who have used (or cannot/should not use) at least 2 laxatives (example: milk of magnesia, polyethylene glycol, docusate sodium, senna) within the last 90 days. For the diagnosis of functional constipation in pediatric patients, Linzess is reserved for members who have used (or cannot/should not use) at least 2 laxatives (example: polyethylene glycol, lactulose, milk of magnesia, docusate sodium, senna) within the last 90 days.
Last P&T Review Date	~~9/2023~~9/2024

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Recommendation:

- Update criteria for Prevention of spontaneous preterm delivery based on new ACOG guideline update that recommends vaginal progesterone in patients with singleton pregnancy and short cervix, regardless of the history of prior preterm birth.

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 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 prior preterm birth~~ 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) ○ 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 ~~history of preterm birth and~~ 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 ~~history of preterm birth and~~ 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	~~9/2023~~9/2024

Recommendation:

- Change naming convention to reflect generic availability of teriparatide
- Revise preferred agents with Tymlos and teriparatide as preferred over Forteo and Evenity as teriparatide is available as a generic and is more cost effective, and to receive preferred pricing on Tymlos
- Change treatment recommendations based on new glucocorticoid induced osteoporosis guidelines that now also recommend treatment for patients with moderate risk on long-term glucocorticoid therapy (patients 40 years and older) and for adult patients on high dose glucocorticoid therapy (regardless of age)

Injectable/Infusible Agents for Osteoporosis and Paget's Disease	
Therapeutic Classes (AHFS)	Bone resorption inhibitors; Parathyroid agents
Medications	ibandronate (Boniva) injection zoledronic acid (Reclast) Prolia (denosumab) ~~Forteo (~~teriparatide~~)~~ (Forteo)--PREFERRED ~~Teriparatide~~ Tymlos (abaloparatide)--PREFERRED Evenity (romosozumab-aqqg) pamidronate
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. ***FORTEO/TERIPARATIDE/TYMLOS REQUESTS WILL ONLY BE APPROVED FOR A TOTAL DURATION OF 24 MONTHS*** *** EVENITY WILL ONLY BE APPROVED FOR A TOTAL OF 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 FOR ALL REQUESTS:** • Documentation (by either attestation or claims data) the member is taking adequate calcium and vitamin D supplementation • The member has a documented (consistent with pharmacy claims) adequate trial of an oral bisphosphonate or has a medical reason (e.g. intolerance, hypersensitivity, contraindication, etc.) for not using an oral bisphosphonate **POSTMENOPAUSAL OR MALE OSTEOPOROSIS:** • If the request is for **very high risk** postmenopausal osteoporosis or postmenopausal osteoporosis, with prior fractures, a documented trial and failure of an oral bisphosphonate will not be required. o Very high risk is defined as having one or more of the following: ▪ History of fracture in the past 12 months ▪ Multiple fractures

- Fractures while on drugs causing skeletal harm (e.g. long-term glucocorticoids)
- Very low T scores (< -3.0)
- High risk for falls
- History of injurious falls
- Very high fracture probability as determined by fracture risk assessment tool (FRAX) (e.g. major osteoporosis fracture >30%, hip fracture > 4.5%)

- Documentation was submitted indicating the member is a postmenopausal woman or a male over 50 years of age and one of the following:
  - A bone mineral density (BMD) value consistent with osteoporosis (i.e., T-scores equal to or less than –2.5)
  - Has had an osteoporotic fracture
  - A T-score between -1 and -2.5 at the femoral neck or spine and a 10 year hip fracture probability >3% or a 10 year major osteoporosis-related fracture probability >20% based on the US-adapted WHO absolute fracture risk model.
- If the request is for Forteo (teriparatide), Teriparatide, Evenity (romosozumab), or Tymlos (abaloparatide), one of the following applies to the member:
  - Documented trial and failure of ibandronate (Boniva) or zoledronic acid (Reclast) AND Prolia (denosumab) or has a medical reason (e.g. intolerance, contraindication, etc.) why these therapies are not suitable to be used
  - Has severe osteoporosis (T-Score -3.5 or below, or T-Score of -2.5 or below plus a fragility fracture)
- If the request is for Forteo or Evenity~~Teriparatide~~, a medical reason why the member is unable to use Tymlos or ~~Evenity~~ teriparatide, if appropriate, based on the diagnosis.
  - Requests for brand Forteo (teriparatide) also require a medical reason why the member is unable to use Teriparatide
- If the request is for Evenity, the member does not have a history of a heart attack or stroke within the preceding year

GLUCOCORTICOID-INDUCED OSTEOPOROSIS:

- For members ≥ 40 years of age on long-term glucocorticoid therapy:
  - Documentation that the member is currently utilizing glucocorticoid therapy for a minimum of 3 months
  - ~~Documentation that the d~~Dosage of the glucocorticoid therapy is greater than 2.5 mg of prednisone daily or its equivalent
  - ~~Member is 40 years of age or older~~
  - Member has a ~~high~~moderate to very high risk of fracture based on ONE of the following:
    - History of osteoporotic fracture
    - BMD less than or equal to -~~2.5~~1 at the hip or spine
    - FRAX 10-year probability of hip or combined major osteoporotic fracture of ≥~~3~~ 1 and ~~20~~10 percent (with glucocorticoid adjustment), respectively
- For adult members (all ages) receiving HIGH dose glucocorticoid therapy:
  - Member has a moderate to very high risk of fracture based on ONE of the following:
    - History of prior fracture
    - Glucocorticoid dose ≥ 30 mg/day or cumulative ≥ 5 grams/year of prednisone or its equivalent

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	▪ Continuing glucocorticoid treatment ≥ 7.5 mg/day of prednisone or its equivalent for ≥ 6 months AND BMD Z score < -3 OR significant BMD loss (> least significant change of DXA) • If the request is for Forteo (teriparatide), Teriparatide or Tymlos (abaloparatide), the member has a documented trial and failure of zoledronic acid (Reclast) or Prolia (denosumab) or a medical reason (e.g. intolerance, contraindication, etc.) as to why the member is unable to use these medications is provided: ○ Requests for brand Forteo (teriparatide) also require a medical reason why the member is unable to use Teriparatide **PAGET'S DISEASE:** • Documentation of a confirmed diagnosis of Paget's disease. • Documentation (from within 60 days of the request) that the member has a serum alkaline phosphatase level of ≥ two times the upper limit of normal OR the member is symptomatic OR the member is at risk for complication from Paget's disease **CRITERIA FOR REAPPROVAL:** • The member has documentation of clinical benefit from the medication
Criteria Statement	Ibandronate (Boniva) Injection, Prolia, or zoledronic acid (Reclast) are reserved for members with a diagnosis of postmenopausal or male osteoporosis who have used (or cannot/should not use) oral bisphosphonates, unless the member has very high risk osteoporosis, an oral bisphosphonate is not required. Forteo, teriparatide, Evenity, or Tymlos are reserved for members with a diagnosis of postmenopausal or male osteoporosis who have used (or cannot/should not use) ibandronate (Boniva) or zoledronic acid (Reclast) AND Prolia. Additionally, Forteo and Evenity are reserved for members who have used (or cannot/should not use) Tymlos or teriparatide. Forteo is reserved for members who have used (or cannot/should not use) teriparatide. Tymlos, Forteo, Teriparatide, Prolia or zoledronic acid (Reclast) are reserved for members with glucocorticoid-induced osteoporosis who are 40 years of age or older on long-term glucocorticoid therapy or are on high dose glucocorticoid therapy regardless of age, and have a moderate to high to very high risk of fracture, and have used (or cannot/should not use) oral bisphosphonates. Forteo, Teriparatide, or Tymlos are reserved for members with glucocorticoid-induced osteoporosis who have used (or cannot/should not use) zoledronic acid (Reclast) or Prolia. Additionally, Forteo is reserved for members who have used (or cannot/should not use) Teriparatide, Zoledronic acid (Reclast) and pamidronate are reserved for members with Paget's disease who have used (or cannot/should not use) oral bisphosphonates.
Last P&T Review Date	9/20239/2024

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Recommendation:

- Add Voydeya—new complement factor D inhibitor for add-on therapy with Soliris/Ultomiris for the treatment of extravascular hemolysis (EVH) in adults with PNH
- Change the name of the policy to include both complement inhibitors for the treatment of PNH
- Add Voydeya in the coverage duration and initial authorization sections based on inclusion criteria in clinical trial and per labeled indication

~~Fabhalta~~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: ~~I~~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) ○ Member has been receiving Soliris (eculizumab) or Ultomiris (ravulizumab) therapy for at least 6 months ○ 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) or Ultomiris (ravulizumab) ○ Voydeya (danicopan) will be used as add-on therapy to Soliris (eculizumab) 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

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	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 or Ultomiris for at least 6 months, and will be used as an add-on therapy to Soliris or Ultomiris.
Last P&T Review Date	~~3/2024~~9/2024

Recommendation:

- Update criteria title to Pulmonary Hypertension (PH) agents to encompass all indications of all drugs included in the criteria. The majority of criteria covers PAH drugs, however, Tyvaso and Adempas also cover other PH groups (WHO Groups 3 and 4).
- Add two new drugs and their classes: combination drug Opsynvi and new MOA drug Winrevair and update criteria accordingly.
- Remove section regarding positive vasoreactivity testing and CCB trial and failure. Prescriber for this condition is a specialist and this would automatically be a covered step in the process of appropriate diagnosis.
- Reword initial authorization criteria for Adempas to fit the labeled indication for more clarity
- Remove requirement for monotherapy before combination therapy per newest guidance that standard of care is optimal on multiple class agents in combination.
- Remove requirement for documentation of medical necessity for dosage increase in reauthorization section to prevent inappropriate denials.

~~Vasodilators for Pulmonary Arterial Hypertension (PAH)~~ Pulmonary Hypertension (PH) Agents	
Therapeutic Classes (AHFS)	Vasodilating agents (respiratory tract); phosphodiesterase type 5 inhibitors
Medications	**PDE-5 Inhibitors:** Formulary, prior authorization required tadalafil (Adcirca/Tadliq), sildenafil (Revatio) tablet Non-Formulary sildenafil (Revatio/Liqrev) oral suspension **Endothelin Receptor Antagonists (ERA)**: Formulary, prior authorization required ambrisentan (Letairis) tablet, bosentan (Tracleer) tablet, Tracleer (bosentan) tablet for suspension, Opsumit (macitentan) ERA and Phosphodiesterase-5 (PDE-5) Inhibitor Combinations: Non-Formulary Opsynvi (macitentan and tadalafil) **Prostaglandin Vasodilators~~noids~~**: Formulary, prior authorization required Orenitram (treprostinil diolamine), treprostinil sodium (Remodulin), Ventavis (iloprost), Tyvaso/Tyvaso DPI (treprostinil) Non-Formulary Flolan (epoprostenol), epoprostenol (Veletri) **Soluble Guanylate Cyclase (sCG) Stimulators:** Formulary, prior authorization required Adempas (riociguat) ~~**Non-Prostanoid IP**~~ **Prostacyclin Receptor Agonists**: Formulary, prior authorization required Uptravi (selexipag) Transforming Growth Factor-beta (TGF-beta) Signaling Modulator: Non-Formulary Winrevair (sotatercept-csrk) **and any other newly marketed PAH treatment agents~~.~~**

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~~Vasodilators for Pulmonary Arterial Hypertension (PAH)~~ Pulmonary Hypertension (PH) 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	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be pulmonologist or cardiologist.
Coverage Duration	**Approval** Orenitram, Tyvaso, Adempas, ~~or~~ Ventavis: 3 months for initial request Opsynvi: 4 months for initial request Uptravi: Request will be approved for the titration pack for 28 days until the highest tolerated dose (maintenance dose) is achieved. Once the member has achieved maintenance dosing, further refills can be approved for a 6 month duration. For all others, if all of the ~~above~~ conditions are met, the initial request will be approved for a 6 month duration. All ~~refill~~ reauthorization requests will be approved for a 6 month duration. If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**PA CRITERIA FOR INITIAL APPROVAL:** • Member has a confirmed diagnosis and ~~R~~request is appropriate for member (e.g. functional class) as indicated in package labeling or standard of care guidelines • ~~If the diagnosis is PAH (WHO Group 1) FC I-III, documentation of the member's acute vasoreactivity testing is provided and ONE of the following:~~ ○ ~~If the results of the acute vasoreactivity testing were positive (defined as a fall in mean pulmonary arterial pressure [PAPm] of at least 10 mm Hg to ≤ 40 mm Hg with an increased or unchanged cardiac output), then documentation is provided that disease has progressed despite maximal medical treatment with a calcium channel blocker~~ ○ ~~Documentation has been provided of medical reason why patient is not able to use a calcium channel blocker.~~ • Documentation of the patient's current weight, dosing, and titration scheduled is provided (if applicable) • For Uptravi, Orenitram, Tyvaso/Tyvaso DPI, Ventavis, Remodulin, Adempas, ONE of the following: ○ Documented trial and failure of one PDE-5 inhibitor (e.g. sildenafil, tadalafil) AND one Endothelin Receptor Antagonist [bosentan (Tracleer), ambrisentan (Letairis), or Opsumit] ○ Diagnosis of WHO Group 1 FC III with evidence of rapid disease progression or FC IV (Uptravi, Orenitram, Tyvaso, Ventavis, Remodulin ONLY) ○ Diagnosis of persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH) WHO Group 4 after surgical treatment, or inoperable CTEPH ~~Chronic Thromboembolic Pulmonary Hypertension (CTEPH) WHO Group 4 and recurrent/persistent CTEPH after surgical treatment or inoperable CTEPH~~ (Adempas ONLY) ○ Diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD) WHO Group 3 (Tyvaso ONLY)

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~~Vasodilators for Pulmonary Arterial Hypertension (PAH)~~ Pulmonary Hypertension (PH) Agents	
	• If the request is for Opsumit the patient must have a documented trial and failure or intolerance to ambrisentan and bosentan, or provide a medical reason why these therapies are not appropriate • If the request is for sildenafil oral suspension, Liqrev (sildenafil) oral suspension, Tracleer (bosentan) tablet for suspension, or Tadliq (tadalafil) oral suspension, documentation has been submitted as to why patient is unable to use the same ingredient in a tablet dosage form (e.g. difficulty swallowing) ~~• If the provider is requesting combination therapy, ONE of the following:~~ ~~○ A PDE-5 inhibitor and an ERA are requested as the combination therapy~~ ~~○ Documentation is provided as to why the member is unable to be treated with existing therapy (e.g. worsening of the symptoms of dyspnea or fatigue, decline in functional class by at least one class or in 6-minute walk test (6MWD) by greater than 30 minutes)~~ • If the request is for Opsynvi, BOTH of the following: ○ Patient has been stable for at least 6 months on combination therapy consisting of a PDE-5 inhibitor AND an ERA ○ Documentation is provided as to why patient is unable to take individual pills for combination therapy (e.g. adherence due to pill burden) • If the request is for Winrevair, ALL of the following: ○ Documented trial and failure of, or contraindication to, at least 6 months of combination therapy including one PDE-5 inhibitor AND one ERA OR Opsynvi ○ Documentation of platelet count of > 50,000/mm^3 **PA CRITERIA FOR REAUTHORIZATION:** • Documentation has been submitted indicating the clinical benefit of therapy (e.g. improvement in functional class, improvement in 6-minute walk test, exercise capacity, or hemodynamics). • ~~If dosing is being increased, documentation of the medical necessity to increase the dosage is provided.~~ • Documentation of the patient's current weight, dosing, and titration schedule~~d~~ is provided (if applicable). • Request is appropriate for member (e.g. functional class) as indicated in package labeling or standard of care guidelines
Criteria Statement	Opsumit is reserved for members who have used (or cannot/should not use) bosentan (Tracleer) tablets and ambrisentan (Letairis) tablets. Sildenafil oral suspension, Liqrev (sildenafil) oral suspension, Tracleer (bosentan) tablet for suspension, or Tadliq (tadalafil) oral suspension are reserved for members who have used (or cannot/should not use) the same ingredients in an oral tablet dosage form. Opsynvi is reserved for members that have been stable on combination therapy: ~~Combination therapy is reserved for members who have used (or cannot/should not use)~~ a phosphodiesterase 5 enzyme inhibitor (PDE-5) and an endothelin receptor antagonist (ERA) ~~OR~~ and documentation as to why the member is unable to be treated with ~~existing therapy~~individual pills for combination therapy. . Winrevair is reserved for members who have documented trial and failure, or contraindication to at least 6 months of combination therapy (PDE-5 inhibitor and ERA or Opsynvi) and have platelet count of > 50,000/mm^3.
Last P&T Review Date	~~3/2024~~9/2024

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Recommendation:

- Update age range since Palforzia for peanut allergy just received an expanded age indication down to 1 year old

Palforzia	
Therapeutic Classes (AHFS)	ALLERGENIC EXTRACTS (THERAPEUTIC)
Medications	Non-Formulary Palforzia (peanut [Arachis hypogaea] allergen powder-dnfp)
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	• Initiation: Patient is age ~~4~~1-17 years. • Up dosing and maintenance: Patient is age ≥ ~~4~~1 years
Prescriber Restrictions	Prescriber is a specialist in the area of allergy/immunology
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 6 months. If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Initial Authorization**: Palforzia is approved when all of the following criteria are met: • Patient has a confirmed diagnosis of peanut allergy • For patients starting initial dose escalation (new to therapy) ○ Patient has not had severe or life-threatening anaphylaxis within the previous 60 days • Patient will follow a peanut-avoidant diet • Patient has been prescribed and has acquired (as demonstrated by pharmacy claims or documentation) injectable epinephrine • No history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease • Patient does not have uncontrolled asthma **Criteria for Re-Authorization:** Palforzia is approved for re-authorization when all of the following criteria are met • Patient will follow a peanut-avoidant diet • Patient is able to tolerate at least the 3 mg dose daily • Patient is able to comply with the daily dosing requirements • Patient does not have recurrent asthma exacerbations or persistent loss of asthma control • Patient has been prescribed and has acquired (as demonstrated by pharmacy claims or documentation) injectable epinephrine
Criteria Statement	Palforzia is reserved for members with an allergy to peanuts, who will follow a peanut-avoidant diet, who have not experienced anaphylaxis in the previous 60 days, don't have uncontrolled asthma, and have been prescribed injectable epinephrine.
Last P&T Review Date	~~6/2024~~9/2024

Alameda Q3 2024 PADs for Review Changes

Recommendation:

- Change naming convention to reflect generic availability of Forteo
- Revise preferred agents for postmenopausal or male osteoporosis with Tymlos and teriparatide as preferred over Forteo and Evenity as teriparatide is available as a generic and is more cost effective
- Change treatment recommendations based on new glucocorticoid induced osteoporosis guidelines that now also recommend treatment for patients with moderate risk on long-term glucocorticoid therapy (patients 40 years and older) and for adult patients on high dose glucocorticoid therapy (regardless of age)

Injectable/Infusible Agents for Osteoporosis and Paget's Disease	
Medications	ibandronate (Boniva) injection zoledronic acid (Reclast) Prolia (denosumab) ~~Forteo (teriparatide)~~ ~~T~~teriparatide (Forteo) Tymlos (abaloparatide) Evenity (romosozumab-aqqg) Pamidronate 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 all conditions are met, the request will be approved for up to 12 months. ***FORTEO/TERIPARATIDE/TYMLOS REQUESTS WILL ONLY BE APPROVED FOR A TOTAL DURATION OF 24 MONTHS*** *** EVENITY WILL ONLY BE APPROVED FOR A TOTAL OF 12 MONTHS*** reauthorization requests will be approved for up to 12 months.
Maximum Billable Units	Variable
Other Criteria	**CRITERIA FOR APPROVAL FOR ALL REQUESTS:** • Dose is appropriate per label or supported by compendia/standard of care guidelines • The member is taking adequate calcium and vitamin D supplementation • The member has a documented (consistent with pharmacy claims) adequate trial of an oral bisphosphonate or has a medical reason (e.g. intolerance, hypersensitivity, contraindication, etc.) for not using an oral bisphosphonate **POSTMENOPAUSAL OR MALE OSTEOPOROSIS:** • If the request is for very high risk postmenopausal osteoporosis or postmenopausal osteoporosis, with prior fractures, a documented trial and failure of an oral bisphosphonate will not be required. o Very high risk is defined as having one or more of the following: ▪ History of fracture in the past 12 months ▪ Multiple fractures

- Fractures while on drugs causing skeletal harm (e.g. long-term glucocorticoids)
- Very low T scores (< -3.0)
- High risk for falls
- History of injurious falls
- Very high fracture probability as determined by fracture risk assessment tool (FRAX) (e.g. major osteoporosis fracture >30%, hip fracture > 4.5%)

- Documentation was submitted indicating the member is a postmenopausal woman or a male over 50 years of age and one of the following:
  - A bone mineral density (BMD) value consistent with osteoporosis (i.e., T-scores equal to or less than –2.5)
  - Has had an osteoporotic fracture
  - A T-score between -1 and -2.5 at the femoral neck or spine and a 10 year hip fracture probability >3% or a 10 year major osteoporosis-related fracture probability >20% based on the US-adapted WHO absolute fracture risk model.
- If the request is for Forteo (teriparatide), Teriparatide, Evenity (romosozumab), or Tymlos (abaloparatide), one of the following applies to the member:
  - Documented trial and failure of ibandronate (Boniva) or zoledronic acid (Reclast) AND Prolia (denosumab) or has a medical reason (e.g. intolerance, contraindication, etc.) why these therapies are not suitable to be used
  - Has severe osteoporosis (T-Score -3.5 or below, or T-Score of -2.5 or below plus a fragility fracture)
- If the request is for Forteo or Evenity~~Teriparatide~~, a medical reason why member is unable to use Tymlos or ~~Evenity~~teriparatide, if appropriate, based on the diagnosis.
  - Requests for brand Forteo (teriparatide) also require a medical reason why the member is unable to use Teriparatide
- If the request is for Evenity, the member does not have a history of a heart attack or stroke within the preceding year

GLUCOCORTICOID-INDUCED OSTEOPOROSIS THERAPY:

- For members ≥ 40 years of age on long-term glucocorticoid therapy:
  - Documentation that the member is currently utilizing glucocorticoid therapy for a minimum of 3 months
  - ~~Documentation that the d~~Dosage of the glucocorticoid therapy is greater than 2.5 mg of prednisone daily or its equivalent
  - ~~Member is 40 years of age or older~~
  - Member has a ~~high~~moderate to very high risk of fracture based on ONE of the following:
    - ~~History of osteoporotic fracture~~
    - ~~BMD less than or equal to -2.51 at the hip or spine~~
    - FRAX 10-year probability of hip or combined major osteoporotic fracture of ≥~~3~~1 and ~~20~~10 percent (with glucocorticoid adjustment), respectively
- For adult members (all ages) receiving HIGH dose glucocorticoid therapy:
  - Member has a moderate to very high risk of fracture based on ONE of the following:
    - History of prior fracture
    - Glucocorticoid dose ≥ 30 mg/day or cumulative ≥ 5 grams/year of prednisone or its equivalent

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	~~o~~ ▪ Continuing glucocorticoid treatment ≥ 7.5 mg/day of prednisone or its equivalent for ≥ 6 months AND BMD Z score < -3 OR significant BMD loss (> least significant change of DXA) • If the request is for Forteo (teriparatide), Teriparatide, or Tymlos (abaloparatide), the member has a documented trial and failure of zoledronic acid (Reclast) or Prolia (denosumab) or a medical reason (e.g. intolerance, contraindication, etc.) as to why the member is unable to use these medications is provided: ○ Requests for brand Forteo (teriparatide) also require a medical reason why the member is unable to use Teriparatide **PAGET'S DISEASE:** • Documentation of a confirmed diagnosis of Paget's disease. • Documentation (from within 60 days of the request) that the member has a serum alkaline phosphatase level of ≥ two times the upper limit of normal OR the member is symptomatic OR the patient is at risk for complication from Paget's disease **CRITERIA FOR REAPPROVAL:** • The member has documentation of clinical benefit from the medication
Last Review Date	~~9/2023~~9/2024

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Recommendation:

- Change naming convention to reflect generic availability of Mozobil
- Add new product Aphexda which shares the same indication as plerixafor and update criteria accordingly
- Remove criteria for pegfilgrastim formulations for acute hematopoietic radiation injury syndrome to approve Neulasta without prior use of a biosimilar since 3 of the pegfilgrastim biosimilars now also have this indication (Ziextenzo, Udenyca and Stimufend)

White Blood Cell Stimulators	
Medications	~~Mozobil (~~plerixafor~~)~~ Aphexda (motixafortide) (Mozobil) Leukine (sargramostim) **Long acting-CSF** Neulasta (pegfilgrastim) Neulasta (pegfilgrastim) Onpro Fulphila (pegfilgrastim-jmdb) - biosimilar Udenyca (pegfilgrastim-cbqv) - biosimilar Ziextenzo (pegfilgrastim-bmez) - biosimilar Nyvepria (pegfilgrastim-apgf) – biosimilar Fylnetra (pegfilgrastim-pbbk) – biosimilar Stimufend (pegfilgrastim-fpgk) – biosimilar Rolvedon (eflapegrastim-xnst) **Short acting-CSF** Neupogen (filgrastim) Zarxio (filgrastim-sndz) - biosimilar Nivestym (filgrastim-aafi) - biosimilar Granix (tbo-filgrastim) – biosimilar Releuko (filgrastim-ayow) - biosimilar 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 "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL
Prescriber Restrictions	Prescriber must be a hematologist/oncologist.
Maximum Billable Units	variable
Coverage Duration	**Initial Approval** 12 weeks or as recommended per FDA approved indications and/or as defined by the medical compendium as defined above and/or per the NCCN or ASCO standard of care guidelines **Later Approval** For all indications except chronic neutropenia: 12 weeks. For chronic neutropenia: 24 weeks.
Other Criteria	**** When this biosimilar is indicated, the member must have documented dates of trial and failure, intolerance, inability to use, or contraindication to the biosimilar medication prior to the brand medication approval, OR 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, in addition to meeting all applicable criteria below. For approval: • If the request is for Leukine: o Documentation is submitted of the patient's current diagnosis, current bodyweight, body surface area and absolute neutrophil count (within 30 days of the request) • If the request is for ~~Mozobil~~plerixafor or Aphexda: o Documentation is submitted of the patient's current diagnosis, current bodyweight, and that the patient is using ~~Mozobil~~product in combination with a granulocyte-colony stimulating factor (G-CSF) agent (i.e. Zarxio or Fulphila) o If the request is for Aphexda, the patient has a documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of plerixafor and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using plerixafor • If the request is for a pegfilgrastim formulation or Rolvedon: o The patient has a documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of a biosimilar and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using a biosimilar. ~~o If the request is for acute hematopoietic radiation injury syndrome, Neulasta can be approved without prior use of a biosimilar or medical reason for not using a biosimilar.~~ • If the request is for a filgrastim formulation: o The patient has a documented treatment failure (i.e. failure to reach and/or maintain target ANC, prolonged febrile neutropenia or infection requiring prolonged anti-infection use) with the use of a biosimilar and/or has another documented medical reason (intolerance, hypersensitivity, etc.) for not using a biosimilar. o If the request is for acute hematopoietic radiation injury syndrome, Neupogen can be approved without prior use of a biosimilar or medical reason for not using a biosimilar. 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	~~9/2023~~9/2024

Recommendation:

- Add new approved drug Beqvez and update criteria accordingly
- Change the name of the policy since agents treat Hemophilia type B (factor IX deficiency)
- Update exclusion and coverage duration since repeat use of agents or using one after the other have not been studied
- Update age restriction—agents are approved only in adults
- Add a specific test requirement for Beqvez per label

Gene Therapy for Hemophilia B	
Medications	Hemgenix (etranacogene dezaparvovec), Beqvez (fidanacogene elaparvovec-dzkt)
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	Patient has previously received ~~this medication~~treatment with Hemgenix or Beqvez
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age for MCAL Patient must be 18 years of age or older
Prescriber Restrictions	Prescriber must be a hematologist
Coverage Duration	If all the criteria are met, the initial request will be approved for a one-time treatment for one gene therapy agent for Hemophilia B
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Diagnosis of Hemophilia B (congenital Factor IX deficiency) with ONE of the following:
	  ○ Currently using Factor IX prophylaxis therapy
	  ○ Has current or historical life-threatening hemorrhage
	  ○ Has repeated, serious spontaneous bleeding episodes
	• Documentation that patient has ≤2% of normal circulating Factor IX)
	• Prescriber attests they have performed liver health assessments, including enzyme testing and hepatic ultrasound and elastography
	• Documented Factor IX inhibitor titer test showing the patient is negative for Factor IX inhibitors
	• For Beqvez: Patient does not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test
	• Patient's weight
	• Medication is prescribed at an FDA approved dose and for FDA indication
	
	The safety and effectiveness of repeat administration of Hemgenix or Beqvez have not been evaluated and will not be approved.
	
	~~**Medical Director/clinical reviewer must override criteria when, in her/his professional judgement, the requested item is medically necessary.**~~
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.

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Recommendation:

- Reword DMD diagnosis requirement for more clarity
- Remove ambulatory requirement since Elevidys is now approved for DMD patients regardless of ambulation status
- Remove baseline micro-dystrophin protein level requirement because it is not commonly measured in practice
- Add antibody titer testing per recommendation in the PI
- Add additional monitoring parameters of liver function, platelet counts and troponin-I to ensure treatment appropriateness
- Add medical necessity review statement

Elevidys	
Medications	Elevidys (delandistrogene moxeparvovec-rokl)
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	• Any deletion in exon 8 and/or exon 9 in the Duchenne muscular dystrophy (DMD) gene • Concurrent use with an exon skipping drugs (such as Exondys 51, Amondys 45, Vyondys 53, Viltepso)
Required Clinical Information	See "other criteria"
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescribed by neurologist or provider who specializes in the treatment of DMD
Coverage Duration	If all the criteria are met, the initial request will be approved for a **one-time** treatment.
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization:** • Medication is prescribed at an FDA approved dose • Documentation of weight • Genetically confirmed diagnosis of DMD and copies of testing were submitted with request • ~~Diagnosis of DMD with a confirmed mutation in the *DMD* gene~~ • ~~Attestation patient is ambulatory~~ • Member has been on a stable dose of corticosteroids for at least 3 months • ~~Baseline micro-dystrophin protein level~~ • Attestation patient has anti-recombinant adeno-associated virus serotype rh74 (anti-AAVrh74) total binding antibody titers of less than 1:400 • Attestation prescriber has assessed patient's liver function, platelet counts, and troponin-I before treatment If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~9/2023~~9/2024

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Recommendation:

- Update criteria as both Abecma and Carvykti received updated indications to be used as earlier lines of treatment for relapsed/refractory multiple myeloma.
- Add inflammatory disorder to "Member does not have an active infection" bullet point to match the language of Anti-CD19 CAR T-cell policy. Also, both are boxed warnings on the label for each agent.

B-Cell Maturation Antigen (BCMA) Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy	
Medications	Abecma (idecabtagene vicleucel), Carvykti (ciltacabtagene 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	N/A
Required Clinical Information	See "Other Criteria" below
Age Restrictions	Member must be 18 years or older 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 per lifetime.
Maximum Billable Units	Variable
Other Criteria	**Initial Authorization** • Member has a diagnosis of relapsed or refractory multiple myeloma (RRMM) • For Abecma, ~~M~~member must have also received at least 42 prior lines of therapy including~~, which must include ALL of the following~~: o An immunomodulatory agent (e.g. lenalidomide, pomalidomide, thalidomide) o A proteasome inhibitor (e.g. bortezomib, carfilzomib, ixazomib) o An anti-CD38 monoclonal antibody (e.g. daratumumab, isatuximab) • For Carvykti, member must also be refractory to lenalidomide AND have received at least 1 prior line of therapy including: o An immunomodulatory agent (e.g. lenalidomide, pomalidomide, thalidomide) o A proteasome inhibitor (e.g. bortezomib, carfilzomib, ixazomib) • Member does not have an active infection or inflammatory disorder • Member will be screened for cytomegalovirus (CMV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) in accordance with clinical guidelines • Member will not receive live virus vaccines for at least 6 weeks prior to the start of lymphodepleting chemotherapy and until immune recovery following treatment • Member has not previously received a BCMA CAR-T therapy **Re-authorization:** • Treatment exceeding 1 dose per lifetime will not be authorized. 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~~9/2024

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PERFORMRX NATIONAL NEW PRODUCTS REVIEW

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
5/14/2024	Cyltezo	adalimumab-adbm 40 mg/0.4 ml subcutaneous syringe; 40 mg/0.4 ml subcutaneous auto-injector	Boehringer Ingelheim	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$3,288 per dose	Humira, Amjevita, Hulio, Idacio, Hyrimoz, Yusimry, Yuflyma, Hadlima, Abrilada, Simlandi	Non-formulary
5/14/2024	Adalimumab-adbm	adalimumab-adbm 40 mg/0.4 ml subcutaneous syringe; 40 mg/0.4 ml subcutaneous auto-injector	Boehringer Ingelheim	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$658 per dose	Humira, Amjevita, Hulio, Idacio, Hyrimoz, Yusimry, Yuflyma, Hadlima, Abrilada, Simlandi	Non-formulary
5/14/2024	Tofidence	tocilizumab-bavi 80 mg/4 ml, 200 mg/10 ml, 400 mg/20 ml intravenous vials	Biogen	Rheumatoid Arthritis, Polyarticular Juvenile Idiopathic Arthritis, Systemic Juvenile Idiopathic Arthritis	$2,220 per 20 ml vial (dosing and price varies depending on indication and patient's weight)	Actemra, Tyenne, Adalimumab, Infliximab, Kineret, Orencia, Simponi, Cimzia, Rinvoq	Add to formulary with PA; (see updated MRG policy)
5/14/2024	Ingrezza	valbenazine 40 mg, 60 mg, 80 mg sprinkle capsules	Neurocrine Biosciences	• Treatment of adults with tardive dyskinesia • Treatment of adults with chorea associated with Huntington's disease	$8,255	Austedo, tetrabenazine	Non-formulary
5/14/2024	Rextovy	naloxone 4 mg nasal spray	Amphastar Pharmaceuticals, Inc.	• For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression for adults and pediatric patients Intended for immediate administration as emergency therapy in settings where opioids may be present. Not a substitute for emergency medical care.	$45 per package	Naloxone nasal spray	Add to formulary
5/14/2024	Xolremdi	mavorixafor 100 mg oral capsules	X4 Pharmaceuticals, Inc.	• To be used in patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes	$40,800 (max dose)	None	Non-formulary (see new MRG policy)

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
5/21/2024	Omvoh	mirikizumab-mrkz 100 mg/ml subcutaneous syringe	Eli Lilly and Company	• Treatment of moderately to severely active ulcerative colitis in adults	$10,361	Adalimumab, Infliximab, Rinvoq, Stelara, Entyvio, Zeposia	Non-formulary (see updated MRG policy)
5/21/2024	Beqvez	fidanacogene elaparvovec-dzkt 1 × 10^{13} vector genomes/ml	Pfizer	• Treatment of adults with moderate to severe hemophilia B (congenital factor IX deficiency) who: o Currently use factor IX prophylaxis therapy, or o Have current or historical life-threatening hemorrhage, or o Have repeated, serious spontaneous bleeding episodes, and, Do not have neutralizing antibodies to adeno-associated virus serotype Rh74var (AAVRh74var) capsid as detected by an FDA-approved test	$3.5 million per one-time treatment	Hemgenix, Ixinity, Idelvion	Non-formulary (see updated PAD policy)
5/21/2024	Fasenra	benralizumab 10 mg/0.5 ml subcutaneous syringe	AstraZeneca	• Add-on maintenance treatment of patients aged 6 years and older with severe asthma, and with an eosinophilic phenotype	$946 for maintenance dose	Nucala, Dupixent	F; PA (Already added via CRF)
5/28/2024	Imdelltra	tarlatamab-dlle 1 mg, 10 mg intravenous vials	Amgen	• Treatment of adult patients with extensive stage small cell lung cancer (ES-SCLC) with disease progression on or after platinum-based chemotherapy This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).	$30,000	Zepzelca, Topotecan	Non-formulary
5/28/2024	Kionex	sodium polystyrene sulfonate 15 g/60 ml oral or rectal suspension	ANI Pharmaceuticals	• Treatment of hyperkalemia	$240 per package of ten doses	Sodium Polystyrene Sulfonate, Veltassa, Lokelma	Non-formulary

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
6/4/2024	Hepzato	melphalan w/50mm catheter intra-arterial solution reconstituted 50 mg melphalan w/62mm catheter intra-arterial solution reconstituted 50 mg	Delcath Systems, Inc.	• Liver-directed treatment for adult patients with uveal melanoma with unresectable hepatic metastases affecting less than 50% of the liver and no extrahepatic disease, or extrahepatic disease limited to the bone, lymph nodes, subcutaneous tissues, or lung that is amenable to resection or radiation	$182,500 per dose	Kimmtrak	Non-formulary
6/11/2024	Myhibbin	mycophenolate mofetil oral suspension 200 mg/ml	Azurity Pharmaceuticals	• Prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants	$700 per bottle	CellCept, Myfortic, tacrolimus	Non-formulary
6/11/2024	Focinvez	fosaprepitant intravenous solution 150 mg/50ml	Spes Pharmaceuticals Inc.	Indicated in adults and pediatric patients 6 months of age and older, in combination with other antiemetic agents, for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC). Limitations of Use: Focinvez has not been studied for treatment of established nausea and vomiting	$458 per dose (number of doses depends on chemo cycle)	Aponvie, Cinvanti, Emend, Zofran, Aloxi	Non-formulary
6/11/2024	Austedo XR	deutetrabenazine oral tablet extended release 24 hour 30, 36, 42, 48 mg	Teva	• Treatment of adults Chorea associated with Huntington's disease • Treatment of adults with Tardive dyskinesia	$9,750 - $14,640	Ingrezza, tetrabenazine	Non-formulary

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
6/18/2024	Rinvoq LQ	upadacitinib oral solution 1 mg/mL	AbbVie	• Treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers • Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis who have had an inadequate response or intolerance to one or more TNF blockers	$515-$1,029 (based on weight)	Xeljanz, Enbrel, adalimumab, Actemra, Cosentyx	Non-formulary
6/18/2024	Vijoice	alpelisib oral packet 50 mg	Novartis	• Treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CARelated Overgrowth Spectrum (PROS) who require systemic therapy This indication is approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)	$34,821	None	Non-formulary
6/18/2024	Duvyzat	givinostat oral suspension 8.86mg/mL	ITF Therapeutics	• Treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older.	$39,644-$95,144	None	Non-formulary (see new MRG policy)

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
6/18/2024	Iqirvo	elafibranor oral tablet 80 mg	Ipsen	• Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have had an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Limitations of Use • Use of IQIRVO is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)	$11,460	Ocaliva	Non-formulary
6/25/2024	Capvaxive	pneumococcal 21-valent conjugate vaccine	Merck Sharp & Dohme	• Prevention of invasive disease caused by Streptococcus pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older • Prevention of pneumonia caused by S. pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F, and 35B in individuals 18 years of age and older	$288 per dose	Prevnar 20, Vaxneuvance, Pneumovax 23	Add to formulary with QL and AL (0.5 ml per 1 dose,1 fill per lifetime; age limit 18 years and older)
6/25/2024	Tyenne	tocilizumab-aazg 162 mg/0.9 ml subcutaneous auto-injector	Fresenius Kabi	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, Systemic Juvenile Idiopathic Arthritis	$764 per dose (dosing and price varies depending on indication and patient's weight)	Actemra, Tofidence, Adalimumab, Infliximab, Kineret, Orencia, Simponi, Cimzia, Rinvoq	Add to formulary with PA; (see updated MRG policy)

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
6/25/2024	Sitagliptin/Metformin	sitagliptin/metformin 50 mg-500 mg, 50 mg-1000 mg oral tablets	Zydus Pharmaceuticals	• To be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	$529	Janumet, Jentadueto	Non-formulary
6/24/2024	mResvia	respiratory syncytial virus vaccine	Moderna	• Prevention of lower respiratory tract disease (LRTD) caused by respiratory syncytial virus (RSV) in individuals 60 years of age and older	$290 per dose	Arexvy, Abrysvo	Add to formulary with QL and AL (0.5 ml per 1 lifetime; age limit 60 years and older)
7/1/2024	Scemblix	asciminib 100mg oral tablet	Novartis	• Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs) • Ph+ CML in CP with the T315I mutation	$21,660	Bosulif, Sprycel, Gleevec, Tasigna	Non-formulary
7/1/2024	Tyenne	tocilizumab-aazg 162 mg/0.9 ml subcutaneous prefilled syringe	Fresenius Kabi	Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, Systemic Juvenile Idiopathic Arthritis	$764 per dose (dosing and price varies depending on indication and patient's weight)	Actemra, Tofidence, Adalimumab, Infliximab, Kineret, Orencia, Simponi, Cimzia, Rinvoq	Add to formulary with PA; (see updated MRG policy)
7/1/2024	Adbry	Tralokinumab-ldrm 300mg/2ml auto-injector	Leo Pharma	• Treatment of moderate-to-severe atopic dermatitis in adults and pediatric patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable	$3,826	Dupixent	Non-formulary
7/8/2024	Entresto	Sacubitril-valsartan oral capsule sprinkle 6-6mg, 15-16mg	Novartis	• To reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal • For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes	$2,736 (per month for max dose)	ACEi, ARBs, beta blockers, diuretics	F; QL (Already added via CRF)

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
7/8/2024	Rystiggo	Rozanolixizumab-noli 420mg/3ml, 560mg/4ml, 840mg/6ml subcutaneous solution	UCB	• For the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or antimuscle-specific tyrosine kinase (MuSK) antibody positive	$72,600 per 6-week treatment cycle for a 70 kg adult	Vyvgart, Soliris, Ultomiris	Non-formulary
7/8/2024	Ondansetron	Ondansetron 16mg oral disintegrating tablet	Lifsa Drugs	• Prevention of: nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m • Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen • Prevention of postoperative nausea and/or vomiting	$1,230	Aloxi, , Anzemet Sancuso, Akynzeo	Non-formulary
7/8/2024	Ohtuvayre	Ensifentrine 3mg/2.5ml inhalation suspension	Verona Pharma	• For the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.	$2,950	No alternatives with the same MOA. Inhaler alternatives include Trelegy, Breztri, etc.	Non-formulary
7/8/2024	Sofdra	Sofpironium bromide external gel 12.45 %	Botanix SB Inc.	• For the treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older	$1,085 per bottle	Qbrexza, Botox	Non-formulary
7/15/2024	Kisunla	donanemab-azbt intravenous solution 350 mg/20ml	Eli Lilly	• For the 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.	$2,780 (The total cost of therapy will vary by patient and will depend on when the patient completes treatment with Kisunla)	Leqembi	Non-formulary

DATE ADDED	BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
7/15/2024	Elfabrio	pegunigalsidase alfa-iwxj intravenous solution 5 mg/2.5ml	Chiesi	• For the treatment of adults with confirmed Fabry disease.	$30,380 (per month for 70kg patient)	Fabrazyme	Non-formulary
7/15/2024	Acthar Gel	Corticotropin subcutaneous auto-injector 80 unit/ml, 40 unit/0.5ml	Mallinckrodt Pharmaceuticals	• Monotherapy for the treatment of infantile spasms in infants and children under 2 years of age. • Treatment of exacerbations of multiple sclerosis in adults. • May be used for the following disorders and diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state.	$8,796 per pen (80mg/1ml) $4,398 per pen (40mg/0.5ml)	Infantile spasms: Sabril, Vigadrone, Vigpoder MS: corticosteroids	F; PA (Already added via CRF)
7/15/2024	Austedo XR	Deutetrabenazine oral tablet extended release 24 hour 18mg	Teva	• Treatment of adults Chorea associated with Huntington's disease • Treatment of adults with Tardive dyskinesia	$9,750 - $14,640	Ingrezza, tetrabenazine	Non-formulary
7/15/2024	Austedo XR	Deutetrabenazine titration oral tablet therapy pack 12 & 18 & 24 & 30 mg	Teva	• Treatment of adults Chorea associated with Huntington's disease • Treatment of adults with Tardive dyskinesia	$9,750 - $14,640	Ingrezza, tetrabenazine	Non-formulary
7/15/2024	Zoryve	Roflumilast external cream 0.15%	Arcutis Biotherapeutics	• For the topical treatment of mild to moderate atopic dermatitis in adult and pediatric patients 6 years of age and older.	$892 per tube	Ketoconazole, Triamcinolone, Hydrocortisone, Pimecrolimus	Non-formulary

*	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.

Alameda September Q3 2024 P&T Old Business

There was a question during Q2 2024 P&T regarding the Tadalafil (Cialis) for BPH policy that was revised as a result of Q1 2024 P&T meeting.
The policy changes after Q1 2024 were as follows:

- Removed requirement for 5-alpha reductase inhibitor trial
- Removed prescriber restriction

Tadalafil (Cialis) for BPH	
Therapeutic Classes (AHFS)	Phosphodiesterase type 5 inhibitor
Medications	Non-formulary Tadalafil (Cialis) 2.5, 5 mg
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 ~~Prescriber must be a urologist~~
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	The following criteria must be met: • Patient has diagnosis of benign prostatic hyperplasia (BPH) • Documentation of trial and failure, intolerance, contraindication, or inability to use at least ONE alpha blocker ~~AND~~ ~~• ONE 5-alpha reductase inhibitor, if indicated for enlarged prostate, for at least 6 months, as combination therapy~~ • Drug is being requested at an FDA approved dose.
Criteria Statement	For benign prostatic hyperplasia (BPH), tadalafil (Cialis) 2.5 and 5 mg are reserved for members who have previously used (or cannot/should not use) at least one alpha blocker such as ~~a combination of~~ alfuzosin, terazosin, doxazosin, or tamsulosin. ~~AND finasteride or dutasteride~~.
Last P&T Review Date	~~3/2023~~3/2024

- Febuxostat (Uloric) MRG was updated as a result of Q2 2024 P&T meeting with an inclusion of intolerance to allopurinol in the policy for cases such as development of a rash to allopurinol.

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~~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	~~6/2023~~6/2024