PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, March 19th 2024
5:00pm – 7:00pm

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

Location: Microsoft Teams
Meeting ID: 292 192 202 751
Password: ujh7kK

IMPORTANT PUBLIC HEALTH AND SAFETY MESSAGE REGARDING PARTICIPATION AT ALAMEDA ALLIANCE FOR HEALTH COMMITTEE MEETINGS

STATE OR LOCAL OFFICIALS CONTINUE TO IMPOSE OR RECOMMEND MEASURES TO PROMOTE SOCIAL DISTANCING. AS A RESULT OF THE COVID-19 VIRUS, AND RESULTING ORDERS AND DIRECTION FROM THE PRESIDENT OF THE UNITED STATES, THE GOVERNOR OF THE STATE OF CALIFORNIA, AND THE ALAMEDA COUNTY HEALTH OFFICER, THE PUBLIC WILL NOT BE PERMITTED TO PHYSICALLY ATTEND THE ALAMEDA ALLIANCE FOR HEALTH MEETING TO WHICH THIS AGENDA APPLIES.
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 mhoy@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: 1 510-210-0967,982358447# IF YOU USE THE LINK AND PARTICIPATE VIA COMPUTER, YOU MAY, THROUGH THE USE OF THE CHAT FUNCTION, REQUEST AN OPPORTUNITY TO SPEAK ON ANY AGENDIZED ITEM, INCLUDING GENERAL PUBLIC COMMENT. YOUR REQUEST TO SPEAK MUST BE RECEIVED BEFORE THE ITEM IS CALLED ON THE AGENDA. IF YOU PARTICIPATE BY TELEPHONE, YOU MAY SUBMIT ANY COMMENTS VIA THE E-COMMENT EMAIL ADDRESS DESCRIBED ABOVE OR PROVIDE COMMENT DURING THE MEETING AT THE END OF EACH TOPIC.

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

AGENDA

ITEM	DESCRIPTION	TIME	VOTE
I)	**Call to order** *Donna Carey, MD, Interim Chief Medical Officer – Alameda Alliance* • Conflict of Interest Check/Disclosure • Agenda Overview	2 min	-
II)	**Informational Updates** *Donna Carey, MD, Interim Chief Medical Officer – Alameda Alliance* *Helen Lee, PharmD, MBA, Senior Pharmacy Director – Alameda Alliance* • Anthem • ICF-DD, Adult Expansion • CAL-AIM initiatives • DHCS Routine Survey • CGM • Medi-Cal Rx • Medi-Cal Rx MCDAC (See Next Page)	15 min	-
III)	**Pharmacy Utilization Reports (Quarter 4, 2023)** *Helen Lee, PharmD MBA, Senior Pharmacy Director – Alameda Alliance* • Top 50 Drugs by Cost • Top 50 PA Reviewed Drugs	2 min	-

MCDAC Drug	Indication	CDL Status	Recommendation Based on - Safety, Efficacy, Essential Need, Misuse Potential, etc.
Amjevita (adalimumab-atto) 20mg/0.4ml prefilled syringe, 40mg/0.8ml prefilled syringe and 40mg/0.8ml prefilled sureclick autoinjector	Rheumatoid Arthritis (RA), Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease (CD), Ulcerative Colitis (UC) and Plaque Psoriasis	F-PA	Keep F-PA
Emflaza (deflazacort) 6mg, 18mg, 30mg, 36mg and 22.75mg/ml suspension	Duchenne muscular dystrophy (DMD) in patients ≥ 2 years old	F-PA	Keep F-PA
Furoscix (furosemide) 80mg/10ml prefilled cartridge co-packaged w/one on-body infusor	Congestion due to fluid overload in adult patients with NYHA class II and class III chronic heart failure	F-PA	Keep F-PA
Inpefa (sotagliflozin) 200mg and 400mg tablets	Heart failure; Cardiovascular risk reduction	F-PA	Keep F-PA
Insulin aspart vial 100u/ml 10ml vial, 100 u/ml penfill 3ml, 100u/ml flexpen 3ml	Type 1 and Type 2 Diabetes	F	Keep F
Insulin aspart protamine-Insulin aspart mix 70/30 suspension 10ml vial and 3ml flexpen	Type 1 and Type 2 Diabetes	F	Keep F
Radicava (edaravone) ORS and Radicava ORS starter kit	Amyptotrophic lateral sclerosis (ALS)	F-PA	Keep F-PA
Zepbound (tirzepatide) 2.5mg/0.5ml, 5mg/0.5ml, 7.5mg/0.5ml, 10mg/0.5ml, 12.5mg/0.5ml, and 15mg/0.5ml pen	Chronic weight management	F-PA	Keep F-PA

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: 3/19/2024 *(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

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

10 min EV

Monographs/Class Reviews	Changes
Inhaled Corticosteroids/Long-Acting Beta-Agonists (ICS/LABA) class review	• No changes

First generation antihistamines class review	• No changes
Opioid containing antitussives class review	• No changes
Zepbound monograph	• No changes
Methergine monograph	• No changes
Medication Request Guidelines	**Changes**
Inhaled Corticosteroids/Long-Acting Beta-Agonists (ICS/LABA) Combinations MRG (part of ICS/LABA class review)	• Change Advair HF to reflect generic availability • Add new NF medication Airsupra
Oxbryta (voxelotor)	• Minor formatting updates
Angiotensin II Receptor Blockers and Renin Inhibitors	• Remove eprosartan and Tekturna from policy. Off market.
Histamine H2 Receptor Antagonists	• Cimetidine 300 mg/5 ml oral solution is discontinued. Remove from policy.
Ophthalmic Antihistamines	• No changes
Verquvo	• No changes
Siklos (hydroxyurea)	• No changes
Tadalafil (Cialis) for BPH	• No changes
Altoprev (lovastatin ER) and Fluvastatin, Fluvastatin ER	• No changes
Arikayce (amikacin)	• No changes
Long-Acting Muscarinic /Long-Acting Beta Agonist/ Corticosteroid inhaled Triple Combination Products	• No changes
Savella (milnacipran) tablet	• No changes
Fexofenadine-pseudoephedrine	• No changes
Injectable Anticoagulants	• No changes
Atovaquone (Mepron)	• No changes
Thrombocytopenia Agents	• No changes
Travoprost (Travatan Z) ophthalmic drops	• No changes
Pyridostigmine (Mestinon)	• No changes
Antifibrotic Respiratory Tract Agents	• No changes
Cystic Fibrosis Agents	• No changes
Elmiron (pentosane polysulfate	• No changes
Linezolid	• No changes

Symlin (pramlintide)	• No changes
Corticosteroid Preparations to Treat Hemorrhoids	• No changes
Physician Administered Drug (PAD) Guidelines	**Changes**
Emergency Use Authorization (EUA) Drugs/Products for COVID-19	• Add in formulation check for appropriateness
Tzield	• No changes
Ophthalmic indications for bevacizumab	• No changes
Interim Formulary Updates	
• See p. 137 in packet	
Summary of PAD Updates	
• See p. 140 in packet	
Pharmacy Policy & Procedure Updates	
• RX-001 – RX-014	• Format updates and Annual Review
ED Oversight Updates	
• None	
90 Day Maintenance List Updates	
• None	
P&T Meeting Minutes	
• P&T Meeting Minutes Q4 December 19, 2023	

V) New Business

Natalee Felten, PharmD, Pharmacist – PerformRx

New PADs

- Pompe disease agents
- Zulresso
- Adzynma

New MRGs

- Presbyopia Agents
- Zurzuvae
- Dificid
- Fabhalta

VI) Class Reviews, Monographs, and Recommendations

Natalee Felten, PharmD, Pharmacist – PerformRx

45 min V

1. Casgevy monograph
2. Lyfgenia monograph
    a. New PAD: Gene Therapy for Sickle Cell Disease
3. Direct oral anticoagulants class review
4. SGLT2s class review

VII)	**Medication Request Guidelines** *Rahel Negash, PharmD, Pharmacist – Alameda Alliance* 1. Emflaza 2. Corlanor (ivabradine) 3. Ezetimibe (Zetia) 4. Estrogen Patches and Injectables - RETIRE 5. Pulmonary Arterial Hypertension (PAH) Criteria 6. Brilinta (ticagrelor) tablet 7. GLP-1 Agonists, SGLT2 inhibitors, DPP-4 Inhibitors and Combinations 8. Parkinson's Disease Agents 9. PCSK-9 Monoclonal Antibodies (mAbs) 10. Xolair (omalizumab) for Asthma and Urticaria 11. Agents for Atopic Dermatitis 12. Pulmonary Biologics for Asthma and Eosinophilic Conditions 13. Biologic Agents for Nasal Polyposis		
VIII)	**Physician Administered Drug (PAD) Policies** *Natalee Felten, PharmD, Pharmacist – PerformRx* 1. Oxlumo (lumasiran) 2. Rituximab 3. Immunoglobulin Therapy (IVIG) 4. Reblozyl (luspatercept-aamt)	10 min	V
IX)	**Informational Updates on New Developments in Pharmacy** *Natalee Felten, PharmD, Pharmacist – PerformRx* • New Product Review	2 min	-
X)	**Old Business** *Natalee Felten, PharmD, Pharmacist – PerformRx* • None	2 min	-
	RECONVENE IN OPEN SESSION		
XI)	**Public Comment**		
XII)	**Adjournment**		

PHARMACY & THERAPEUTICS COMMITTEE

Tuesday, March 19th 2024
5:00pm – 7:00pm

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

FUTURE P&T MEETINGS	
NEXT MEETING	**2024 P&T MEETINGS**
June 11 2024	September 24, 2024
	December 17, 2024

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 Helen Lee at 510-747- 6241 or hlee@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 4th Quarter 2023

- The top 50 drugs accounted for **1,474 claims** for **1,011 members** and cost **$1,119,278,** which is a decrease of $7,941 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.
- Vemlidy is up to number 2 with 44 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 3, 4 and 28, with 141 total claims for 72 members. There was an increase of 8 claims and of 4 members from the previous quarter.
- Tagrisso is at number 5 with 3 claims for one member. Utilization has not changed since 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	25	9	$91,700.93
2	195609	Vemlidy Oral Tablet 25 MG	44	19	$69,242.38
3	221271	Ozempic (0.25 or 0.5 MG/DOSE) Subcutaneous Solution Pen-injector 2 MG/3ML	69	35	$62,221.82
4	209911	Ozempic (1 MG/DOSE) Subcutaneous Solution Pen-injector 4 MG/3ML	55	26	$49,470.05
5	190947	Tagrisso Oral Tablet 80 MG	3	1	$47,468.35
6	214809	Skyrizi Pen Subcutaneous Solution Auto-injector 150 MG/ML	2	2	$38,807.70
7	193034	Ocaliva Oral Tablet 5 MG	4	1	$35,670.20
8	170343	Jakafi Oral Tablet 5 MG	2	1	$33,547.06
9	177191	Eliquis Oral Tablet 5 MG	54	20	$28,827.69
10	165796	Abiraterone Acetate Oral Tablet 250 MG	4	1	$27,917.60
11	199757	Verzenio Oral Tablet 50 MG	2	1	$27,874.64
12	122702	Januvia Oral Tablet 100 MG	52	19	$27,010.38

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
13	190802	Genvoya Oral Tablet 150-150-200-10 MG	7	2	$26,136.12
14	207961	Rybelsus Oral Tablet 7 MG	27	12	$24,363.36
15	223763	Arexvy Intramuscular Suspension Reconstituted 120 MCG/0.5ML	81	81	$23,058.21
16	185813	Trulicity Subcutaneous Solution Pen-injector 1.5 MG/0.5ML	24	10	$21,600.89
17	224366	Spikevax Intramuscular Suspension Prefilled Syringe 50 MCG/0.5ML	127	127	$20,928.46
18	139308	Promacta Oral Tablet 25 MG	3	1	$19,883.25
19	219135	Skyrizi Subcutaneous Solution Cartridge 360 MG/2.4ML	1	1	$19,522.26
20	192429	Taltz Subcutaneous Solution Auto-injector 80 MG/ML	3	1	$19,516.62
21	185810	Trulicity Subcutaneous Solution Pen-injector 0.75 MG/0.5ML	21	7	$18,874.10
22	201117	Steglatro Oral Tablet 15 MG	56	26	$17,920.35
23	216866	Comirnaty Intramuscular Suspension 30 MCG/0.3ML	115	115	$17,637.15
24	201116	Steglatro Oral Tablet 5 MG	50	23	$17,589.42
25	207962	Rybelsus Oral Tablet 14 MG	19	7	$17,165.98
26	182488	Glatiramer Acetate Subcutaneous Solution Prefilled Syringe 40 MG/ML	3	1	$16,013.49
27	224365	Comirnaty Intramuscular Suspension Prefilled Syringe 30 MCG/0.3ML	99	99	$15,753.40
28	218338	Ozempic (2 MG/DOSE) Subcutaneous Solution Pen-injector 8 MG/3ML	17	11	$15,299.66
29	204204	Shingrix Intramuscular Suspension Reconstituted 50 MCG/0.5ML	78	77	$15,213.68
30	197908	Tymlos Subcutaneous Solution Pen-injector 3120 MCG/1.56ML	6	2	$14,722.08

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
31	170142	Xarelto Oral Tablet 20 MG	24	11	$14,289.01
32	199760	Verzenio Oral Tablet 200 MG	1	1	$14,111.72
33	120505	Sprycel Oral Tablet 20 MG	1	1	$14,081.85
34	219119	Spikevax Intramuscular Suspension 50 MCG/0.5ML	85	85	$14,010.85
35	199758	Verzenio Oral Tablet 100 MG	1	1	$13,937.32
36	197146	Cosentyx Sensoready (300 MG) Subcutaneous Solution Auto-injector 150 MG/ML	2	1	$13,596.94
37	202548	Humira Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	1	1	$13,442.57
38	225702	Humira (2 Pen) Subcutaneous Pen-injector Kit 40 MG/0.8ML	2	1	$13,427.56
39	182336	Farxiga Oral Tablet 10 MG	25	11	$13,408.79
40	212379	Cabenuva Intramuscular Suspension Extended Release 600 & 900 MG/3ML	2	2	$11,940.58
41	218096	Rinvoq Oral Tablet Extended Release 24 Hour 45 MG	1	1	$11,303.81
42	217440	Apretude Intramuscular Suspension Extended Release 600 MG/3ML	3	2	$11,237.97
43	127437	FreeStyle Lite Test In Vitro Strip	137	81	$10,886.79
44	184849	Jardiance Oral Tablet 25 MG	19	11	$10,731.44
45	93533	Entecavir Oral Tablet 0.5 MG	27	15	$10,445.55
46	205122	Actemra ACTPen Subcutaneous Solution Auto-injector 162 MG/0.9ML	3	1	$10,425.63
47	192096	Odefsey Oral Tablet 200-25-25 MG	3	1	$10,178.94
48	176224	Linzess Oral Capsule 145 MCG	20	8	$9,782.33

Rank	DDID	Label Name	Claims	Unique Members	Total Cost
49	183204	Otezla Oral Tablet 30 MG	2	1	$9,014.92
50	215736	Insulin Glargine-yfgn Subcutaneous Solution Pen-injector 100 UNIT/ML	62	37	$8,066.66
TOTAL			**1,474**	**1,011**	**$1,119,278.51**

Medi-Cal Top 50 Drugs by Cost for 4th Quarter 2023

- The top 50 drugs accounted for **31,667 claims** for **27,121 members** and cost **$41,548,265.19,** which is an increase of $1,442,357.83 in spend from the previous quarter.
- Ozempic has fallen from the number 2 to number 3, with 1,474 claims for 1,182 members. This is a decrease of 10 claims from last quarter.
- Humira is down to number 4 from the number 3 spot with 109 claims for 87 members. This is a decrease of 8 claims since last quarter.
- Stelara has moved up to the number 2 spot from number 5, with 56 claims for 40 members. This is an increase of 14 claims from last quarter.
- Jardiance 25mg has fallen from number 4 to number 5 with 1,397 claims for 1,310 members. This is an increase of 47 claims from last quarter.
- Biktarvy remains at the number 1 spot with 676 claims for 543 members. An increase of 29 claims from last quarter.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	44426	BIKTARVY 50-200-25 MG TABLET	676	543	$4,625,183.00
2	28159	STELARA 90 MG/ML SYRINGE	56	40	$2,099,404.00
3	53536	OZEMPIC 0.25-0.5 MG/DOSE PEN	1474	1182	$1,974,148.49
4	43506	HUMIRA(CF) PEN 40 MG/0.4 ML	109	87	$1,933,617.41
5	36723	JARDIANCE 25 MG TABLET	1397	1310	$1,850,045.62
6	36716	JARDIANCE 10 MG TABLET	1151	1047	$1,473,543.88
7	48208	OZEMPIC 1 MG/DOSE (4 MG/3 ML)	821	683	$1,390,989.13
8	49591	SKYRIZI 150 MG/ML PEN	60	55	$1,249,293.27
9	42624	VEMLIDY 25 MG TABLET	360	313	$1,169,418.16
10	97400	JANUVIA 100 MG TABLET	705	648	$988,401.96
11	48277	DUPIXENT 300 MG/2 ML PEN	137	109	$986,409.34
12	27418	INVEGA SUSTENNA 234 MG/1.5 ML	144	104	$858,361.46
13	40133	TAGRISSO 80 MG TABLET	26	21	$826,320.69

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
14	33935	ELIQUIS 5 MG TABLET	740	608	$791,329.10
15	97724	ENBREL 50 MG/ML SURECLICK	59	47	$787,212.56
16	37789	COSENTYX SNRDY 300MG DOSE-2PEN	55	42	$773,706.03
17	25200	FREESTYLE LITE TEST STRIP	3824	3537	$762,603.77
18	40092	GENVOYA TABLET	100	82	$742,850.21
19	49099	CABENUVA ER 600 MG-900 MG SUSP	95	83	$733,199.08
20	97005	HUMIRA PEN 40 MG/0.8 ML	58	48	$723,423.00
21	47136	TRIKAFTA 100-50-75 MG/150 MG	16	11	$709,313.33
22	46965	RYBELSUS 7 MG TABLET	346	321	$689,188.06
23	44014	HUMIRA(CF) PEN 80 MG/0.8 ML	20	14	$672,573.80
24	98637	BASAGLAR 100 UNIT/ML KWIKPEN	1273	1059	$641,648.45
25	34394	FARXIGA 10 MG TABLET	468	414	$614,559.04
26	22913	ALBUTEROL HFA 90 MCG INHALER	13546	11403	$593,453.09
27	40953	DESCOVY 200-25 MG TABLET	166	132	$590,267.27
28	43968	SYMTUZA 800-150-200-10 MG TAB	73	59	$571,650.95
29	47426	VYONDYS-53 100 MG/2 ML VIAL	2	2	$556,879.20
30	49754	WEGOVY 2.4 MG/0.75 ML PEN	230	181	$507,021.73
31	37633	ODEFSEY TABLET	75	64	$498,681.87
32	37682	ABILIFY MAINTENA ER 400 MG SYR	107	80	$496,664.15
33	52125	OZEMPIC 2 MG/DOSE (8 MG/3 ML)	304	271	$496,397.71
34	37171	TRULICITY 1.5 MG/0.5 ML PEN	302	267	$488,723.62

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
35	46966	RYBELSUS 14 MG TABLET	232	209	$482,861.74
36	37169	TRULICITY 0.75 MG/0.5 ML PEN	315	261	$474,324.09
37	38702	INVEGA TRINZA 819 MG/2.63 ML	49	47	$473,278.61
38	36999	TRIUMEQ 600-50-300 MG TABLET	70	61	$456,390.68
39	43222	DUPIXENT 300 MG/2 ML SYRINGE	59	49	$448,596.22
40	36172	OTEZLA 30 MG TABLET	48	43	$438,295.07
41	37789	COSENTYX SENSOREADY 150 MG PEN	23	16	$426,530.09
42	47258	IBRANCE 125 MG TABLET	14	11	$406,431.70
43	44495	ZTLIDO 1.8% TOPICAL SYSTEM	983	871	$404,599.89
44	43505	HUMIRA(CF) 40 MG/0.4 ML SYRING	23	16	$403,627.89
45	30819	XARELTO 20 MG TABLET	344	303	$398,460.33
46	43699	MAVYRET 100-40 MG TABLET	25	23	$392,465.15
47	43148	ILARIS 150 MG/ML VIAL	6	6	$374,395.73
48	97472	ZINC SULFATE POWDER	491	331	$374,277.65
49	44106	HEMLIBRA 105 MG/0.7 ML VIAL	4	3	$364,412.80
50	54456	FERRIPROX 1,000 MG TAB(2X/DAY)	6	4	$362,835.12
TOTAL			**31,667**	**27,121**	**$41,548,265.19**

636 IHSS Top 50 Prior Authorization Requests by Volume for 4th Quarter 2023

- Top 50 PA requests = 134. There were 191 total PA requests for quarter 4.
  - 64 requests (48%) were approved. This approval rate is lower, by 1%, than what was observed last quarter.
  - 70 requests (52%) were denied or partially approved.
- Jardiance 10mg is at numbers 1 & 2 with 20 total requests and 10 approvals (50%).
  - The formulary alternative is Steglatro, with trial and failure of metformin.
- Vemlidy 25 mg is down to number 3 and had a total of 9 requests, from which there were 6 approvals (67%).
  - Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets.
- Entecavir is at number 4 with 8 requests and 3 approvals (38%). This is 3 more requests than the previous quarter.
  - Entecavir requires a diagnosis of Hepatitis B and an appropriate dose
- Lidocaine 5% patch is at number 5 and had 7 requests with 3 approvals (43%).
  - This medication 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 $\leq$ 50 for 3 months.
- Linzess, Ozempic 0.25-0.5mg/dose, and Restasis all have 4 requests.
  - Linzess requires a diagnosis of irritable bowel syndrome with constipation (IBS-C) with trial and failure of soluble fiber OR a diagnosis of chronic idiopathic constipation with trial and failure of soluble fiber and 2 other formulary laxatives.
  - Ozempic requires a trial and failure of metformin.
  - Restasis multidose requires trial and failure of cyclosporine (Restasis) 0.05% dropperette (generic) and two different artificial tear products, one of which must be high viscosity artificial tears.

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
1	Jardiance Oral Tablet 10 MG	10	4	40%	5	50%	1	10%
2	Jardiance Oral Tablet 25 MG	10	6	60%	4	40%	0	0%
3	Vemlidy Oral Tablet 25 MG	9	6	67%	2	22%	1	11%
4	Entecavir Oral Tablet 0.5 MG	8	3	38%	0	0%	5	63%
5	Lidocaine External Patch 5 %	7	3	43%	3	43%	1	14%
6	Linzess Oral Capsule 145 MCG	4	4	100%	0	0%	0	0%
7	Ozempic (0.25 or 0.5 MG/DOSE) Subcutaneous Solution Pen-injector 2 MG/3ML	4	0	0%	4	100%	0	0%
8	Restasis Ophthalmic Emulsion 0.05 %	4	3	75%	1	25%	0	0%

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
9	Emgality Subcutaneous Solution Auto-injector 120 MG/ML	3	1	33%	1	33%	1	33%
10	Rybelsus Oral Tablet 3 MG	3	2	67%	1	33%	0	0%
11	Skyrizi Pen Subcutaneous Solution Auto-injector 150 MG/ML	3	0	0%	3	100%	0	0%
12	Trelegy Ellipta Inhalation Aerosol Powder Breath Activated 100-62.5-25 MCG/ACT	3	1	33%	2	67%	0	0%
13	Tretinoin External Cream 0.025 %	3	0	0%	3	100%	0	0%
14	Wegovy Subcutaneous Solution Auto-injector 0.25 MG/0.5ML	3	1	33%	2	67%	0	0%
15	Wegovy Subcutaneous Solution Auto-injector 0.5 MG/0.5ML	3	1	33%	2	67%	0	0%
16	ZTlido External Patch 1.8 %	3	0	0%	3	100%	0	0%
17	Armour Thyroid Oral Tablet 90 MG	2	2	100%	0	0%	0	0%
18	Basaglar KwikPen Subcutaneous Solution Pen-injector 100 UNIT/ML	2	1	50%	1	50%	0	0%
19	Bimatoprost Ophthalmic Solution 0.03 %	2	0	0%	2	100%	0	0%
20	cycloSPORINE Ophthalmic Emulsion 0.05 %	2	1	50%	1	50%	0	0%
21	Esomeprazole Magnesium Oral Capsule Delayed Release 40 MG	2	1	50%	1	50%	0	0%
22	Euflexxa Intra-articular Solution Prefilled Syringe 20 MG/2ML	2	1	50%	1	50%	0	0%
23	Farxiga Oral Tablet 10 MG	2	2	100%	0	0%	0	0%
24	Linzess Oral Capsule 290 MCG	2	1	50%	1	50%	0	0%
25	Lumigan Ophthalmic Solution 0.01 %	2	1	50%	0	0%	1	50%
26	Mounjaro Subcutaneous Solution Pen-injector 2.5 MG/0.5ML	2	0	0%	2	100%	0	0%
27	Phentermine HCl Oral Tablet 37.5 MG	2	1	50%	1	50%	0	0%
28	Rybelsus Oral Tablet 7 MG	2	1	50%	1	50%	0	0%
29	Siliq Subcutaneous Solution Prefilled Syringe 210 MG/1.5ML	2	2	100%	0	0%	0	0%
30	Sutab Oral Tablet 1479-225-188 MG	2	0	0%	2	100%	0	0%

RANK	DRUGS	Total	Approved		Denied		Partially Approved	
31	Tranexamic Acid Oral Tablet 650 MG	2	2	100%	0	0%	0	0%
32	Victoza Subcutaneous Solution Pen-injector 18 MG/3ML	2	0	0%	2	100%	0	0%
33	Wegovy Subcutaneous Solution Auto-injector 1 MG/0.5ML	2	1	50%	1	50%	0	0%
34	Wegovy Subcutaneous Solution Auto-injector 1.7 MG/0.75ML	2	2	100%	0	0%	0	0%
35	Xifaxan Oral Tablet 550 MG	2	2	100%	0	0%	0	0%
36	Zavzpret Nasal Solution 10 MG/ACT	2	0	0%	1	50%	1	50%
37	Abiraterone Acetate Oral Tablet 250 MG	1	0	0%	0	0%	1	100%
38	Acyclovir External Cream 5 %	1	0	0%	1	100%	0	0%
39	Admelog SoloStar Subcutaneous Solution Pen-injector 100 UNIT/ML	1	1	100%	0	0%	0	0%
40	ALPRAZolam Oral Tablet 0.5 MG	1	0	0%	1	100%	0	0%
41	ALPRAZolam Oral Tablet 1 MG	1	1	100%	0	0%	0	0%
42	Atovaquone-Proguanil HCl Oral Tablet 250-100 MG	1	1	100%	0	0%	0	0%
43	Baraclude Oral Tablet 0.5 MG	1	1	100%	0	0%	0	0%
44	BD Pen Needle Nano U/F Miscellaneous 32G X 4 MM	1	0	0%	0	0%	1	100%
45	Betamethasone Dipropionate Aug External Ointment 0.05 %	1	1	100%	0	0%	0	0%
46	Breztri Aerosphere Inhalation Aerosol 160-9-4.8 MCG/ACT	1	1	100%	0	0%	0	0%
47	Buprenorphine HCl-Naloxone HCl Sublingual Film 8-2 MG	1	1	100%	0	0%	0	0%
48	Candesartan Cilexetil Oral Tablet 4 MG	1	0	0%	1	100%	0	0%
49	Cholestyramine Oral Packet 4 GM	1	0	0%	1	100%	0	0%
50	Cimetidine Oral Tablet 400 MG	1	1	100%	0	0%	0	0%
TOTAL		**134**	**64**	**48%**	**57**	**42%**	**13**	**10%**

Medi-Cal Top 50 Prior Authorization Requests by Volume for 4th Quarter 2023

- The top 50 drugs accounted for **179,112 claims** for **160,306 members** and cost **$3,981,958.05.**
- Albuterol remains at the number 1 spot with 13,546 claims for 11,403 members. An increase of 2,268 claims from last quarter.
- Ibuprofen moved up to number 2 from number 3 with 7,845 claims for 7,104 members. This is an increase of 108 claims from last quarter.
- Fluticasone remains at number 4 with 7,384 claims for 6,819 members. There was an increase of 116 claims from last quarter.
- Aspirin has fallen from number 2 to number 3 with 7,839 claims for 7,265 members. This is a decrease of 56 claims from last quarter.
- Diclofenac gel has risen from the number 7 spot to number 5 with 5,441 claims for 4,785 members. This is an increase of 505 claims from last quarter.

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
1	22913	ALBUTEROL HFA 90 MCG INHALER	13546	11403	$593,453.09
2	35742	IBUPROFEN 600 MG TABLET	7845	7104	$111,546.36
3	00161	ASPIRIN EC 81 MG TABLET	7839	7265	$86,335.09
4	62263	FLUTICASONE PROP 50 MCG SPRAY	7384	6819	$149,107.28
5	45680	DICLOFENAC SODIUM 1% GEL	5441	4785	$146,787.22
6	60563	LORATADINE 10 MG TABLET	5184	4599	$86,106.31
7	16965	ACETAMINOPHEN 500 MG CAPLET	4875	4463	$64,675.71
8	02683	AMLODIPINE BESYLATE 5 MG TAB	4671	4265	$63,580.70
9	49291	CETIRIZINE HCL 10 MG TABLET	4614	4183	$75,310.71
10	43722	ATORVASTATIN 40 MG TABLET	4531	4176	$66,268.72
11	02682	AMLODIPINE BESYLATE 10 MG TAB	4335	3912	$60,762.99
12	43721	ATORVASTATIN 20 MG TABLET	3966	3717	$55,176.59
13	04348	OMEPRAZOLE DR 20 MG CAPSULE	3839	3327	$60,396.08

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
14	25200	FREESTYLE LITE TEST STRIP	3824	3537	$762,603.77
15	94444	MONTELUKAST SOD 10 MG TABLET	3712	3397	$53,906.19
16	10857	METFORMIN HCL 1,000 MG TABLET	3700	3442	$62,048.40
17	00781	GABAPENTIN 300 MG CAPSULE	3608	2994	$66,018.55
18	10810	METFORMIN HCL 500 MG TABLET	3566	3163	$55,754.61
19	46430	FAMOTIDINE 20 MG TABLET	3487	3089	$50,687.65
20	12486	HYDROCODONE-ACETAMIN 5-325 MG	3345	2429	$47,301.67
21	43720	ATORVASTATIN 10 MG TABLET	3250	3031	$44,055.17
22	86212	POLYETHYLENE GLYCOL 3350 POWD	3141	2915	$79,020.94
23	29840	BENZONATATE 100 MG CAPSULE	3135	2870	$42,892.98
24	40120	PANTOPRAZOLE SOD DR 40 MG TAB	3054	2577	$45,755.30
25	94422	VITAMIN D2 1.25MG(50,000 UNIT)	3030	2801	$45,652.00
26	53936	FLUCELVAX QUAD 2023-2024 SYR	2945	2945	$130,962.96
27	39661	AMOXICILLIN 500 MG CAPSULE	2924	2738	$39,410.79
28	35744	IBUPROFEN 800 MG TABLET	2831	2464	$45,370.53
29	20045	ONDANSETRON ODT 4 MG TABLET	2825	2569	$40,822.45
30	09101	DOCUSATE SODIUM 100 MG SOFTGEL	2801	2476	$37,557.35
31	00223	VITAMIN D3 25 MCG TABLET	2741	2582	$34,990.79
32	04695	FEROSUL 325 MG TABLET	2643	2390	$36,221.17
33	70330	HYDROCODONE-ACETAMIN 10-325 MG	2500	1113	$48,156.76

Rank	GCN	Label Name	Claims	Unique Members	Total Cost
34	35793	NAPROXEN 500 MG TABLET	2485	2222	$41,513.38
35	14851	LOSARTAN POTASSIUM 50 MG TAB	2485	2303	$34,916.70
36	16391	TRAZODONE 50 MG TABLET	2476	1944	$39,873.16
37	99882	VITAMIN D3 50 MCG SOFTGEL	2444	2348	$31,492.65
38	34824	HYDROCHLOROTHIAZIDE 25 MG TAB	2381	2168	$33,458.65
39	16965	ACETAMINOPHEN 500 MG TABLET	2331	2101	$24,936.27
40	94781	FOLIC ACID 1 MG TABLET	2295	1978	$38,886.99
41	48191	TAMSULOSIN HCL 0.4 MG CAPSULE	2280	2017	$33,902.95
42	31242	TRIAMCINOLONE 0.1% OINTMENT	2266	2121	$44,950.12
43	93375	AMOXICILLIN 400 MG/5 ML SUSP	2180	2111	$36,366.52
44	14850	LOSARTAN POTASSIUM 25 MG TAB	2172	1990	$28,930.89
45	35930	CHILDREN IBUPROFEN 100 MG/5 ML	2097	1945	$39,792.53
46	94200	FREESTYLE 28G LANCETS	2075	1997	$41,305.77
47	39802	CEPHALEXIN 500 MG CAPSULE	2072	1955	$31,001.77
48	35930	IBUPROFEN 100 MG/5 ML SUSP	2006	1880	$34,450.67
49	14853	LOSARTAN POTASSIUM 100 MG TAB	1993	1850	$30,154.12
50	35741	IBUPROFEN 400 MG TABLET	1942	1836	$27,328.03
TOTAL			**179,112**	**160,306**	**$3,981,958.05**

Inhaled Corticosteroid & Beta Agonist Combinations

Executive Summary

CLASS OVERVIEW

This review covers inhaled corticosteroids (ICS) in combination with long-acting beta agonists (LABAs) or short-acting beta agonists (SABAs) for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Asthma is a chronic inflammatory disorder of the airways, characterized by bronchial hyper-responsiveness leading to intermittent cough, wheezing and shortness of breath. Mainstay treatment options include SABAs, ICS inhalers, ICS-LABA combinations, leukotriene receptor antagonists (LTRAs) and the anticholinergic agents. Historically, treatment started with SABA products for those with mild or intermittent symptoms, although use of single maintenance and reliever therapy (MART/SMART) regimens are becoming increasingly recommended in the asthma treatment landscape.

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by airflow limitation leading to dyspnea, cough, sputum production, wheezing, and chest tightness. Mainstay treatment options include SABAs, short-acting muscarinic antagonists (SAMAs), LABAs and long-acting antimuscarinic antagonists (LAMAs). ICS products are also a part of therapy but should only be used in certain circumstances. The Global Initiative for Chronic Obstructive Lung Disease updated guidance on patient stratification and initial treatment recommendations in 2023, as well as a new proposed definition of COPD.

Various single-ingredient ICS products, LABA products, and combination ICS/LABA products are available. Selection of therapy is typically based on patient factors including age, preference, and previous experience in addition to insurance coverage. Recently generics for Symbicort and Advair HFA have been launched, and Dulera may follow suit sometime in 2023 or 2024 pending approval by the FDA of a generic product by Lupin. There is one novel ICS-LABA product in phase 3 development; a combination of beclomethasone and formoterol named Fostair. Breo Ellipta recently received an expanded indication for treatment of asthma in children down to 5 years of age; it was previously only approved for use in adults.

In January 2023, Airsupra (albuterol-budesonide) received FDA approval. This first-in-class product combines an inhaled corticosteroid with a short-acting bronchodilator and is approved for as-needed control and prevention of asthma symptoms in adults. It's labeled use is limited to as needed bronchodilation; a daily maintenance inhaler is still required. Consequently, GINA guidelines for 2023 include ICS-SABA (if available) as an alternative controller in adolescents and adults for Steps 3–5, with most of the benefit seen in Step 3. ICS-formoterol remains the preferred reliever option. This means Airsupra will compete with products such as generic Symbicort or inhaled ICS inhalers used alongside albuterol, which are both comparatively less costly than Airsupra.

UTILIZATION FINDINGS

There were 71 claims for 49 members totaling $10,167, for an average cost per claim of $143. The most highly utilized medication was fluticasone 100 mcg-salmeterol (Advair Diskus) blister powder for inhalation with 59 claims, followed by budesonide-formoterol (Symbicort) HFA actuation aerosol inhaler, with 9 claims. There was 1 prior authorization request with no approval.

RECOMMENDATIONS

- No changes

CLINICAL SUMMARY

Asthma

Asthma has classically been difficult to define in a manner acceptable to all disciplines (clinicians, physiologists and pathologists). The Expert Panel Report 3 (EPR-3) of the National Asthma Education and Prevention Program defines asthma as "a common chronic disorder of the airways that is complex and characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and an underlying inflammation. The interaction of these features of asthma determines the clinical manifestations and severity of asthma and the response to treatment." The Global Initiative for Asthma (GINA) defines asthma as "a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation."

Initial pharmacologic treatment of asthma depends largely on the severity and frequency of symptoms and occurs in a step-wise fashion up or down depending on the level of response/control achieved by a given intervention. For intermittent asthma symptoms, single-ingredient therapy with short-acting beta agonists (SABAs) had long been the standard of care for bronchodilation in acute control situations. However, recent evidence demonstrates that SABA-only treatment increases the risk of severe exacerbations and death and that the addition of an ICS when reliever therapy is administered reduces those risks. Additionally, indirect evidence from a large, double-blind study in patients with mild asthma comparing budesonide-formoterol as needed (PRN) to SABA-only PRN and SABA PRN + regular ICS supports the use of low dose combination ICS-formoterol (the ICS being either budesonide or [BDP]). Accordingly, GINA guidelines for adults and adolescents 12+ years have been updated to recommend ICS-formoterol as both the preferred “controller” and “reliever” regimens, a treatment regimen commonly known as MART or SMART [maintenance and reliever therapy]. GINA guidelines also recommend ICS-formoterol MART regimens in children 6-11 years as a preferred management option in step 3 and 4 of the treatment algorithm. Notably, this PRN use is not an FDA-approved, labeled use of ICS-formoterol products. Beyond clinical outcomes, GINA guidelines emphasize use of a single inhaler for controller and reliever therapy is advantageous from the perspective of a more simplified regimen for the patient to follow.

Asthma guidelines published by the National Asthma Education and Prevention Program (NAEPP) Expert panel report IV (EPR-4) have also recently updated pursuant to the new evidence, and MART therapy with ICS-formoterol is the recommended regimen for ages 5 and older in step 3 and step 4 of the asthma treatment guidelines. PRN use of SABA agents is still recommended in the NAEPP guidelines in mild asthma across age groups, taking a more traditional line than the GINA guidelines. Another notable update to both NAEPP and GINA guidelines includes adding on long-acting muscarinic agents (LAMAs) for later-line therapy in certain patients whose asthma is severe and uncontrolled. Further specifics regarding the applicable age groups and agents used can be found in individual guidelines.

COPD

The GOLD guidelines define COPD as “a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction.” Previous definitions of COPD included the subsets of chronic bronchitis, emphysema, and asthma. COPD is now considered to be a spectrum comprised of varying components of each of these. The newest definition is distinctly simplified and emphasizes the variability of the condition experienced from patient to patient, its progressive nature, and does not limit etiology to environmental causes (i.e. smoking or air pollution). Though environmental exposures may be the main cause, guidelines now recognize COPD to have genetic causes that increase risk in some patients. Spirometry that yields non-fully reversible airflow limitation (i.e., FEV1/FVC < 0.7 post-bronchodilation) in the presence of other risk factors clinically confirms COPD. Guidelines also now recognize precursor conditions such as pre-COPD (structural changes or respiratory symptoms without airflow obstruction), which put them at high risk for progression to COPD. The condition is common, preventable, and treatable.

Initial pharmacological treatment of COPD is based off the individualized assessment of symptoms and exacerbation risk following the ABE model, which replaces the ABCD model. Groups C and D have been combined into group E, which

contain patients experiencing heightened frequency or severity of exacerbations. Group A: mMRC 0-1, CAT <10 and 0-1 moderate exacerbations (not leading to hospital admission). Group B: mMRC ≥2, CAT ≥10 and 0-1 moderate exacerbations (not leading to hospital admission). Group E: any mMRC or CAT and ≥ 2 moderate exacerbations or ≥1 leading to hospital admission. Group A patients should be initiated on a bronchodilator, Group B patients should be initiated on a LABA + LAMA (either combined into a single inhaler or as two separate inhalers), and Group E patients can be initiated on a LABA + LAMA and consider LABA + LAMA + ICS if blood eosinophils are 300 or more. Following implementation of therapy, patients should be reassessed for attainment of treatment goals and identification of any barriers for successful treatment. If response to initial treatment is appropriate, maintain it. If not, consider the predominant treatable trait to target (dyspnea or exacerbations).

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Fluticasone/salmeterol (Advair® HFA)	Treatment of asthma	Age ≥ 12 years: Starting dose based on asthma severity, previous therapy, current control and risk of future exacerbation – 2 inhalations BID; maximum 2 inhalations of 230/21 mcg BID
Fluticasone/salmeterol (AirDuo® Respiclick, AirDuo® Digihaler)		Age ≥ 12 years: For patients not on an ICS – 1 inhalation (55/14 mcg) BID Starting dose based on asthma severity and previous therapy – 1 inhalation (55/14 mcg, 113/14 mcg, 232/14 mcg) BID; maximum 1 inhalation (232/14 mcg) BID
Dulera® (mometasone/formoterol)		Age 5-12 years: 2 inhalations (50 mcg/5 mcg) BID Age ≥ 12 years: Starting dose based on asthma severity, previous therapy, current control and risk of future exacerbation – 2 inhalations (100/5 mcg or 200/5 mcg) BID; maximum 2 inhalations (200/5 mcg) BID
Fluticasone/salmeterol (Advair® Diskus), Wixela Inhub® (fluticasone/salmeterol)	Treatment of asthma Maintenance treatment of COPD and to reduce exacerbations of COPD in adults	<u>Asthma</u> Age 4-11 years: For patients not controlled on an ICS alone – 1 inhalation (100/50 mcg) BID Age ≥ 12 years: Starting dose based on asthma severity, previous therapy, current control and risk of future exacerbation – 1 inhalation BID; maximum 500/50 mcg BID <u>COPD</u> 1 inhalation (250/50 mcg) BID; higher doses (e.g. 500/50 mcg BID) are not indicated due to lack of established efficacy advantage
Fluticasone/vilanterol (Breo® Ellipta®)		<u>Asthma</u> Age 5-11 years: 1 inhalation (50/25 mcg) QD Age 12-17 years: 1 inhalation 100/25 mcg) QD Age ≥ 18 years: Starting dose based on asthma severity, previous therapy, current control and risk of future exacerbation – 1 inhalation (100/25 mcg or 200/25 mcg) QD; maximum 1 inhalation (200/25 mcg) QD <u>COPD</u> 1 inhalation (100/25 mcg) QD; the 200/25 mcg dose is not indicated in this setting

Medication	Indications	Dosing/Administration
Budesonide/formoterol (Symbicort®, Breyna®)		Asthma Age 6-11 years: 2 inhalations (80/4.5 mcg) BID Age ≥ 12 years: 2 inhalations (80/4.5 mcg or 160/4.5 mcg) BID COPD 2 inhalations (160/4.5 mcg) BID
Airsupra® (albuterol sulfate/budesonide)	As-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in adult patients with asthma	Asthma Age ≥ 18 years: 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms; maximum 6 doses (12 inhalations) in a 24-hour period.

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Fluticasone/salmeterol (Advair® HFA) Dulera® (mometasone/formoterol)	None	Patients with status asthmaticus or other acute episodes of asthma where intensive measures are required. Hypersensitivity to component ingredients.
Fluticasone/salmeterol (AirDuo® Respiclick, AirDuo® Digihaler)		Patients with status asthmaticus or other acute episodes of asthma where intensive measures are required. Known or severe hypersensitivity to milk proteins or component ingredients.
Fluticasone/salmeterol (Advair Diskus) Wixela Inhub® (fluticasone/salmeterol) Fluticasone/vilanterol (Breo® Ellipta®)		Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. Known or severe hypersensitivity to milk proteins or component ingredients.
Budesonide/formoterol (Symbicort®, Breyna®)		Primary treatment of status asthmaticus or acute episodes of asthma or COPD requiring intensive measures. Hypersensitivity to component ingredients.
Airsupra® (albuterol sulfate/budesonide)	None	Hypersensitivity to component ingredients.

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Fluticasone/salmeterol (AirDuo® Respiclick, AirDuo® Digihaler) Dulera® (mometasone/formoterol) Fluticasone/salmeterol (Advair® Diskus, Advair® HFA) Wixela Inhub® (fluticasone/salmeterol) Fluticasone/vilanterol (Breo® Ellipta®) Budesonide/formoterol (Symbicort®, Breyna®)	Do not use for acute bronchospasm or acute episode of COPD Concerns related to adverse effects: adrenal suppression, asthma-related deaths, decreased bone density, bronchospasm, immunosuppression, lower respiratory infections, oral candidiasis, serious effects/fatalities, and vasculitis have been reported; Concerns related to disease states: cardiovascular diseases, diabetes, hepatic impairment, hypokalemia, ocular disease, seizures, and hyper or hypothyroidism; May increase the risk of asthma-related hospitalization for pediatrics/adolescents; May cause a reduction in growth velocity in pediatrics
Airsupra® (albuterol sulfate/budesonide)	Caution for markers of destabilization of asthma; paradoxical bronchospasm; cardiovascular effects; exceeding maximum dosage and fatality; hypersensitivity reactions; caution with convulsive disorders, hyperthyroidism, diabetes mellitus, ketoacidosis; potential hypokalemia; potential worsening of infections (tuberculosis, fungal, bacterial, viral, parasitic, herpes, measles); oropharyngeal candidiasis may occur; possible adrenal suppression and hypercorticism, decreased bone mineral density, possible glaucoma/cataracts

PRACTICE GUIDELINES

ASTHMA:

US National Heart Lung and Blood Institute 2020 Focused Updates to the Asthma Management Guidelines: Clinician's Guide. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/clinician-guide-2020-focused-updates-asthma-management-guidelines.

AGES 0–4 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 0–4 Years				
Treatment	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5	STEP 6
Preferred	PRN SABA and At the start of RTI: Add short course daily ICS▲	Daily low-dose ICS and PRN SABA	Daily low-dose ICS-LABA and PRN SABA▲ or Daily low-dose ICS + montelukast,* or daily medium-dose ICS, and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily montelukast* or Cromolyn,* and PRN SABA		Daily medium-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast* and PRN SABA	Daily high-dose ICS + montelukast*+ oral systemic corticosteroid and PRN SABA
			For children age 4 years only, see Step 3 and Step 4 on Management of Persistent Asthma in Individuals Ages 5–11 Years diagram.			

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 4–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 3 or higher is required. Consider consultation at Step 2.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting $beta_2$-agonist; SABA, inhaled short-acting $beta_2$-agonist; RTI, respiratory tract infection; PRN, as needed

▲ Updated based on the 2020 guidelines.

* Cromolyn and montelukast were not considered for this update and/or have limited availability for use in the United States. The FDA issued a Boxed Warning for montelukast in March 2020.

NOTES FOR INDIVIDUALS AGES 0–4 YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment. • Consider short course of oral systemic corticosteroid if exacerbation is severe or individual has history of previous severe exacerbations.

Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲

Notes	• If clear benefit is not observed within 4–6 weeks and the medication technique and adherence are satisfactory, the clinician should consider adjusting therapy or alternative diagnoses.

Abbreviations	EIB, exercise-induced bronchoconstriction; SABA, inhaled short-acting $beta_2$-agonist. ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.

AGES 5–11 YEARS: STEPWISE APPROACH FOR MANAGEMENT OF ASTHMA

	Intermittent Asthma	Management of Persistent Asthma in Individuals Ages 5–11 Years				
Treatment	**STEP 1**	**STEP 2**	**STEP 3**	**STEP 4**	**STEP 5**	**STEP 6**
Preferred	PRN SABA	Daily low-dose ICS and PRN SABA	Daily and PRN combination low-dose ICS-formoterol▲	Daily and PRN combination medium-dose ICS-formoterol▲	Daily high-dose ICS-LABA and PRN SABA	Daily high-dose ICS-LABA + oral systemic corticosteroid and PRN SABA
Alternative		Daily LTRA,* or Cromolyn,* or Nedocromil,* or Theophylline,* and PRN SABA	Daily medium-dose ICS and PRN SABA or Daily low-dose ICS-LABA, or daily low-dose ICS + LTRA,* or daily low-dose ICS +Theophylline,* and PRN SABA	Daily medium-dose ICS-LABA and PRN SABA or Daily medium-dose ICS + LTRA* or daily medium-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* or daily high-dose ICS + Theophylline,* and PRN SABA	Daily high-dose ICS + LTRA* + oral systemic corticosteroid or daily high-dose ICS + Theophylline* + oral systemic corticosteroid, and PRN SABA
		Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲			Consider Omalizumab**▲	

Assess Control

- First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
- **Step up** if needed; reassess in 2–6 weeks
- **Step down** if possible (if asthma is well controlled for at least 3 consecutive months)

Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.

Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

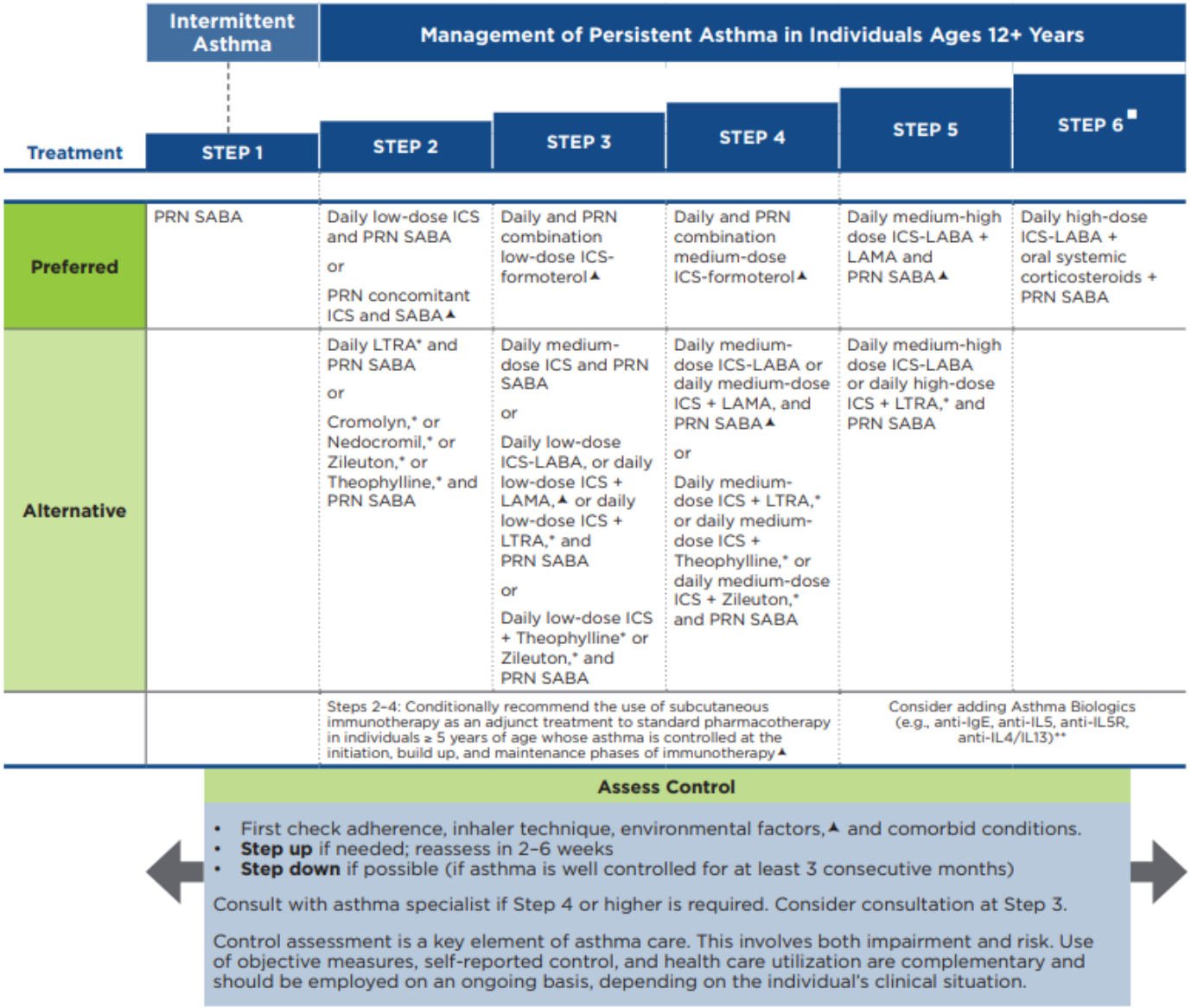
▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including montelukast, and Theophylline were not considered in this update and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

** Omalizumab is the only asthma biologic currently FDA-approved for this age range.

NOTES FOR INDIVIDUALS AGES 5–11 YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • In Steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 8 puffs (36 mcg).▲ • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.
Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲
Notes	• The terms ICS-LABA and ICS-formoterol indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler. • Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol. • In individuals ages 5–11 years with persistent allergic asthma in which there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, FeNO measurement is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessment.
Abbreviations	EIB (exercise-induced bronchoconstriction); FeNO (fractional exhaled nitric oxide); ICS (inhaled corticosteroid); LABA (long-acting $beta_2$-agonist); SABA (inhaled short-acting $beta_2$-agonist). ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.


Intermittent Asthma
Management of Persistent Asthma in Individuals Ages 12+ Years
Treatment
STEP 1
STEP 2
STEP 3
STEP 4
STEP 5
STEP 6
Preferred
PRN SABA
Daily low-dose ICS and PRN SABA
or
PRN concomitant ICS and SABA▲
Daily and PRN combination low-dose ICS-formoterol▲
Daily and PRN combination medium-dose ICS-formoterol▲
Daily medium-high dose ICS-LABA + LAMA and PRN SABA▲
Daily high-dose ICS-LABA + oral systemic corticosteroids + PRN SABA
Alternative
Daily LTRA* and PRN SABA
or
Cromolyn,* or Nedocromil,* or Zileuton,* or Theophylline,* and PRN SABA
Daily medium-dose ICS and PRN SABA
or
Daily low-dose ICS-LABA, or daily low-dose ICS + LAMA,▲ or daily low-dose ICS + LTRA,* and PRN SABA
or
Daily low-dose ICS + Theophylline* or Zileuton,* and PRN SABA
Daily medium-dose ICS-LABA or daily medium-dose ICS + LAMA, and PRN SABA▲
or
Daily medium-dose ICS + LTRA,* or daily medium-dose ICS + Theophylline,* or daily medium-dose ICS + Zileuton,* and PRN SABA
Daily medium-high dose ICS-LABA or daily high-dose ICS + LTRA,* and PRN SABA
Steps 2–4: Conditionally recommend the use of subcutaneous immunotherapy as an adjunct treatment to standard pharmacotherapy in individuals ≥ 5 years of age whose asthma is controlled at the initiation, build up, and maintenance phases of immunotherapy▲
Consider adding Asthma Biologics (e.g., anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13)**
Assess Control
First check adherence, inhaler technique, environmental factors,▲ and comorbid conditions.
Step up if needed; reassess in 2–6 weeks
Step down if possible (if asthma is well controlled for at least 3 consecutive months)
Consult with asthma specialist if Step 4 or higher is required. Consider consultation at Step 3.
Control assessment is a key element of asthma care. This involves both impairment and risk. Use of objective measures, self-reported control, and health care utilization are complementary and should be employed on an ongoing basis, depending on the individual's clinical situation.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; SABA, inhaled short-acting beta$_2$-agonist

▲ Updated based on the 2020 guidelines.

* Cromolyn, Nedocromil, LTRAs including Zileuton and montelukast, and Theophylline were not considered for this update, and/or have limited availability for use in the United States, and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The FDA issued a Boxed Warning for montelukast in March 2020.

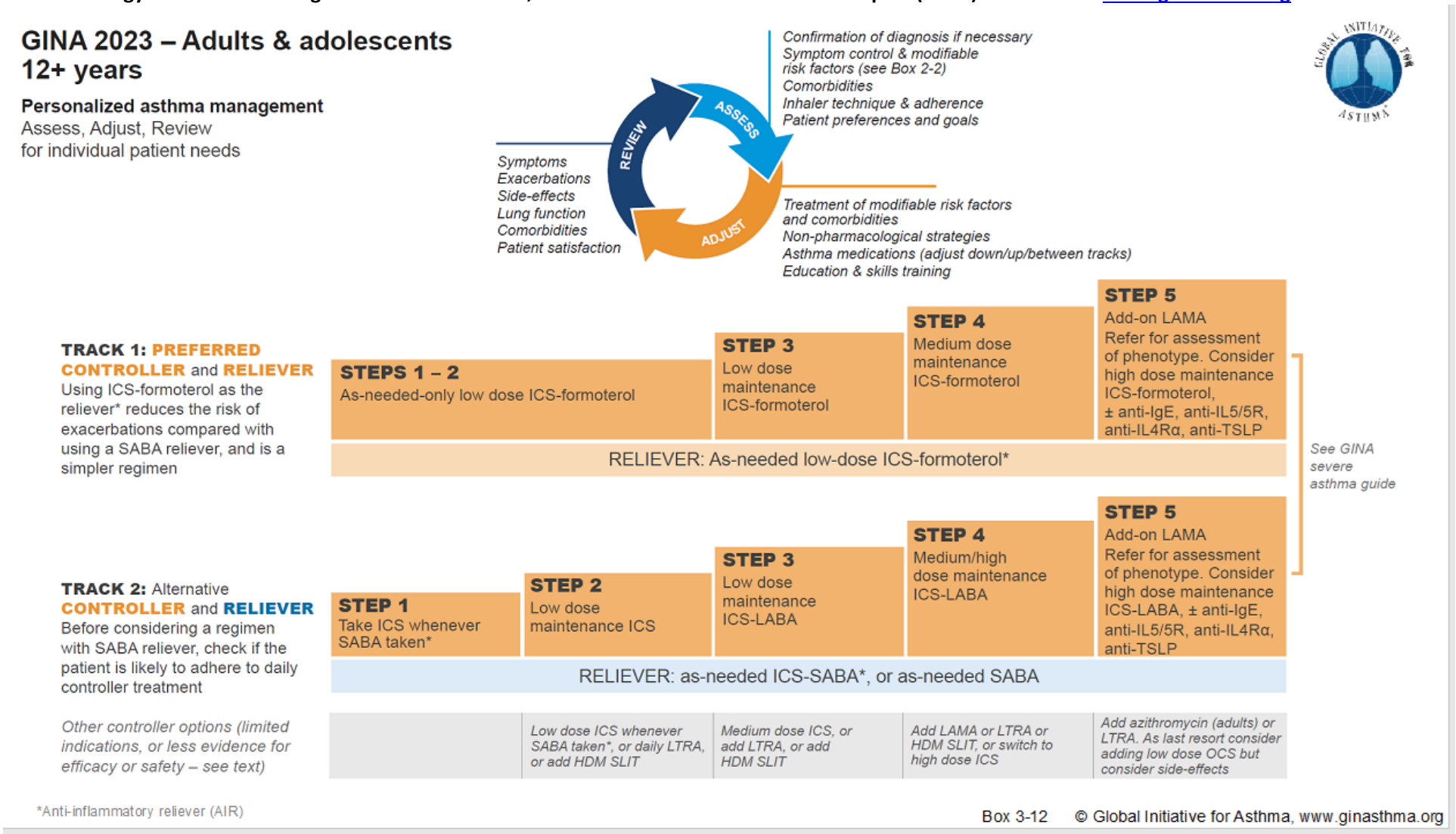
** The AHRQ systematic reviews that informed this report did not include studies that examined the role of asthma biologics (e.g. anti-IgE, anti-IL5, anti-IL5R, anti-IL4/IL13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in Steps 5 and 6.

■ Data on the use of LAMA therapy in individuals with severe persistent asthma (Step 6) were not included in the AHRQ systematic review and thus no recommendation is made.

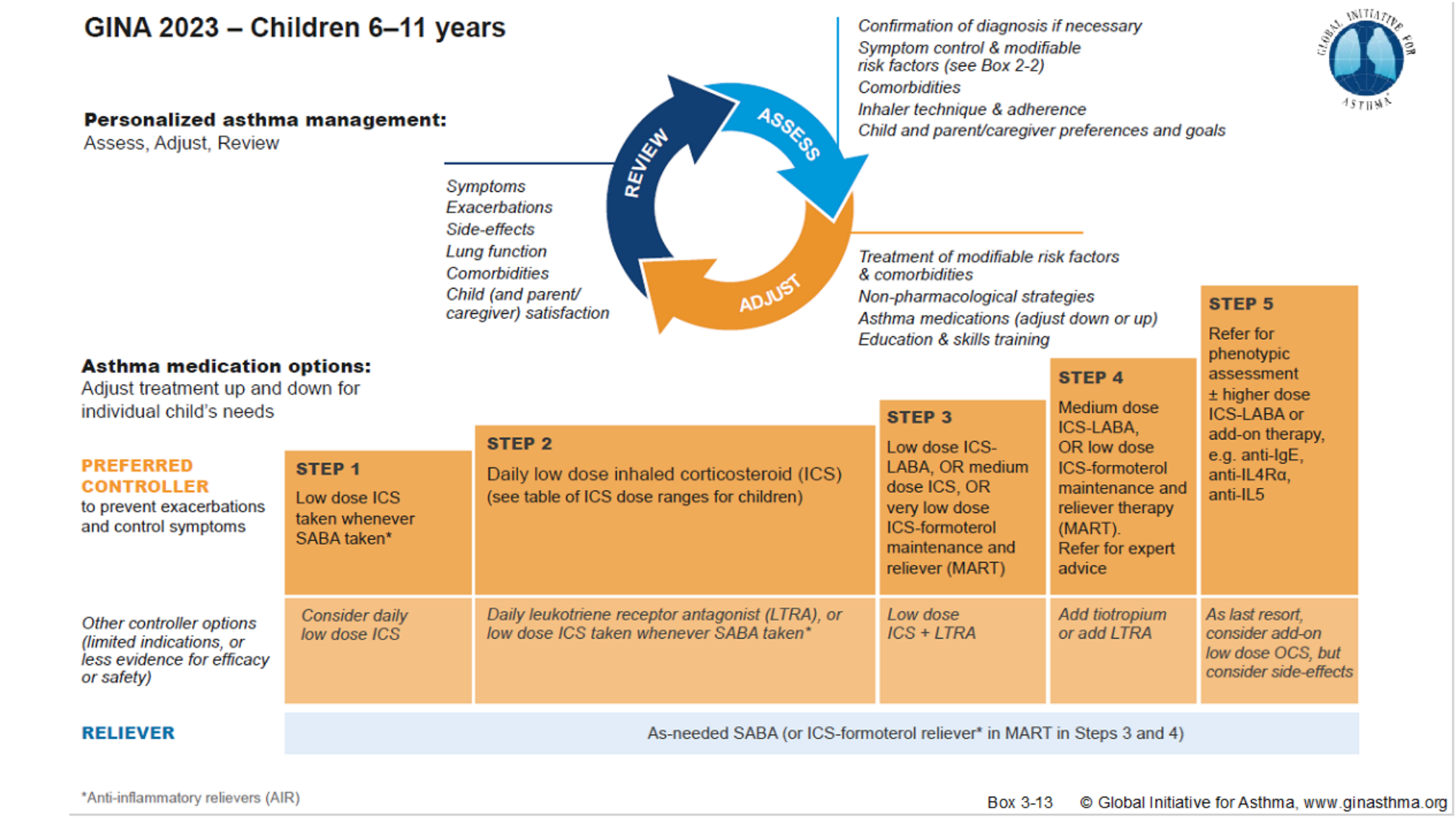
NOTES FOR INDIVIDUALS AGES 12+ YEARS DIAGRAM

Quick-relief medications	• Use SABA as needed for symptoms. The intensity of treatment depends on the severity of symptoms: up to 3 treatments at 20-minute intervals as needed. • In steps 3 and 4, the preferred option includes the use of ICS-formoterol 1 to 2 puffs as needed up to a maximum total daily maintenance and rescue dose of 12 puffs (54 mcg).▲ • **Caution:** Increasing use of SABA or use >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and may require a step up in treatment.
Each step: Assess environmental factors, provide patient education, and manage comorbidities▲	• In individuals with sensitization (or symptoms) related to exposure to pests‡: conditionally recommend integrated pest management as a single or multicomponent allergen-specific mitigation intervention.▲ • In individuals with sensitization (or symptoms) related to exposure to identified indoor allergens, conditionally recommend a multi-component allergen-specific mitigation strategy.▲ • In individuals with sensitization (or symptoms) related to exposure to dust mites, conditionally recommend impermeable pillow/mattress covers only as part of a multicomponent allergen-specific mitigation intervention, but not as a single component intervention.▲
Notes	• The terms ICS-LABA and ICS-formoterol indicate combination therapy with both an ICS and a LABA, usually and preferably in a single inhaler. • Where formoterol is specified in the steps, it is because the evidence is based on studies specific to formoterol. • In individuals ages 12 years and older with persistent allergic asthma in which there is uncertainty in choosing, monitoring, or adjusting anti-inflammatory therapies based on history, clinical findings, and spirometry, FeNO measurement is conditionally recommended as part of an ongoing asthma monitoring and management strategy that includes frequent assessment. • Bronchial thermoplasty was evaluated in Step 6. The outcome was a conditional recommendation against the therapy.
Abbreviations	EIB, exercise-induced bronchoconstriction; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; SABA, inhaled short-acting beta$_2$-agonist. ▲Updated based on the 2020 guidelines. ‡ Refers to mice and cockroaches, which were specifically examined in the Agency for Healthcare Research and Quality systematic review.

Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma 2023 Report (GINA). Available at www.ginasthma.org.



GINA 2023 – Children 6–11 years

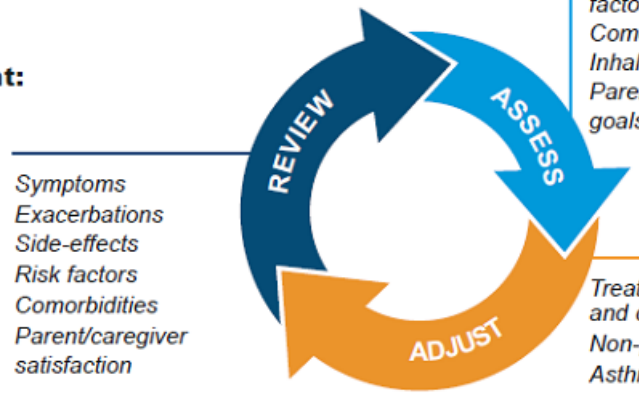


*Anti-inflammatory relievers (AIR)

Box 3-13

GINA 2023 – Children 5 years and younger

Personalized asthma management:
Assess, Adjust, Review response



Exclude alternative diagnoses
Symptom control & modifiable risk factors
Comorbidities
Inhaler technique & adherence
Parent/caregiver preferences and goals

Symptoms
Exacerbations
Side-effects
Risk factors
Comorbidities
Parent/caregiver satisfaction

Treat modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

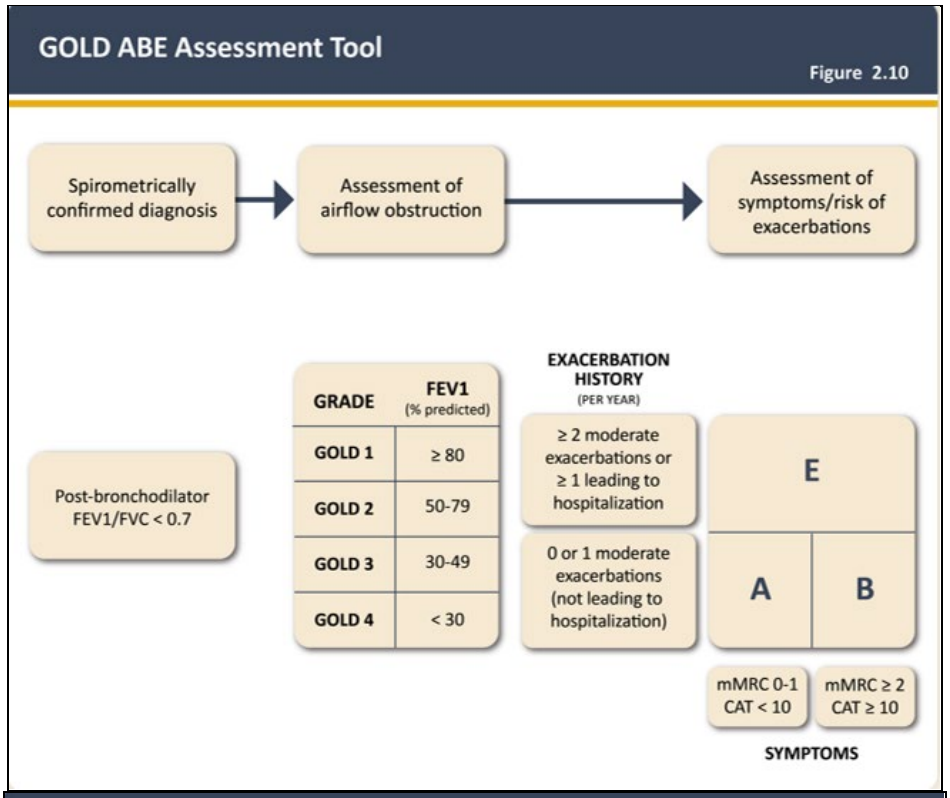
	STEP 1	STEP 2	STEP 3	STEP 4
PREFERRED CONTROLLER CHOICE	*(Insufficient evidence for daily controller)*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for pre-school children)	Double 'low dose' ICS *(See Box 6-7)*	Continue controller & refer for specialist assessment
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider intermittent short course ICS at onset of viral illness*	*Daily leukotriene receptor antagonist (LTRA), or intermittent short course of ICS at onset of respiratory illness*	*Low dose ICS + LTRA Consider specialist referral*	*Add LTRA, or increase ICS frequency, or add intermittent ICS*
RELIEVER	As-needed short-acting beta$_2$-agonist			
CONSIDER THIS STEP FOR CHILDREN WITH:	Infrequent viral wheezing and no or few interval symptoms	Symptom pattern not consistent with asthma but wheezing episodes requiring SABA occur frequently, e.g. ≥3 per year. Give diagnostic trial for 3 months. Consider specialist referral. Symptom pattern consistent with asthma, and asthma symptoms not well-controlled or ≥3 exacerbations per year.	Asthma diagnosis, and asthma not well-controlled on low dose ICS Before stepping up, check for alternative diagnosis, check inhaler skills, review adherence and exposures	Asthma not well-controlled on double ICS

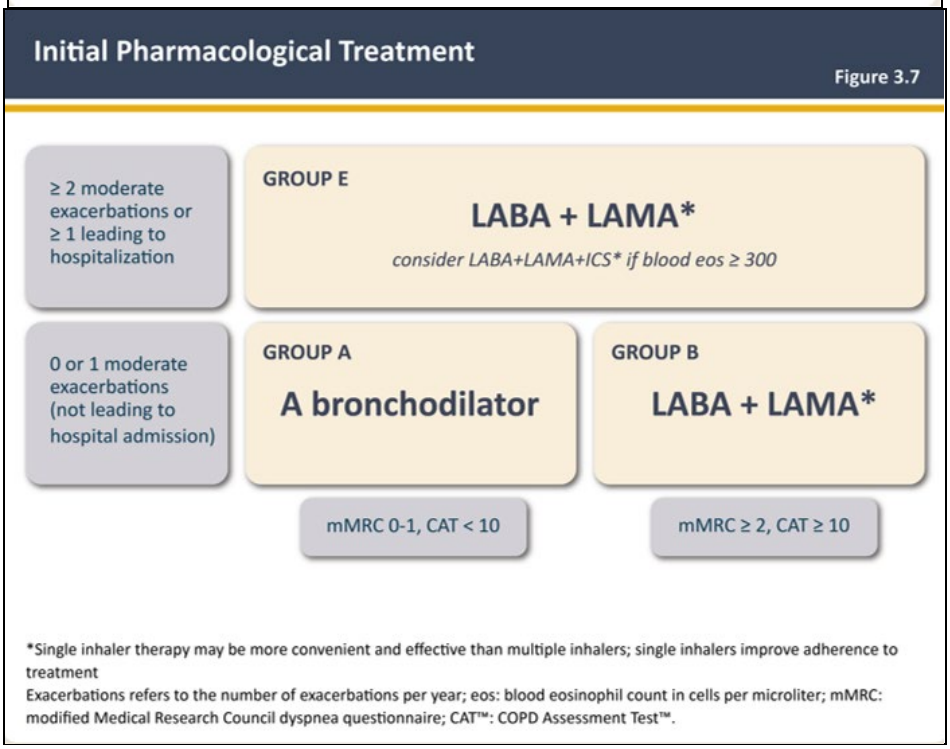
Box 6-6 © Global Initiative for Asthma, www.ginasthma.org

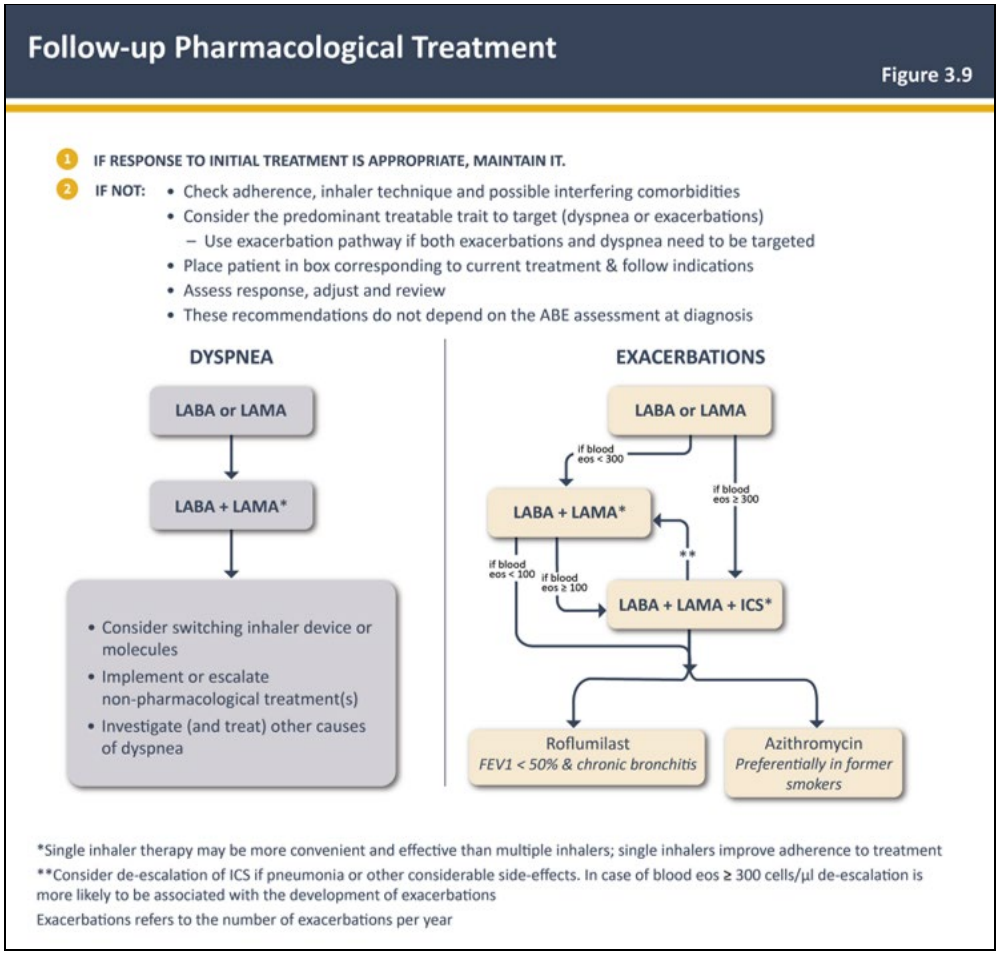
COPD:

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of chronic obstructive pulmonary disease: 2024 Report. Available at www.goldcopd.org.

Pharmacological Treatment for COPD:







Bronchodilators in Stable COPD:

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms (Evidence A)
- Inhaled bronchodilators are recommended over oral bronchodilators (Evidence A)
- Regular and as-needed use of SABA or SAMA improves FEV1 and symptoms (Evidence A)
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV1 and symptoms (Evidence A)
- LABAs and LAMAs are preferred over short-acting agents expect for patient with only occasional dyspnea (Evidence A), and for immediate relief of symptoms in patients already on long-acting bronchodilators for maintenance therapy
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates (Evidence A)
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (Evidence A) and decrease hospitalizations (Evidence B)
- When initiating treatment with long-acting bronchodilators the preferred choice is a combination of a LABA and a LAMA. In patients with persistent dyspnea on a single long-acting bronchodilator treatment should be escalated to two (Evidence A)
- Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy (Evidence A)
- Combination treatment with a LABA + LAMA reduces exacerbations compared to monotherapy (Evidence B)

- Combinations can be given as single inhaler or multiple inhaler treatment. Single inhaler therapy may be more convenient and effective than multiple inhalers
- Theophylline exerts a small bronchodilator effect in Stable COPD (Evidence A) and that is associated with modest symptomatic benefits (Evidence B)

Anti-Inflammatory Therapy in Stable COPD:

Inhaled Corticosteroids

- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (Evidence A)
- An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD (Evidence A)
- We do not encourage the use of a LABA + ICS combination in COPD. If there is an indication for an ICS the combination LABA + LAMA + ICS has been shown to be superior to LABA + ICS and it therefore the preferred choice
- Triple inhaled therapy of LABA + LAMA + ICS improves lung function, symptoms and health status, and reduces exacerbations, compared to LABA + ICS, LABA + LAMA, or LAMA monotherapy (Evidence A). Recent data suggests beneficial effect of triple inhaled therapy versus fixed-dose LABA + LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations
- If patients with COPD have features of asthma, treatment should always contain an ICS
- Independent of ICS use, there is evidence that a blood eosinophil count < 2% increases the risk of pneumonia (Evidence C)
- Combination can be given as single or multiple inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers

Oral Glucocorticoids

- Long term use of oral glucocorticoids has numerous side effects (Evidence A) with no evidence of benefits (Evidence C)

PDE4 Inhibitors

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
    - Roflumilast improves lung function and reduces moderate and severe exacerbations (Evidence A)

Antibiotics

- Long term azithromycin and erythromycin therapy reduces exacerbations over one year (Evidence A)
- Preferentially, but not only in former smokers with exacerbations despite appropriate therapy, azithromycin can be considered (Evidence B)
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance (Evidence A) and hearing test impairments (Evidence B)

Mucoregulators and Antioxidant Agents

- Regular treatment with mucolytics such as erdosteine, carbocysteine and NAC reduces the risk of exacerbations in select populations (Evidence B)
- Antioxidant mucolytics are recommended only in selected patients (Evidence A)

Other Anti-Inflammatory Agents

- Statin therapy is not recommended for prevention of exacerbations (Evidence A)
- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy (Evidence A). However, observational studies suggest that statins may have

positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications (Evidence C)
- Leukotriene modifiers have not been tested adequately in COPD patients

Other Pharmacological Treatments:

Alpha-1 Antitrypsin Augmentation Therapy
- Intravenous augmentation therapy may slow down the progression of emphysema (Evidence B)

Antitussives
- There is no conclusive evidence of a beneficial role of antitussives in people with COPD (Evidence C)

Vasodilators
- Vasodilators do not improve outcomes and may worsen oxygenation (Evidence B)

Opioids
- Low dose long acting oral and parenteral opioids may be considered for treating dyspnea in COPD patients with severe disease (Evidence B)

Pulmonary Hypertension Therapy
- Drugs approved for primary pulmonary hypertension are not recommended for patients with a pulmonary hypertension secondary to COPD (Evidence B)

Key Points for the Management of Exacerbations:
- Short acting inhaled beta2-agonists, with or without short acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation (Evidence C)
- Systemic corticosteroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not normally be more than 5 days (Evidence A)
- Antibiotics, when indicated, can shorted recover time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should normally be 5 days (Evidence B)
- Methylxanthines are not recommended due to increased side effect profiles (Evidence B)
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival (Evidence A)

Recommendation Definitions

Evidence Level	Sources of Evidence	Definition
A	RCTs Rich body of high quality evidence without any significant limitation or bias	Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations. Requires high qual0ity evidence from ≥2 clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patients without any bias.
B	RCTs with important limitations Limited body of evidence	Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta analyses of RCTs. Also pertains when few RCTs exist, or important limitations are evident (methodologic flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation, or the results are somewhat inconsistent).
C	Non-randomized trials Observational studies	Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	Panel consensus judgement	Provision of guidance is deemed valuable but clinical literature addressing the subject is insufficient. Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Papi A, Chipps BE, Beasley R, et al. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163	A phase 3, double blind, RCT in patients with moderate-severe uncontrolled asthma already receiving ICS maintenance therapy. Subjects (n=3132) were assigned 1:1:1 to either of the below options as a PRN rescue inhaler: • 180 µg of albuterol and 160 µg of budesonide fixed-dose inhaler (high dose group) • 180 µg of albuterol and 80 µg of budesonide fixed-dose inhaler (low dose group) • 180 µg of albuterol Children 4-11 years were assigned to the albuterol only or low dose combo group. Existing maintenance inhaler therapy was continued during the trial. Inclusion criteria: 4 years or older with 1 or more severe asthma exacerbation in the previous 12 months, FEV1 40-90% predicted normal value (no upper limit for ages 4-17), FEV1 reversibility of at least 12%, Asthma control questionnaire-5 (ACQ5) score 1.5 or greater at visit 2, have been receiving medium-high dose ICS or low-high dose ICS/LABA with or without another controller for at least 3 months and stable dose. Exclusion criteria: COPD or other notable lung disease, use of systemic glucocorticoid within past 3 months, use of biologic treatments 3 months prior to screening.	Primary: First event of severe asthma exacerbation in a time-to-event analysis, which was performed in the intention-to-treat population.
Results: The intention-to-treat analysis showed that the risk of a severe asthma exacerbation, in a time-to-event analysis, was significantly lower, by 26%, in the higher-dose combination group than in the albuterol-alone group (hazard ratio, 0.74; 95% confidence interval [CI], 0.62 to 0.89; P=0.001). The hazard ratio in the lower-dose combination group, as compared with the albuterol-alone group, was 0.84 (95% CI, 0.71 to 1.00; P=0.052). **Conclusions:** The authors concluded the risk of severe asthma exacerbation was significantly lower with as-needed use of a fixed-dose combination of 180 µg of albuterol and 160 µg of budesonide than with as-needed use of albuterol alone among patients with uncontrolled moderate-to-severe asthma who were receiving a wide range of inhaled glucocorticoid-containing maintenance therapies. Numerically, both high and low dose groups showed reduced rates of exacerbations vs albuterol alone. They are consistent with other findings where inclusion of ICS to a rescue medication regimen yields reduced exacerbation risk.		

Citation	Design	Endpoints
Fukuda N, Horita N, Kaneko A, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2023;6(6):CD012066. Published 2023	A systematic review/meta-analysis to compare the benefits and harms of ICS/LABA vs LAMA/LABA in patients with stable COPD. Nineteen (n=22,354) parallel or cross-over RCTs were included for review comparing ICS/LABA vs LAMA/LABA. Trials had to be a minimum of one month in duration. The median number of participants per study was 700. In each study, between 54% and 91% (median 70%) of participants were males. Study participants had an average age of 64 years and percentage predicted FEV_1 of 51.5% (medians of study means).	Primary: participants with one or more exacerbations of COPD; serious adverse events; quality of life [as measured by the St. George's Respiratory Questionnaire (SGRQ) total score change from baseline]; FEV1.

Jun 5. doi:10.1002/14651858.CD012066.pub3	Included studies had a generally low risk of selection, performance, detection, attrition, and reporting biases. All but two studies were sponsored by pharmaceutical companies, which had varying levels of involvement in study design, conduct, and data analysis.	Secondary: pneumonia occurrences, all cause death, SGRQ total score change from baseline (4 points or greater).

Results:

Primary outcomes

The odds of having an exacerbation were similar for LAMA+LABA compared with LABA+ICS (OR 0.91, 95% CI 0.78 to 1.06; I^2 = 61%; 13 studies, 20,960 participants; moderate-certainty evidence). The odds of having a serious adverse event were also similar (OR 1.02, 95% CI 0.91 to 1.15; I^2 = 20%; 18 studies, 23,183 participants; high-certainty evidence). Participants receiving LAMA+LABA had a similar improvement in quality of life, as measured by the SGRQ, to those receiving LABA+ICS (MD -0.57, 95% CI -1.36 to 0.21; I^2 = 78%; 9 studies, 14,437 participants; moderate-certainty evidence) but showed a greater improvement in trough FEV_1 (MD 0.07, 95% CI 0.05 to 0.08; I^2 = 73%; 12 studies, 14,681 participants; moderate-certainty evidence).

Secondary outcomes

LAMA+LABA decreased the odds of pneumonia compared with LABA+ICS from 5% to 3% (OR 0.61, 95% CI 0.52 to 0.72; I^2 = 0%; 14 studies, 21,829 participants; high-certainty evidence) but increased the odds of all-cause death from 1% to 1.4% (OR 1.35, 95% CI 1.05 to 1.75; I^2 = 0%; 15 studies, 21,510 participants; moderate-certainty evidence). The odds of achieving a minimal clinically important difference of four or more points on the SGRQ were similar between LAMA+LABA and LABA+ICS (OR 1.06, 95% CI 0.90 to 1.25; I^2 = 77%; 4 studies, 13,614 participants; moderate-certainty evidence).

Conclusions: The authors concluded that combination LAMA+LABA therapy probably holds similar benefits to LABA+ICS for exacerbations and quality of life, as measured by the St George's Respiratory Questionnaire, for people with moderate to severe COPD, but offers a larger improvement in FEV_1 and a slightly lower risk of pneumonia. There is little to no difference between LAMA+LABA and LAMA+ICS in the odds of having a serious adverse event. Whilst all-cause death may be lower with LABA+ICS, there was a very small number of events in the analysis, translating to a low absolute risk. Findings are based on moderate- to high-certainty evidence from heterogeneous trials with an observation period of less than one year. This review should be updated again in a few years.

Citation	Design	Endpoints
Chen H, Feng Y, Wang K, Yang J, Du Y. Association between inhaled corticosteroids and upper respiratory tract infection in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *BMC Pulm Med*. 2020;20(1):282. Published 2020 Oct 28. doi:10.1186/s12890-020-01315-3.	A meta-analysis of RCTs to assess the association between ICSs use and the risk of upper respiratory tract infection (URTI) in patients with COPD. Seventeen RCTs (20,478 patients) were included. Inclusion criteria included: (1) patients with COPD; (2) The interventions included any type of inhaled corticosteroids, including ICSs alone or combined with long-acting bronchodilators; (3) non-ICSs treatment as control, including placebo or other inhaled drugs of corticosteroid free; (4) only trials reporting data on URTI as the outcome were included; (5) Only RCTs were included. Exclusion criteria: (1) non-RCTs, such as observational studies, case series and reviews; (2) non-English articles; (3) Patients with asthma or unknown diagnosis; (4) ICSs was used in both the treatment group and the control group.	Assess the risk of URTI associated with use of ICS.

Results:

- ICSs significantly increased the risk of URTI in COPD patients (RR, 1.13; 95% CI 1.03–1.24; $P = 0.01$; heterogeneity: $I^2 = 7\%$).
- Further subgroup analyses suggested that short-term use of ICSs increased the risk of URTI (RR, 1.29; 95% CI 1.06–1.56; $P = 0.01$; heterogeneity: $I^2 = 14\%$) but not for long-term use (RR, 1.08; 95% CI 0.97–1.2; $P = 0.14$; heterogeneity: $I^2 = 0\%$).
- Short-term use of high-dose fluticasone increased the risk of URTI (RR, 1.33; 95% CI 1.03–1.71; $P = 0.03$; heterogeneity: $I^2 = 0\%$) but not for long-term use (RR, 1.12; 95% CI 0.97–1.29; $P = 0.13$; heterogeneity: $I^2 = 50\%$). Medium-dose (RR, 0.97; 95% CI 0.71–1.32; $P = 0.84$; heterogeneity: $I^2 = 0\%$) and low-dose (RR, 1.39; 95% CI 0.92–2.1; $P = 0.12$; heterogeneity: $I^2 = 30\%$) fluticasone did not increase the risk of URTI regardless of duration.
- Neither mometasone (RR, 1.05; 95% CI 0.87–1.26; $P = 0.61$; heterogeneity: $I^2 = 0\%$) nor budesonide (RR, 1.08; 95% CI 0.77–1.5; $P = 0.67$; heterogeneity: $I^2 = 46\%$) increased the risk of URTI, regardless of dosage or duration.

Conclusions: Long-term use of ICSs does not increase the risk of URTI in patients with COPD. Short-term use of high-dose fluticasone increases the risk of URTI in patients with COPD, but not mometasone or budesonide.

Citation	Design	Endpoints
Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019;380:2020–30.	A randomized, open-label, parallel-group 52-week controlled trial conducted at 16 trial centers. Patients were randomized in a 1:1:1 ratio. Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 µg, with two inhalations from a pressurized metered-dose inhaler PRN for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 µg, one inhalation twice daily, plus albuterol (Ventolin), 100 µg, two inhalations from a pressurized metered-dose inhaler PRN for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 µg of budesonide and 6 µg of formoterol, one inhalation PRN for symptom relief. Inclusion criteria:18-75 years of age with a diagnosis of asthma; the use of SABA as the sole asthma therapy in the previous 3 months; patient report of the use of SABA on at least 2 occasions in the previous month Randomized to receive: Albuterol 100 µg MDI Budesonide 200 µg plus PRN albuterol Budesonide-formoterol 200 µg/6 µg	Primary endpoints: annualized rate of asthma exacerbations

Results: The analysis included 668 of 675 patients who underwent randomization. The annualized exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (absolute rate, 0.195 vs. 0.400; relative rate, 0.49; 95% confidence interval [CI], 0.33 to 0.72; P<0.001) and did not differ significantly from the rate in the budesonide maintenance group (absolute rate, 0.195 in the budesonide–formoterol group vs. 0.175 in the budesonide maintenance group; relative rate, 1.12; 95% CI, 0.70 to 1.79; P=0.65). The number of severe exacerbations was lower in the budesonide–formoterol group than in both the albuterol group (9 vs. 23; relative risk, 0.40; 95% CI, 0.18 to 0.86) and the budesonide maintenance group (9 vs. 21; relative risk, 0.44; 95% CI, 0.20 to 0.96). The mean (±SD) dose of inhaled budesonide was 107±109 µg per day in the budesonide–formoterol group and 222±113 µg per day in the budesonide maintenance group. The incidence and type of adverse events reported were consistent with those in previous trials and with reports in clinical use.

Citation	Design	Endpoints
Trial 1 – AirDuo™ RespiClick® [package insert] Teva Respiratory, LLC., Jerusalem, Israel; 2017.	Randomized, double-blind, parallel-group, phase 3, 12-week clinical trial fluticasone/salmeterol with fluticasone furoate alone or placebo. All treatments were given as 1 inhalation twice daily and other maintenance therapies were discontinued. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to Qvar 40 mcg twice daily during the run-in period. Inclusion criteria: Adult and adolescent patients age 12 years and older, baseline FEV1 40% to 85% of predicted normal; asthma not optimally controlled on current therapy Randomized to receive: Fluticasone/Salmeterol Multidose Dry Powder Inhaler (MDPI) 55/14 mcg and 113/14 mcg with Fluticasone Propionate MDPI 55 mcg and 113 mcg and Placebo	Primary endpoints: change from baseline in trough FEV1 at week 12 for all patients and standardized baseline-adjusted FEV1 AUEC0-12h at week 12 analyzed for a subset of 312 patients who performed post-dose serial spirometry
Results: Patients receiving fluticasone/salmeterol 55/14 mcg and fluticasone/salmeterol 113/14 mcg had significantly greater improvements in trough FEV1 (fluticasone/salmeterol 55/14 mcg, LS mean change of 0.319 L at 12 weeks and fluticasone/salmeterol 113/14 mcg, LS mean change of 0.315 L at 12 weeks) compared with fluticasone furoate 55 mcg (LS mean change of 0.172 L at 12 weeks), fluticasone furoate 113 mcg (LS mean change of 0.204 L at 12 weeks), and placebo (LS mean change of 0.053 L at 12 weeks). Estimated mean differences between fluticasone/salmeterol 55/14 mcg and fluticasone/salmeterol 113/14 mcg compared to placebo are 0.266 L (95% CI: 0.172, 0.360) and 0.262 L [95% confidence interval (CI): 0.168, 0.356], respectively. The estimated mean differences between fluticasone furoate 55 mcg and fluticasone furoate 113 mcg compared to placebo are 0.119 L (95% CI: 0.025, 0.212) and 0.151 L (95% CI: 0.057, 0.244), respectively. The estimated mean difference between fluticasone/salmeterol 113/14 mcg and fluticasone furoate 113 mcg is 0.111 L (95% CI: 0.017, 0.206). The estimated mean difference between fluticasone/salmeterol 55/14 mcg and fluticasone furoate 55 mcg is 0.147 L (95% CI: 0.053, 0.242).		

Citation	Design	Endpoints
Trial 2 – AirDuo™ RespiClick® [package insert] Teva Respiratory, LLC., Jerusalem, Israel; 2017.	Randomized, double-blind, parallel-group, phase 3, 12-week clinical trial fluticasone/salmeterol with fluticasone furoate alone or placebo. Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to fluticasone furoate 55 mcg twice daily during the run-in period. Randomized to receive:	Primary endpoints: change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0-12h}$ at week 12 analyzed for a subset of 312 patients who performed post-dose serial spirometry.

	Fluticasone/Salmeterol Multidose Dry Powder Inhaler (MDPI) 113/14 mcg and 232/14 mcg with Fluticasone Propionate MDPI 113 mcg and 232 mcg and Placebo	
Results: Patients receiving fluticasone/salmeterol 113/14 mcg and fluticasone/salmeterol 232/14 mcg had significantly greater improvements in trough FEV1 (fluticasone/salmeterol 113/14 mcg, LS mean change of 0.271 L at 12 weeks and fluticasone/salmeterol 232/14 mcg, LS mean change of 0.272 L at 12 weeks) compared with fluticasone furoate 113 mcg (LS mean change of 0.119 L at 12 weeks), fluticasone furoate 232 mcg (LS mean change of 0.179 L at 12 weeks), and placebo (LS mean change of -0.004 L at 12 weeks). Estimated mean differences between fluticasone/salmeterol 113/14 mcg and fluticasone/salmeterol 232/14 mcg compared to placebo are 0.274 L (95% CI: 0.189, 0.360) and 0.276 L (95% CI: 0.191, 0.361), respectively. The estimated mean differences between fluticasone furoate 113 mcg and fluticasone furoate 232 mcg compared to placebo are 0.123 L (95% CI: 0.038, 0.208) and 0.183 L (95% CI: 0.098, 0.268), respectively. The estimated mean difference between fluticasone/salmeterol 232/14 mcg and fluticasone furoate 232 mcg is 0.093 L (95% CI: 0.009, 0.178). The estimated mean difference between fluticasone/salmeterol 113/14 mcg and fluticasone furoate 113 mcg is 0.152 L (95% CI: 0.066, 0.237).		

Citation	Design	Endpoints
A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared With Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients With Persistent Asthma Symptomatic Despite Low-dose or Mid-dose Inhaled Corticosteroid Therapy. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02139644?term=NCT02139644&rank=1. Last updated on April 12, 2017.	• 12-week, phase 3, randomized, double-blind, placebo-controlled, parallel-group enrolled 787 participants. • All treatments were given as 1 inhalation twice a day from the Respiclick inhaler, and other maintenance therapies were discontinued. • Compared – Fluticasone Propionate Multidose Dry powder Inhaler 55 mcg and 113 mcg (1 inhalation twice a day) – Fluticasone/Salmeterol Multidose Dry Powder Inhaler 55/14 mcg and 113/14 mcg (1 inhalation twice a day) – Placebo Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to QVAR 40 mcg twice daily during the run-in period. Inclusion criteria: Adult and adolescent patients (aged 12 years and older, with baseline FEV1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy (low- or mid-dose inhaled corticosteroid (ICS) or ICS/Long-acting Beta-agonist (LABA) therapy). Exclusion critera: A history of a life-threatening asthma exacerbation, an asthma exacerbation requiring systemic corticosteroids within the previous 30 days, or any hospitalization for asthma within the previous 2 months. Pregnant or lactating. Treatment with strong CYP3A4 inhibitor or initiation or dose escalation of immunotherapy. Current smoker, used tobacco products within the last year or has a	Primary: change from baseline in trough FEV1 at week 12 for all patients and standardized baseline-adjusted FEV1 AUEC0-12h at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry.

	smoking history of 10 pack years or more. HIV, active hepatitis B virus, or hepatitis C infection.	
Results: Patients receiving fluticasone furoate 55 mcg and fluticasone furoate 113 mcg had significantly greater improvements in trough FEV1 (fluticasone furoate 55 mcg, LS mean change of 0.172 L at 12 weeks and fluticasone furoate 113 mcg, LS mean change of 0.204 L at 12 weeks) compared with placebo (LS mean change of 0.053 L at 12 weeks). Estimated mean differences between fluticasone furoate 55 mcg and fluticasone furoate 113 mcg compared to placebo are 0.119 L (95% CI: 0.025, 0.212) and 0.151 L (95% CI: 0.057, 0.244), respectively. Improvements in FEV1 for both fluticasone furoate dose groups were sustained over the 12 hours of testing at week 12. No diminution in the 12 hour bronchodilator effect was observed with fluticasone furoate as assessed by FEV1 following 12 weeks of therapy.		

Citation	Design	Endpoints
A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared With Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients With Persistent Asthma Symptomatic Despite Inhaled Corticosteroid Therapy. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02141854?term=NCT02141854&rank=1. Last updated on May 31, 2017.	• 12-week, phase 3, randomized, double-blind, placebo-controlled, parallel-group enrolled 882 participants. All treatments were given as 1 inhalation twice a day from the RESPICLICK inhaler, and other maintenance therapies were discontinued. • Compared – Fluticasone Propionate Multidose Dry Powder Inhaler (ARMONAIR RESPICLICK) 113 mcg and 232 mcg (1 inhalation twice a day) – Fluticasone/Salmeterol Multidose Dry Powder Inhaler (AIRDUO RESPICLICK) 113/14 mcg and 232/14 mcg (1 inhalation twice a day) – Placebo Patients received single-blinded placebo MDPI and were switched from their baseline ICS therapy to ARMONAIR RESPICLICK 55 mcg twice daily during the run-in period. Inclusion criteria: Adult and adolescent patients (aged 12 years and older, with baseline FEV1 40% to 85% of predicted normal) with asthma that was not optimally controlled on their current therapy. Exclusion critera: A history of a life-threatening asthma exacerbation, an asthma exacerbation requiring systemic corticosteroids within the previous 30 days, or any hospitalization for asthma within the previous 2 months. Pregnant or lactating. Treatment with any known strong cytochrome P450 (CYP) 3A4 or initiation or dose escalation of immunotherapy. Current smoker, used tobacco products within the last year or has a smoking history of 10 pack years or more. HIV, active hepatitis B virus, or hepatitis C infection.	Primary: change from baseline in trough FEV1 at week 12 for all patients and standardized baseline-adjusted FEV1 AUEC0-12h at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry.
Results: Patients receiving fluticasone furoate 113 mcg and fluticasone furoate 232 mcg had significantly greater improvements in trough FEV1 (fluticasone furoate 113 mcg, LS mean change of 0.119 L at 12 weeks and fluticasone furoate 232 mcg, LS mean change of 0.179 L at 12 weeks) compared with placebo (LS mean change of -0.004 L at 12 weeks). Estimated mean differences between fluticasone furoate 113 mcg and fluticasone furoate 232 mcg compared to placebo are 0.123 L (95% CI: 0.038, 0.208) and 0.183 L (95% CI: 0.098, 0.268), respectively. Improvements in FEV1 for both fluticasone furoate dose groups were sustained over the 12 hours of testing at week 12 (Figure 5). No diminution in the 12 hour bronchodilator effect was observed with fluticasone furoate as assessed by FEV1 following 12 weeks of therapy.		

Citation	Design	Endpoints
Agustí A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol	12-week, randomized, multicenter (61 centers in Europe and Asia), double-blind, double-dummy, parallel-group, comparative efficacy/safety study.	The primary efficacy end-point of the study was the 24-h effect of FF/VI on lung function after 12 weeks of treatment (day 84), as compared with FP/SAL.

in moderate to very severe COPD. Eur Respir J. 2014;43(3):763-72. doi: 10.1183/09031936.00054213.	Adults aged ≥40 years, with a smoking history of ≥10 pack-years and a post-bronchodilator (salbutamol) FEV1/forced vital capacity ratio of ≤0.70 and a FEV1 ≤70% predicted. At least one moderate to severe COPD exacerbation within the last 3 years. Patients with current diagnosis of asthma, serious underlying disease or infections, hospitalization due to COPD within 12 weeks of screening, or acute worsening of COPD within 6 weeks of screening were excluded. Patients were randomized in a 1:1 ratio to receive in a double-blind manner FF/VI 100/25 µg once daily in the morning via the ELLIPTA dry powder inhaler or FP/SAL 500/50 µg twice daily via the Accuhaler for 12 weeks.	Secondary efficacy end-points were: 1) time to 100 mL increase from baseline from 0–4 h on day 1; and 2) change from baseline in trough FEV1 on day 85, i.e. the comparison of the FEV1 recorded 24 h post-dose on day 84 with the baseline measure. Safety endpoints were concerned with adverse events known to be associated with ICS and/or LABA therapy and included bone disorders, cardiovascular effects, effects on potassium, effects on glucose, hypersensitivity, local steroid effects, ocular effects, pneumonia, lower respiratory tract infections excluding pneumonia, systemic steroid effects and tremors.
Results: An improvement from baseline in 0–24 h wmFEV1 on day 84 was observed with both FF/VI (mean±sd 130±222 mL) and FP/SAL (108±221 mL); the difference in improvement between the two arms (22 mL) did not reach statistical significance (p=0.282). Since the primary endpoint was not statistically significant, all secondary endpoints are to be considered descriptive only. The mean change from baseline in trough FEV1 on day 85 had a mean treatment difference of 23 mL (95% CI -20–66) in favor of FF/VI. The median time to reach an increase in FEV1 of ≥100 mL on day 1 had a 12 minute difference in favor of FF/VI. The proportion of rescue-free 24-h periods was similar between treatments. The occurrence of on-treatment adverse events and drug-related adverse events was similar between the two study arms. None of the adverse events leading to withdrawal and none of the on-treatment severe adverse events were considered by the study investigators to be treatment related. **Conclusion:** This study shows that the efficacy and safety of once daily fluticasone furoate/vilanterol is not significantly different than twice daily fluticasone propionate/salmeterol. The drug profiles for these two combinations are very similar, but the once daily dosing of FF/VI is an advantage for patient adherence. There was no placebo arm so there is some limitation to the interpretation of data for all the endpoints.		

Citation	Design	Endpoints
Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest.	A phase 3, multicenter, randomized, double-blind, double-dummy, parallel group study. Patients aged ≥ 12 years with diagnosed asthma who could demonstrate a ≥ 12% and ≥ 200-mL reversibility of FEV1 following albuterol inhalation and had a best evening FEV1 of 40% to 85% of the predicted normal value.	The primary end point was the change from baseline in 0- to 24-h serial weighted mean FEV1 after 24 weeks of treatment. Secondary end points include individual serial FEV1 assessments at week 24, time to onset of bronchodilator effect at randomization visit only, 0- to 4-h serial weighted mean

2013;144(4):1222-1229. doi: 10.1378/chest.	Patients were randomized in a 1:1 ratio to either FF/VI 100/25 µg (emitted dose, 92/22 µg) once daily in the evening, through an ELLIPTA dry powder inhaler, or FP/SAL 250/50 µg bid (morning and evening) through DISKUS/ACCUHALER for 24 weeks.	FEV1 post dose at the randomization visit and at week 24, percentage of patients experiencing a ≥ 12% and ≥ 200-mL increase from baseline in FEV1 at 12 and 24 hours at week 24, and change from baseline in clinic visit trough FEV1 at week 24. Safety assessments were 24-h urinary cortisol excretion at baseline and at the end of the 24-week treatment period; vital signs (diastolic and systolic BP, pulse rate); incidence of severe asthma exacerbations; liver safety; and ECG, clinical chemistry, and hematology screening assessments as well as patient reported adverse effects. Patients were withdrawn if they experienced a severe exacerbation or worsening asthma.
Results: The adjusted mean treatment difference was not statistically significant for the primary endpoint. FF/VI (341 mL) and FP/SAL (377 mL) (−37 mL; 95% CI, −88 to 15 mL; P = .162). There were no important differences seen in secondary endpoints. The incidence of adverse effects was similar between both groups. **Conclusion:** This study shows that the efficacy and safety of once daily fluticasone furoate/vilanterol is not significantly different than twice daily fluticasone propionate/salmeterol. Adverse effects reported were similar between groups and were consistent with previously reported adverse effects with this drug combination. Once daily dosing is more convenient for patients but other than that there was no significant difference between the two combinations. The short time duration of this study may be seen as a limitation.		

Citation	Design	Endpoints
Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 10;319(14):1485-1496. doi: 10.1001/jama.2018.2769.	Meta-analyses of RCTs or observational studies evaluating the use of single product combination ICSs + LABAs as the controller together with quick relief SABA therapy, termed single maintenance and reliever therapy (SMART), vs ICSs +/- LABAs used as the controller therapy and quick relief SABA therapy for patients aged 5 years or older with persistent asthma using a random-effects model Databases MEDLINE (via OVID), EMBASE, the Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews were searched from database inception through August 2016 and updated through November 28, 2017 N = 16 RCTs evaluating 22,748 patients	Primary: Risk ratio (RR) and risk difference (RD) of asthma exacerbation

Results: Among patients aged 12 years or older, SMART was associated with a reduced risk of asthma exacerbations compared with the same dose of ICS + LABA as the controller therapy (RR, 0.68 [95% CI, 0.58 to 0.80]; RD, -6.4% [95% CI, -10.2% to -2.6%]) and a higher dose of ICS + LABA as the controller therapy (RR, 0.77 [95% CI, 0.60 to 0.98]; RD, -2.8% [95% CI, -5.2% to -0.3%]). Similar results were seen when SMART was compared with ICSs alone as the controller therapy. Among patients aged 4 to 11 years, SMART was associated with a reduced risk of asthma exacerbations compared with a higher dose of ICS as the controller therapy (RR, 0.55 [95% CI, 0.32 to 0.94]; RD, -12.0% [95% CI, -22.5% to -1.5%]) or the same dose of ICS + LABA as the controller therapy (RR, 0.38 [95% CI, 0.23 to 0.63]; RD, -23.2% [95% CI, -33.6% to -12.1%]).
Conclusion: In patients 12 years of age and older, the use of SMART compared with ICSs as the controller therapy (with or without a LABA) and SABA as the relief therapy was associated with a lower risk of asthma exacerbations. Evidence for patients aged 4 to 11 years was limited.

Citation	Design	Endpoints
Stynes G, Svedsater H, Wex J, et al. Once-daily fluticasone furoate/vilanterol 100/25 mcg versus twice daily combination therapies in COPD - mixed treatment comparisons of clinical efficacy. Respir Res. 2015 Feb 15;16:25. doi: 10.1186/s12931-015-0184-8.	A mixed treatment comparison (MTC), using covariate-adjusted Bayesian hierarchical models, of RCTs evaluating ICS/LABA therapy to any other comparator. Clinical publication databases, clinical trial registers, and accompanying references were searched with no date limit. N = 33 trials	Probability of non-inferiority for comparisons of once daily furoate/vilanterol (FF/VI) 100/25 mcg versus twice daily fluticasone propionate/salmeterol (FP/SAL) 500/50 mcg and budesonide/formoterol (BUD/FORM) 400/12 mcg Primary: Change from baseline in FEV1 Secondary: Annual rate of moderate or severe exacerbations; and change from baseline in St George's Respiratory Questionnaire (SGRQ or SGRQ-C) Total score

Results:

FEV1: FF/VI 100/25 mcg demonstrated >99% probability of non-inferiority to FP/SAL 500/50 mcg and BUD/FORM 400/12 mcg using a 50 mL margin.

Annual rate of moderate/severe exacerbations: FF/VI 100/25 mcg demonstrated 73% and 77% probability of non-inferiority to FP/SAL 500/50 mcg and BUD/FORM 400/12 mcg, respectively, using a 10% rate ratio margin.

SGRQ Total score, the corresponding probabilities of non-inferiority were 99% and 98%, respectively, on a 2-unit margin.

Significant covariate effects identified: increased age was associated with deterioration in FEV1 and reduced exacerbation frequency; shorter study duration was associated with reduced exacerbation frequency.

Conclusion: FF/VI 100/25 mcg was comparable to FP/SAL and BUD/FORM on lung function and health status outcomes, but the non-inferiority in terms of moderate/severe exacerbation rate was not demonstrated to the same degree of confidence. The study was limited by a weak treatment network for the exacerbation analysis.

Citation	Design	Endpoints
Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD006829.	Meta-analysis of randomized, double-blind controlled trials listed in the Cochrane Airways Group Specialized Register of trials through November 2011 comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD. N = 14 studies, 11,794 subjects	Primary: primary outcomes were exacerbations, mortality and pneumonia Dichotomous data were analyzed as random-effects model odds ratios (OR) or rate ratios (RR) with 95% CIs, and continuous data as mean differences with 95% CIs.

doi: 10.1002/14651858.CD006829.pub2.		

Results: There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone (RR 0.76; 95% CI 0.68 to 0.84). When analyzed as the number of people experiencing one or more exacerbations over the course of the study, there was moderate quality evidence that fluticasone plus salmeterol (FPS) lowered the odds of an exacerbation with an OR of 0.83 (95% CI 0.70 to 0.98). There was moderate quality evidence of no significant difference in mortality between people on combined inhalers and those on LABA (OR 0.92; 95% CI 0.76 to 1.11). Pneumonia occurred more commonly in people randomized to combined inhalers, supported by moderate quality evidence (OR 1.55; 95% CI 1.20 to 2.01) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of ICSs.
Conclusion: The claimed superiority of ICS/LABA compared to LABA alone in preventing exacerbations is questionable. Effects on hospitalizations were inconsistent and require further exploration, and there is possibly (moderate quality evidence) of an increased risk of pneumonia with ICS/LABA. Both treatments are likely to have similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV1 improved more on ICS/LABA than on LABA but probably clinically insignificant. Increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations with consideration given to individual patient preference.

Citation	Design	Endpoints
Cope S, Kraemer M, Zhang J, Capkun-Niggli G, Jansen JP. Efficacy of indacaterol 75 µg versus fixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:415-20. doi: 10.2147/COPD.S31526.	Bayesian network meta-analysis of placebo-controlled RCTs comparing the efficacy of indacaterol 75 µg with that of a fixed-dose combination of formoterol and budesonide (FOR/BUD) and a fixed-dose combination salmeterol and fluticasone propionate (SAL/FP) for the treatment of COPD A search of MEDLINE and EMBASE searched from 1989 to 2010 was performed N = 15 studies	Difference in change from baseline in trough FEV1 and transitional dyspnea index at 12 weeks

Results:
Without adjustment for covariates, indacaterol 75 µg performed better in terms of FEV1 compared to FOR/BUD 9/160 µg (difference in change from baseline 0.09 L [95% credible interval 0.04-0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03-0.11]) but this difference diminished after adjusting for covariates (FOR/BUD 9/160 µg (0.09 L [-0.01-0.18]) and FOR/BUD 9/320 µg (0.07 L [-0.03-0.16]). Indacaterol 75 µg was comparable to SAL/FP 50/250 µg (0.00 L [-0.07-0.07]) and SAL/FP 50/500 µg (0.01 L [-0.04-0.05]) in terms of FEV1 with and without adjusting for covariates. For transitional dyspnea index, indacaterol 75 µg was comparable with SAL/FP 50/500 µg (-0.49 points [-1.87-0.89]), the only comparative data available for this outcome measure. Other than in term of FEV1 and the comparison between indacaterol 75 µg and FOR/BUD, adjusting for covariates (including differences in the proportion of current smokers and patients with severe or very severe COPD) had a minor impact on the point estimates for FEV1 at 12 weeks and credible intervals were wider.
Conclusion: Indacaterol 75 µg is expected to be at least as efficacious as both doses of FOR/BUD and comparable to both doses of SAL/FP in terms of lung function. In terms of breathlessness (transitional dyspnea index), the results are inconclusive due to limited data.

Citation	Design	Endpoints
O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed	A randomized, parallel 52-week, double-blind, phase 3 trial involving patients 12 years of age or older with mild asthma Patients were randomly assigned to one of three groups:	Primary endpoints: Electronically recorded well-controlled asthma weeks (eWCAW) defined as the fulfillment both of the following

in mild asthma. N Engl J Med. 2018 May 17;378(20):1865-1876. doi: 10.1056/NEJMoa1715274.	1. Twice-daily placebo plus terbutaline (terbutaline Turbuhaler, AstraZeneca) 0.5 mg used PRN (terbutaline group) 2. Twice-daily placebo plus budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca) 200 µg of budesonide and 6 µg of formoterol used PRN (budesonide–formoterol group) 3. Twice-daily budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 µg plus terbutaline (terbutaline Turbuhaler, AstraZeneca) used PRN (budesonide maintenance group). Inclusion criteria: 12 years of age and older with a documented diagnosis of asthma for ≥ 6 months prior to visit 1. Patients who are in need of Step 2 treatment according to the GINA guidelines. Patients treated with PRN inhaled short-acting bronchodilator only should have a pre-bronchodilator FEV_1 ≥ 60% pf predicted normal (PN) and post-bronchodilator FEV_1 ≥ 80%. To be randomized patients must have used Bricanyl Turbuhaler PRN on at least 3 separate days during the last week of the run in period.	1. Two or more of: a. ≤ 2 days with a daily asthma symptom score >1 b. ≤ 2 days of PRN medication use c. Morning PEF ≥ 80 % of predicted normal everyday 2. Both of the following: a. No nighttime awakenings due to asthma No additional inhaled and or systemic glucocorticosteroid treatment due to asthma
Results: Of the 5721 patients who were enrolled, 3849 underwent randomization: 1280 patients were assigned to the terbutaline group, 1279 to the budesonide–formoterol group, and 1290 to the budesonide maintenance group. 3836 patients had data that could be evaluated for the full analysis and safety data sets, and 3363 patients (87.4%) completed the trial. Budesonide–formoterol used PRN was superior to terbutaline used PRN with regard to the primary outcome of the mean percentage of electronically recorded weeks with well-controlled asthma per patient (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046). Budesonide-formoterol was inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; odds ratio, 0.64; 95% CI, 0.57 to 0.73) The odds of having a week with well-controlled asthma during the 52-week trial period were 14% higher in the budesonide–formoterol group than in the terbutaline group. Adverse events were more frequent in the terbutaline group than the budesonide-formoterol group or the budesonide maintenance group. No notable differences between the adverse effects were seen except that more adverse events led to discontinuation in the terbutaline group. **Conclusion:** Budesonide-formoterol used PRN was a more effective treatment than terbutaline alone in patients with mild asthma. Budesonide-formoterol used PRN was superior to terbutaline for both symptom control and prevention of moderate to severe exacerbations, based on the patients electronically recorded weeks. Budesonide-formoterol used PRN was inferior to budesonide maintenance therapy in achieving electronically recorded well controlled asthma. A strength of this trial was that it included a 1 year duration and a high rate of 80% adherence was observed (with twice daily reminders). One limitation of this trial could be that the patients had to input into their own electric diary and this could be very subjective.		

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (10/1/2023 - 12/31/2023)

Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Inhaled Corticosteroid and Long-Acting Beta Agonist (ICS-LABA) Combos								
Dulera (mometasone-formoterol) 50 mcg-5 mcg, 100 mcg-5 mcg, 200 mcg-5 mcg/actuation HFA aerosol inhaler	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
fluticasone-vilanterol (Breo Ellipta) 50 mcg-25 mcg, 100 mcg-25 mcg, 200 mcg-25 mcg/dose powder for inhalation	0	0	$0.00	$0.00	1	0 (0%)	100-25mcg & 200-25mcg: F-PA 50-25mcg (brand): NF	No change
fluticasone 55 mcg-salmeterol 14 mcg, 113 mcg-14 mcg, 232 mcg-14 mcg/actuation (AirDuo RespiClick) breath activated powder	2	2	$202.12	$101.06	0	0 (0%)	F	No change
AirDuo Digihaler (fluticasone propionate -salmeterol) 55 mcg-14 mcg, 113 mcg-14 mcg, 232 mcg-14 mcg/actuation breath act,powder sensor	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
fluticasone 100 mcg-salmeterol 50 mcg, 250 mcg-50 mcg, 500 mcg-50 mcg/dose (Advair Diskus) blistr powdr for inhalation	59	38	$7,843.81	$132.95	0	0 (0%)	F	No change
fluticasone propionate -salmeterol (Advair HFA) 45 mcg-21 mcg, 115 mcg-21 mcg, 230 mcg-21 mcg/actuation aerosol inhaler	1	1	$232.45	$232.45	0	0 (0%)	F-PA	No change
budesonide-formoterol (Symbicort) HFA 80 mcg-4.5 mcg, 160 mcg-4.5 mcg/actuation aerosol inhaler	9	8	$1,889.12	$209.90	0	0 (0%)	F	No change
Airsupra (albuterol sulfate-budesonide) 90 mcg-80 mcg Inhaler	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Total	**71**	**49**	**$10,167.50**	**$143.20**	**1**	**0 (0%)**		

PRIOR AUTHORIZATION CRITERIA

Recommendation:

- Change Advair HF to reflect generic availability
- Add new NF medication Airsupra

Inhaled Corticosteroids/Long-Acting Beta-Agonists (ICS/LABA) Combinations	
Therapeutic Classes (AHFS)	Corticosteroids (respiratory tract)
Medications	**Formulary, PA required** Dulera (mometasone/formoterol) ~~Advair HFA (~~fluticasone/salmeterol~~)~~ (Advair HFA) fluticasone/vilanterol (Breo Ellipta) **Non-Formulary** AirDuo Digihaler (fluticasone/salmeterol) Airsupra (albuterol sulfate-budesonide) 90 mcg-80 mcg Inhaler Or any newly marketed agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Asthma • Documentation of adequate trial and failure, intolerance or inability to use formulary inhaled corticosteroid/long-acting beta agonist combination fluticasone/salmeterol (AirDuo) OR fluticasone/salmeterol (Advair Diskus/ Wixela Inhub) OR budesonide/formoterol (Symbicort) COPD • Documentation of adequate trial and failure, intolerance or inability to use formulary inhaled corticosteroid/long-acting beta agonist combination fluticasone/salmeterol (Advair Diskus/ Wixela Inhub) OR budesonide/formoterol (Symbicort)
Criteria Statement	Dulera, fluticasone/vilanterol (Breo Ellipta), AirDuo Digihaler, ~~or~~fluticasone/salmeterol (Advair HFA), or Airsupra are reserved for members who have used (or cannot/should not use) fluticasone/salmeterol (AirDuo) OR fluticasone/salmeterol (Advair Diskus/ Wixela Inhub) OR budesonide/formoterol (Symbicort), dependent on diagnosis.
Last P&T Review Date	~~12/2023~~3/2024

REFERENCES

1. Fanta C. Diagnosis of asthma in adolescents and adults. Barnes PJ, Bochner BS, Hollingsworth H, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on November 12, 2018.
2. Han MK, Dransfield MT, Martinez FJ. Chronic obstructive pulmonary disease: Definition, clinical manifestations, diagnosis and staging. Stoller JK, Hollingsworth H, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on November 12, 2018.
3. US National Heart Lung and Blood Institute 2020 Focused Updates to the Asthma Management Guidelines: Clinician's Guide. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/clinician-guide-2020-focused-updates-asthma-management-guidelines. Accessed November 15, 2021.
4. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention (GINA) 2023. Available from: https://ginasthma.org/gina-reports/. Accessed on November 17, 2023.
5. Tamondong-Lachica DR, Skolnik N, Hurst JR, et al. GOLD 2023 Update: Implications for Clinical Practice. *Int J Chron Obstruct Pulmon Dis*. 2023;18:745-754. Published 2023 May 5. doi:10.2147/COPD.S404690.
6. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Pocket Guide to COPD Diagnosis, Management, and Prevention 2024 Report. Available at https://goldcopd.org/2022-gold-reports/. Accessed on November 21, 2023.
7. Biomedtracker. Cambridge, MA: Informa Business Intelligence, Inc. Available at: https://www.biomedtracker.com/. Accessed on November 17, 2023.
8. "DailyMed." DailyMed. N.p., n.d. Web. 17 Nov 2023. Available at https://dailymed.nlm.nih.gov/dailymed/
9. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on November 17, 2023.
10. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on November 17, 2023.
11. A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared With Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients With Persistent Asthma Symptomatic Despite Low-dose or Mid-dose Inhaled Corticosteroid Therapy. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02139644?term=NCT02139644&rank=1. Last updated on April 12, 2017. Accessed on November 15, 2018.
12. A 12-Week, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Fluticasone Propionate Multidose Dry Powder Inhaler Compared With Fluticasone/Salmeterol Multidose Dry Powder Inhaler in Adolescent and Adult Patients With Persistent Asthma Symptomatic Despite Inhaled Corticosteroid Therapy. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT02141854?term=NCT02141854&rank=1. Last updated on May 31, 2017. Accessed on November 15, 2018.
13. Agustí A, de Teresa L, De Backer W, et al. A comparison of the efficacy and safety of once-daily fluticasone furoate/vilanterol with twice-daily fluticasone propionate/salmeterol in moderate to very severe COPD. Eur Respir J. 2014;43(3):763-72. doi: 10.1183/09031936.00054213. Accessed on November 15, 2018.
14. Woodcock A, Bleecker ER, Lötvall J, et al. Efficacy and safety of fluticasone furoate/vilanterol compared with fluticasone propionate/salmeterol combination in adult and adolescent patients with persistent asthma: a randomized trial. Chest. 2013;144(4):1222-1229. doi: 10.1378/chest. Accessed on November 15, 2018.
15. Sobieraj DM, Weeda ER, Nguyen E, et al. Association of Inhaled Corticosteroids and Long-Acting β-Agonists as Controller and Quick Relief Therapy With Exacerbations and Symptom Control in Persistent Asthma: A Systematic Review and Meta-analysis. JAMA. 2018 Apr 10;319(14):1485-1496. doi: 10.1001/jama.2018.2769. Accessed on November 19, 2018.
16. Stynes G, Svedsater H, Wex J, et al. Once-daily fluticasone furoate/vilanterol 100/25 mcg versus twice daily combination therapies in COPD - mixed treatment comparisons of clinical efficacy. Respir Res. 2015 Feb 15;16:25. doi: 10.1186/s12931-015-0184-8. Accessed on November 19, 2018.
17. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012 Sep 12;(9):CD006829. doi: 10.1002/14651858.CD006829.pub2. Accessed on November 19, 2018.
18. Cope S, Kraemer M, Zhang J, Capkun-Niggli G, Jansen JP. Efficacy of indacaterol 75 µg versus fixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis. Int J Chron Obstruct Pulmon Dis. 2012;7:415-20. doi: 10.2147/COPD.S31526. Accessed on November 19, 2018.
19. Beasley R, Holliday M, Reddel HK, Braithwaite I, Ebmeier S, Hancox RJ, et al. Controlled trial of budesonide-formoterol as needed for mild asthma. N Engl J Med. 2019;380:2020–30.
20. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. N Engl J Med. 2018 May 17;378(20):1865-1876. doi: 10.1056/NEJMoa1715274.
21. Chen H, Feng Y, Wang K, Yang J, Du Y. Association between inhaled corticosteroids and upper respiratory tract infection in patients with chronic obstructive pulmonary disease: a meta-analysis of randomized controlled trials. *BMC Pulm Med*. 2020;20(1):282. Published 2020 Oct 28. doi:10.1186/s12890-020-01315-3.
22. Papi A, Chipps BE, Beasley R, et al. Albuterol-Budesonide Fixed-Dose Combination Rescue Inhaler for Asthma. *N Engl J Med*. 2022;386(22):2071-2083. doi:10.1056/NEJMoa2203163.
23. Fukuda N, Horita N, Kaneko A, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2023;6(6):CD012066. Published 2023 Jun 5. doi:10.1002/14651858.CD012066.pub3

Antihistamines, First Generation

Executive Summary

CLASS OVERVIEW

First-generation antihistamines have been used reliably for decades to treat a variety of histamine-mediated disorders such as allergic rhinitis, urticaria, and motion sickness. They are also used as premedication to prevent anaphylactic reactions prior to intravenous infusions, including some chemotherapy regimens. These drugs are available in prescription and over-the-counter formulations at a relatively low cost. While still used for a wide variety of ailments, they are often recommended as alternatives to first-line therapies (i.e. second generation antihistamines) due to significant adverse events. This may include sedation, urinary retention, mental confusion, and other anticholinergic effects. Due to the paucity of new data and lack of new drug releases, this review will focus on consensus guidelines and systematic reviews.

UTILIZATION FINDINGS

There were 144 claims for 107 members, for a total of $798, and an average cost per claim of $5. The most highly utilized medication was hydroxyzine oral tablet, with 56 claims, followed by promethazine/dextromethorphan (promethazine-DM) 6.25 mg-15 mg/5 mL oral syrup with 36 claims.

RECOMMENDATIONS

- No changes

CLINICAL SUMMARY

Allergic rhinitis is characterized by sneezing, rhinorrhea, nasal obstruction, and itching of the eyes, nose, and mouth. It is also associated with postnasal drip, cough, and fatigue and occurs in 10-30% of individuals in the United States, with the prevalence increasing particularly in urban areas. Urticaria, or hives, involves pruritic erythematous plaques sometimes accompanied with angioedema and has a prevalence of 20% in the general population. Potential triggers may include drugs, food, insect stings/bites, or infection. Allergic conjunctivitis refers to inflammation of the mucous membrane that lines the inside surface of the eye lids and is caused by airborne allergens contacting the eye. It is usually benign and self-limiting or easily treated with pharmacologic therapy.

Allergic triggers release histamine, which is produced predominantly by mast cells (may also be released by basophils, neutrophils, and platelets). Secretory granule exocytosis rapidly releases histamine after immunoglobulin E (IgE) or non-IgE stimulation, binding to histamine 1-4 (H1-4) receptors located on target cells. H1 receptor binding increases venular permeability, nasal mucous production, heart rate, and cardiac output and leads to bronchial and intestinal smooth muscle contraction, widened pulse pressure, flushing, and T-cell neutrophil and eosinophil chemotaxis. H2 receptor binding increases venular permeability, gastric acid secretion, and airway mucous production but inhibits neutrophil and eosinophil influx. H3 receptors are found in the brain and some sympathetic nerve fibers but their role is not precisely understood. H4 receptors modulate T-helper response and initiate chemotaxis in eosinophils.

First-generation antihistamines compete with histamine for H1-receptor sites on effector cells in the gastrointestinal tract, blood vessels, respiratory tract, and central nervous system, leading to their anticholinergic and sedative effects. Although sometimes referred to as H1 antagonists, both first and second generation antihistamines downregulate constitutive H1 receptors. They are therefore inverse agonists, shifting equilibrium from the active form of the H1 receptor to the inactive form. This essentially reduces the activity of histamine on afferent C nerve fibers and other receptor sites. Higher doses may also inhibit the release of pruritic mediators from mast cells.

First generation antihistamines are indicated for many allergic, histamine-mediated conditions such as allergic rhinitis, conjunctivitis, urticaria, as an adjunct for treating anaphylactic reactions, premedication for IV infusions, and nausea and vomiting related to motion sickness, anesthesia, and labor. Unlike second generation antihistamines, they are lipophilic and readily cross the blood brain barrier, leading to somnolence. This may be beneficial for patients who suffer from exacerbations of pruritis at bedtime. While not recommended by the American Academy of Sleep Medicine, diphenhydramine is also used routinely in the treatment of chronic insomnia. Daytime sedation may be hazardous for some patient populations (e.g. elderly). Due to unfavorable adverse effect profiles, first generation antihistamines are generally reserved for more severe allergic reactions, prophylaxis, or in scenarios where somnolence is not concerning or desired. However, this class is preferred in the treatment and prevention of infusion reactions, motion sickness, and severe allergic reactions.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Single-Drug First Generation Antihistamine Products		
Doxylamine (Nighttime Sleep-Aid, Sleep Aid, Unisom®, Wal-Som) 25 mg oral tablet	• Insomnia, sleep onset or sleep maintenance	• **Insomnia, sleep onset or sleep maintenance:** 25 mg once daily 30 minutes before bedtime, as needed.
Diphenhydramine (Alka-Seltzer Plus Allergy, Compoz, NightTime Sleep Aid, Nytol®, Rest Simply, Simply Sleep, Sleep Aid, Sleep II, Sleep Tablet, Sleep-Tabs, Sominex®) 25 mg oral tablet, gel cap, caplet Diphenhydramine (Aler-Tab, Aller-G-Time, Allergy, Allergy Medicine, Allergy Relief, Anti-Hist, Banophen®, Benadryl® Allergy, Complete Allergy, Diphen®, Geri-Dryl®, Total Allergy, Wal-Dryl Allergy) 25 mg oral tablet, ultratab, caplet Diphenhydramine (NightTime Sleep Aid, NightTime Sleep Gel, Nytol, Ormir, Sleep Aid, Sleep Time, Unisom® SleepGels, Unisom® SleepMinis, Wal-Sleep, Z-Sleep, ZzzQuil®) 25, 50 mg oral capsule, softgel Diphenhydramine (Aler-Caps®, Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Antihistamine Allergy, Banophen®, Benadryl®, Complete Allergy, Diphenhist®, Medi-Phedryl, Pharbedryl®, Wal-Dryl Allergy) 25, 50 mg oral capsule Diphenhydramine (Children's Allergy, Children's Allergy Relief, Children's Wal-Dryl Allergy) 12.5 mg orally disintegrating tablet Diphenhydramine (Unisom® SleepMelts, Wal-Sleep Z, Wal-Som) 25 mg orally disintegrating tablets Diphenhydramine (Children's Allergy Relief, Allergy Relief) 12.5, 25 mg chewable tablet Diphenhydramine (PediaClear® Cough, Vanamine PD) 6.25 mg/mL oral drops	• Symptomatic relief of allergic symptoms caused by histamine release including nasal allergies and allergic dermatosis • Antitussive • Insomnia, occasional • Prevention or treatment of motion sickness • Management of Parkinsonian syndrome including drug-induced extrapyramidal symptoms (dystonic reactions) alone or in combination with centrally acting anticholinergic agents • Anaphylaxis, severe [adjunct to epinephrine; second-line (off-label)]	• **Allergic reactions:** 25-50 mg every 4 to 8 hours; max 300 mg daily • **Rhinitis, sneezing due to common cold:** 25 to 50 mg every 4 to 6 hours; maximum 300 mg daily • **Antitussive:** 25 mg every 4 hours; maximum 150 mg daily • **Insomnia, occasional:** 50 mg at bedtime • **Motion sickness treatment or prophylaxis:** 25-50 mg every 6 to 8 hours (take 30 minutes prior to motion for prophylaxis) • **Parkinsonism:** 25 to 50 mg 3 or 4 times daily • **Anaphylaxis, severe [adjunct to epinephrine; second-line (off-label)]:** IV: 25-50 mg over 10-15 minutes • **IM, IV (Parkinsonism, allergic reactions):** 10 to 50 mg per dose; single doses up to 100 mg may be used if needed; not to exceed 400 mg daily

Medication	Indications	Dosing/Administration
Diphenhydramine (Children's Wal-Dryl Allergy) 12.5 mg/5 mL prefilled spoon Diphenhydramine (Sleep Aid, Sleep Time, Wal-Sleep, Z-Sleep, ZzzQuil) 50 mg/30 mL oral solution Diphenhydramine (Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Children's Allergy, Children's Aurodryl Allergy, Children's Benadryl® Allergy, Children's Diphenhydramine, Children's Wal-Dryl, Diphedryl®, Geri-Dryl®, M-Dryl®, Pediacare Allergy Solution, Siladryl® SA, Total Allergy) 12.5 mg/5 mL oral solution Diphenhydramine (Naramin®) 12.5 mg/5 mL oral liquid in packet Diphenhydramine (Diphen®) 12.5 mg/5 mL oral elixir Diphenhydramine 50 mg/mL IV syringe		
Hydroxyzine 25 mg/mL, 50 mg/mL IM solution Hydroxyzine 10 mg/5 mL oral solution Hydroxyzine 10, 25, 50 mg oral tablet Hydroxyzine pamoate (Vistaril®) 25, 50, 100 mg oral capsule	• Antiemetic • Anxiety • Peripartum adjunct • Pruritis	• **Antiemetic:** 25 - 100 mg/dose IM • **Anxiety:** 50 -100 mg PO 4 times daily or 50-100 mg IM every 4 to 6 hours as needed • **Peripartum adjunct:** 25-100 mg IM • **Perioperative adjunct:** 50-100 mg PO or 25-100 mg IM one time • **Pruritus:** 25 mg PO 3 to 4 times a day
Carbinoxamine 4 mg oral tablet Carbinoxamine 4 mg/5 mL oral liquid Carbinoxamine (Karbinal® ER) 4 mg/5 mL extended release oral suspension	• Symptomatic treatment of seasonal and perennial allergic rhinitis • Vasomotor rhinitis • Allergic conjunctivitis • Mild, uncomplicated allergic skin manifestations of urticaria and angioedema • Dermatographism • As adjunctive therapy for anaphylactic reactions • Amelioration of the severity of allergic reactions to blood or plasma	• **Immediate release:** 4-8 mg 3-4 times daily • **Extended release:** 6-16 mg every 12 hours

Medication	Indications	Dosing/Administration
Promethazine 6.25 mg/5 mL oral syrup Promethazine 12.5, 25, 50 mg oral tablet Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV ampule Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV vial	• Perennial and seasonal allergic rhinitis • Vasomotor rhinitis • allergic conjunctivitis due to inhalant allergens and foods • mild, uncomplicated allergic skin manifestations of urticaria and angioedema • amelioration of allergic reactions to blood or plasma • Dermographism • Adjunct therapy for anaphylactic reactions • Prevention and control of nausea and vomiting associated with anesthesia and surgery • Active and prophylactic treatment of motion sickness • Surgical analgesia/hypnotic, pre-post-op adjunct • Sedation • Preop, postop, and obstetric sedation • Nausea and vomiting of pregnancy (off-label)	• **Allergic conditions, treatment: oral, rectal:** 25 mg at bedtime or 12.5 mg before meals and at bedtime (usual range: 6.25 to 12.5 mg 3 times daily); IM, IV: 25 mg, may repeat in 2 hours when necessary • **Motion sickness:** oral, rectal: 25 mg 30 to 60 minutes before departure; repeat 8 to 12 hours later as needed; maintenance: 25 mg twice daily • **Nausea and vomiting (including pregnancy):** Oral, IM, IV, rectal: 12.5-25 mg every 4 to 6 hours as needed • **Labor, adjunct to analgesia: IM, IV: Early labor:** 50 mg; Established labor: 25-75 mg in combination with analgesic at reduced dosage; may repeat every 4 hours for up to 2 additional doses; max: 100 mg/day while in labor • **Surgical analgesia/hypnotic; pre-/postoperative adjunct:** IM, IV: 25-50 mg in combination with analgesic or hypnotic (at reduced dosage) • **Sedation:** Oral, IM, IV, rectal: 25-50 mg/dose
Cyproheptadine 4 mg oral tablet Cyproheptadine 2 mg/5 mL, 4 mg/10 mL oral syrup	• Perennial and seasonal allergic rhinitis • Vasomotor rhinitis • allergic conjunctivitis • Mild, uncomplicated allergic skin manifestations of urticaria and angioedema • Amelioration of allergic reactions to blood or plasma • Cold urticaria • Dermatographism • Adjunctive anaphylactic therapy • Decreased appetite secondary to chronic disease (off-label) • Serotonin syndrome (off-label) • Spacticity associated with spinal cord damage (off-label)	• **Allergic conditions:** 4 mg three times daily; maintenance: 4-20 mg daily in divided doses; max 0.5 mg/kg/day • **Decreased appetite secondary to chronic disease (off-label):** 2 mg four times per day for one week, then 4 mg four times per day • **Serotonin syndrome (off-label):** 12 mg one time, then 2 mg every 2 hours or 4-8 mg every 6 hours as needed for symptom control • **Spacticity associated with spinal cord damage (off-label):** 2-4 mg every 8 hours; max 8 mg every 8 hours
Chlorcyclizine (Ahist®) 25 mg oral tablet	• Temporarily relieves these symptoms due to hay fever or other upper respiratory allergies (runny nose, sneezing, itching of the nose or throat, itchy, watery eyes)	• **Upper respiratory allergies:** 1 tablet by mouth every 6-8 hours, not to exceed 3 tablets in 24 hours, or as directed by a doctor
Dexbrompheniramine (Ala-Hist® IR) 2 mg oral tablet Dexbrompheniramine (Pediavent®) 1 mg chewable tablet	• Symptomatic treatment of seasonal and perennial allergic rhinitis or upper respiratory allergies	• **Allergic rhinitis:** 2 mg every 4 to 6 hours; max 18 mg/day

Medication	Indications	Dosing/Administration
Dexbrompheniramine (Pediavent®) 2 mg/5 mL oral liquid Dexchlorpheniramine (Ryclora®) 2 mg/5 mL oral solution		
Triprolidine (Dr Manzanilla Infant, Histex® PD, Histex® PDX, M-Hist PD, PediaClear®, PediaClear® PD Allergy, Vanaclear PD) 0.313 mg/mL, 0.625 mg/mL, 0.938 mg/mL, 1.25 mg/mL oral drops Triprolidine (Miclara® LQ) 1.25 mg/5 mL, 2.5 mg/5 mL oral syrup Dr Manzanilla Pediatric, Histex® (triprolidine) 2.5 mg/5 mL oral syrup Histex® (triprolidine) 1.25 mg chewable tablet	• Symptomatic treatment of seasonal and perennial allergic rhinitis or upper respiratory allergies	• **Allergies:** 2.5 mg every 4 to 6 hours; max: 10 mg/day
Chlorpheniramine (Aller-Chlor, Allergy, Allergy Relief, Allergy-Time, ChlorHist®, Chlor-Trimeton®, Pharbechlor®, Wal-Finate) 4 mg oral tablet Chlorpheniramine (Allergy Relief, Chlor-Trimeton Allergy, Chlorphen SR) 12 mg oral tablet Chlorpheniramine (Chlor-Trimeton, Ed Chlorped® Jr) 2 mg/5 mL oral syrup	• Allergic symptoms • Symptomatic treatment of seasonal and perennial allergic rhinitis • Urticaria • Pruritis • Motion sickness (off-label)	• **Immediate release:** 4 mg every 4 to 6 hours; max 24 mg in 24 hours • **Extended release:** 12 mg every 12 hours; max 24 mg in 24 hours
Clemastine (Allergy Relief, Dayhist®, Dayhist® Allergy) 1.34, 2.68 mg oral tablet Clemastine 0.5 mg/5 mL oral syrup	• Symptomatic treatment of seasonal and perennial allergic rhinitis • Urticaria/andioedema • Common cold, hay fever, upper respiratory allergies (OTC labeling)	• 1.34 mg twice daily; may be increased as needed to a max of 2.68 mg three times a day (8.04 mg/day) • **OTC labeling:** 1.34 mg twice daily; max 2.68 mg/day
Pyrilamine (PediaClear-8®) 12.5 mg/15 mL oral syrup	• Temporarily relieves runny nose and alleviates sneezing, itching of the nose or throat, and itchy, watery eyes due to hay fever or other upper respiratory allergies.	• Children 6 to under 12 years: 30 mL (2 dose cups) every 6 to 8 hours, not to exceed 4 doses in 24 hours, or as directed by a doctor
Prescription-Only First Generation Antihistamine Combination Products		
Promethazine/phenylephrine/codeine (promethazine VC-codeine) 6.25 mg-5 mg-10 mg/5 mL oral syrup	• Cough and upper respiratory symptoms	• **Cough and upper respiratory symptoms:** 5 mL every 4 to 6 hours (maximum: 30 mL [codeine 60 mg/promethazine 37.5 mg/phenylephrine 30 mg] per 24 hours).
Brompheniramine/ pseudoephedrine/ dextromethorphan (Bromfed® DM) 2 mg-30 mg-10 mg/5 mL oral syrup	• Cough and upper respiratory symptoms	• **Cough and upper respiratory symptoms:** Brompheniramine 2 mg, pseudoephedrine 30 mg, and dextromethorphan 10 mg per 5 mL:

Medication	Indications	Dosing/Administration
		10 mL every 4 hours (maximum: 60 mL/24 hours)
Promethazine/dextromethorphan (promethazine-DM) 6.25 mg-15 mg/5 mL oral syrup	• Cough and upper respiratory symptoms:	• **Cough and upper respiratory symptoms:** 5 mL every 4 to 6 hours; maximum: 30 mL in 24 hours
Promethazine/phenylephrine (promethazine VC) 6.25 mg-5 mg/5 mL oral syrup	• Upper respiratory symptoms	• **Upper respiratory symptoms:** 5 mL (promethazine 6.25 mg/phenylephrine 5 mg) every 4 to 6 hours; maximum: 30 mL (promethazine 37.5 mg/phenylephrine 30 mg)/24 hours

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Single-Drug First Generation Antihistamine Products		
Doxylamine (Nighttime Sleep-Aid, Sleep Aid, Unisom®, Wal-Som) 25 mg oral tablet	• None	• Do not use in children <12 years of age.
Diphenhydramine (Alka-Seltzer Plus Allergy, Compoz, NightTime Sleep Aid, Nytol®, Rest Simply, Simply Sleep, Sleep Aid, Sleep II, Sleep Tablet, Sleep-Tabs, Sominex®) 25 mg oral tablet, gel cap, caplet Diphenhydramine (Aler-Tab, Aller-G-Time, Allergy, Allergy Medicine, Allergy Relief, Anti-Hist, Banophen®, Benadryl® Allergy, Complete Allergy, Diphen®, Geri-Dryl®, Total Allergy, Wal-Dryl Allergy) 25 mg oral tablet, ultratab, caplet Diphenhydramine (NightTime Sleep Aid, NightTime Sleep Gel, Nytol, Ormir, Sleep Aid, Sleep Time, Unisom® SleepGels, Unisom® SleepMinis, Wal-Sleep, Z-Sleep, ZzzQuil®) 25, 50 mg oral capsule, softgel Diphenhydramine (Aler-Caps®, Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Antihistamine Allergy, Banophen®, Benadryl®, Complete Allergy, Diphenhist®, Medi-Phedryl, Pharbedryl®, Wal-Dryl Allergy) 25, 50 mg oral capsule	• None	• Neonates or premature infants • Breast-feeding • When used for self-medication, do not use in children <6 years, to make a child sleep, or with any other diphenhydramine-containing products

Medication	Boxed Warnings	Contraindications
Diphenhydramine (Children's Allergy, Children's Allergy Relief, Children's Wal-Dryl Allergy) 12.5 mg orally disintegrating tablet Diphenhydramine (Unisom® SleepMelts, Wal-Sleep Z, Wal-Som) 25 mg orally disintegrating tablets Diphenhydramine (Children's Allergy Relief, Allergy Relief) 12.5, 25 mg chewable tablet Diphenhydramine (PediaClear® Cough, Vanamine PD) 6.25 mg/mL oral drops Diphenhydramine (Children's Wal-Dryl Allergy) 12.5 mg/5 mL prefilled spoon Diphenhydramine (Sleep Aid, Sleep Time, Wal-Sleep, Z-Sleep, ZzzQuil) 50 mg/30 mL oral solution Diphenhydramine (Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Children's Allergy, Children's Aurodryl Allergy, Children's Benadryl® Allergy, Children's Diphenhydramine, Children's Wal-Dryl, Diphedryl®, Geri-Dryl®, M-Dryl®, Pediacare Allergy Solution, Siladryl® SA, Total Allergy) 12.5 mg/5 mL oral solution Diphenhydramine (Naramin®) 12.5 mg/5 mL oral liquid in packet Diphenhydramine (Diphen®) 12.5 mg/5 mL oral elixir Diphenhydramine 50 mg/mL IV syringe		

Medication	Boxed Warnings	Contraindications
Hydroxyzine 25 mg/mL, 50 mg/mL IM solution Hydroxyzine 10 mg/5 mL oral solution Hydroxyzine 10, 25, 50 mg oral tablet Hydroxyzine pamoate (Vistaril®) 25, 50, 100 mg oral capsule	• None	• Early pregnancy • Prolonged QT interval • Hypersensitivity to cetirizine or levocetirizine • Injection should not be used SQ, IA, or IV
Carbinoxamine 4 mg oral tablet Carbinoxamine 4 mg/5 mL oral liquid Carbinoxamine (Karbinal® ER) 4 mg/5 mL extended release oral suspension	• None	• Coadministration with monoamine oxidase inhibitors (MAOIs) • Children <2 years of age • Breast-feeding women
Promethazine 6.25 mg/5 mL oral syrup Promethazine 12.5, 25, 50 mg oral tablet Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV ampule Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV vial	• Respiratory depression in pediatric patients: Promethazine should not be used in pediatric patients younger than 2 years because of the potential for fatal respiratory depression • Severe tissue injury including gangrene (injection): Promethazine injection can cause severe chemical irritation and damage to tissues regardless of the route of administration. Due to the risks of intravenous (IV) injection, the preferred route of administration of promethazine is deep intramuscular (IM) injection. SQ injection is contraindicated.	• Coma • Treatment of lower respiratory tract symptoms, including asthma • Children <2 years of age • Intra-arterial or subcutaneous administration
Cyproheptadine 4 mg oral tablet Cyproheptadine 2 mg/5 mL, 4 mg/10 mL oral syrup	• None	• Use in newborn or premature infants or breast-feeding mothers • Concomitant use of monoamine oxidase inhibitor therapy • Angle-closure glaucoma • Stenosing peptic ulcer • Symptomatic prostatic hypertrophy • Bladder neck obstruction • Pyloroduodenal obstruction • Elderly, debilitated patients
Chlorcyclizine (Ahist®) 25 mg oral tablet	• None	• None

Medication	Boxed Warnings	Contraindications
Dexbrompheniramine (Ala-Hist® IR) 2 mg oral tablet Dexbrompheniramine (Pediavent®) 1 mg chewable tablet Dexbrompheniramine (Pediavent®) 2 mg/5 mL oral liquid Dexchlorpheniramine (Ryclora®) 2 mg/5 mL oral solution	• None	• When used for self-medication, do not use with or within 14 days of stopping an MAOI • Use in newborns or premature infants • Breast-feeding mothers • Treatment of lower respiratory tract symptoms, including asthma • Concomitant MAOI therapy
Triprolidine (Dr Manzanilla Infant, Histex® PD, Histex® PDX, M-Hist PD, PediaClear®, PediaClear® PD Allergy, Vanaclear PD) 0.313 mg/mL, 0.625 mg/mL, 0.938 mg/mL, 1.25 mg/mL oral drops Triprolidine (Miclara® LQ) 1.25 mg/5 mL, 2.5 mg/5 mL oral syrup Dr Manzanilla Pediatric, Histex® (triprolidine) 2.5 mg/5 mL oral syrup Histex® (triprolidine) 1.25 mg chewable tablet	• None	• When used for self-medication, do not use if you are taking sedatives or tranquilizers or with any other triprolidine-containing products
Chlorpheniramine (Aller-Chlor, Allergy, Allergy Relief, Allergy-Time, ChlorHist®, Chlor-Trimeton®, Pharbechlor®, Wal-Finate) 4 mg oral tablet Chlorpheniramine (Allergy Relief, Chlor-Trimeton Allergy, Chlorphen SR) 12 mg oral tablet Chlorpheniramine (Chlor-Trimeton, Ed Chlorped® Jr) 2 mg/5 mL oral syrup	• None	• Narrow-angle glaucoma • Bladder neck obstruction • Symptomatic prostate hypertrophy • During acute asthmatic attacks • Stenosing peptic ulcer • Pyloroduodenal obstruction • Avoid use in premature and term newborns due to possible association with SIDS
Clemastine (Allergy Relief, Dayhist®, Dayhist® Allergy) 1.34, 2.68 mg oral tablet Clemastine 0.5 mg/5 mL oral syrup	• None	• Concomitant use with monoamine oxidase inhibitors • Newborn or premature infants • Breast-feeding women • Lower respiratory tract symptoms (e.g. asthma)
Pyrilamine (PediaClear-8®) 12.5 mg/15 mL oral syrup	• None	• None
Prescription-Only First Generation Antihistamine Combination Products		

Medication	Boxed Warnings	Contraindications
Promethazine/ phenylephrine/ codeine (promethazine VC-codeine) 6.25 mg-5 mg-10 mg/5 mL oral syrup	• Addiction, abuse, and misuse • Life-threatening respiratory depression • Accidental ingestion • Ultra-rapid metabolism of codeine and other risk factors for life-threatening respiratory depression in children • Promethazine and respiratory depression in children • Risk of medication errors • Interactions with drugs affecting cytochrome P450 isoenzymes: • Risks from concomitant use with benzodiazepines or other CNS depressants • Neonatal opioid withdrawal syndrome	• Idiosyncratic reaction to promethazine or other phenothiazines • Pediatric patients <12 years of age • Postoperative management in pediatric patients <18 years of age who have undergone tonsillectomy and/or adenoidectomy • Significant respiratory depression • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • GI obstruction (known or suspected), including paralytic ileus • Narrow angle glaucoma • Urinary retention • Severe hypertension • Severe coronary artery disease • Peripheral vascular insufficiency • Concurrent use with monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days
Brompheniramine/ pseudoephedrine/ dextromethorphan (Bromfed® DM) 2 mg-30 mg-10 mg/5 mL oral syrup	• None	• Severe hypertension or coronary artery disease • Concomitant or within 2 weeks of MAO inhibitor therapy • Newborns or premature infants • Breast-feeding • Treatment of lower respiratory tract conditions, including acute asthma
Promethazine/dextromethorphan (promethazine-DM) 6.25 mg-15 mg/5 mL oral syrup	• Respiratory depression - Pediatrics: promethazine should not be used in pediatric patients <2 years of age because of the potential for fatal respiratory depression.	• Coma • Treatment of lower respiratory tract symptoms, including asthma • Use with or within 14 days of monoamine oxidase inhibitor therapy • Children <2 years of age
Promethazine/phenylephrine (promethazine VC) 6.25 mg-5 mg/5 mL oral syrup	• Pediatrics: Promethazine hydrochloride should not be used in pediatric patients less than 2 years of age because of the potential for fatal respiratory depression.	• Treatment of lower respiratory tract symptoms, including asthma • Comatose states • Hypertension • Peripheral vascular insufficiency • Concurrent use with MAO inhibitor therapy • Children <2 years of age

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
	Single-Drug First Generation Antihistamine Products
Doxylamine (Nighttime Sleep-Aid, Sleep Aid, Unisom®, Wal-Som) 25 mg oral tablet	**Concerns related to adverse effects:** • **CNS depression:** May cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks which require mental alertness (eg, operating machinery or driving). • **Sleeplessness:** If sleeplessness persists for >2 weeks, consult health care provider. **Disease-related concerns:**

Medication	Warnings/Precautions
	• **Increased intraocular pressure/glaucoma:** Use with caution in patients with increased intraocular pressre or angle-closure glaucoma. • **Prostatic hyperplasia/urinary obstruction:** Use with caution in patients with prostatic hyperplasia and/or GU obstruction. • **Respiratory disease:** Use with caution in patients with asthma or other chronic breathing disorders. **Concurrent drug therapy issues:** • **Sedatives:** Effects may be potentiated when used with other sedative drugs or ethanol. **Special populations:** • **Pediatric:** Do not use for insomnia in children <12 years of age. Antihistamines may cause paradoxical excitation in young children.
Diphenhydramine (Alka-Seltzer Plus Allergy, Compoz, NightTime Sleep Aid, Nytol®, Rest Simply, Simply Sleep, Sleep Aid, Sleep II, Sleep Tablet, Sleep-Tabs, Sominex®) 25 mg oral tablet, gel cap, caplet Diphenhydramine (Aler-Tab, Aller-G-Time, Allergy, Allergy Medicine, Allergy Relief, Anti-Hist, Banophen®, Benadryl® Allergy, Complete Allergy, Diphen®, Geri-Dryl®, Total Allergy, Wal-Dryl Allergy) 25 mg oral tablet, ultratab, caplet Diphenhydramine (NightTime Sleep Aid, NightTime Sleep Gel, Nytol, Ormir, Sleep Aid, Sleep Time, Unisom® SleepGels, Unisom® SleepMinis, Wal-Sleep, Z-Sleep, ZzzQuil®) 25, 50 mg oral capsule, softgel Diphenhydramine (Aler-Caps®, Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Antihistamine Allergy, Banophen®, Benadryl®, Complete Allergy, Diphenhist®, Medi-Phedryl, Pharbedryl®, Wal-Dryl Allergy) 25, 50 mg oral capsule Diphenhydramine (Children's Allergy, Children's Allergy Relief, Children's Wal-Dryl Allergy) 12.5 mg orally disintegrating tablet Diphenhydramine (Unisom® SleepMelts, Wal-Sleep Z, Wal-	• **Concerns related to adverse effects:** may cause CNS depression • **Disease-related concerns:** use caution in patients with asthma, cardiovascular disease, increased intraocular pressure/glaucoma, prostatic hyperplasia/urinary obstruction, pyloroduodenal obstruction, thyroid dysfunction • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist • **Dosage form specific issues:** some oral liquid products may contain alcohol; some dosage forms may contain sodium benzoate/benzoic acid, a metabolite of benzyl alcohol; large amounts of benzyl alcohol have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; some dosage forms may contain polysorbate 80 (also known as Tweens) which has been associated with hypersensitivity reactions following exposure; some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression; some products may contain phenylalanine; subcutaneous or intradermal use has been associated with tissue necrosis; some preparations contain soy protein • **Special populations:** may cause excitation in young children • **Other warnings/precautions:** do not use with other products containing diphenhydramine; oral products are not for OTC use in children <6 years of age

Medication	Warnings/Precautions
Som) 25 mg orally disintegrating tablets Diphenhydramine (Children's Allergy Relief, Allergy Relief) 12.5, 25 mg chewable tablet Diphenhydramine (PediaClear® Cough, Vanamine PD) 6.25 mg/mL oral drops Diphenhydramine (Children's Wal-Dryl Allergy) 12.5 mg/5 mL prefilled spoon Diphenhydramine (Sleep Aid, Sleep Time, Wal-Sleep, Z-Sleep, ZzzQuil) 50 mg/30 mL oral solution Diphenhydramine (Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Children's Allergy, Children's Aurodryl Allergy, Children's Benadryl® Allergy, Children's Diphenhydramine, Children's Wal-Dryl, Diphedryl®, Geri-Dryl®, M-Dryl®, Pediacare Allergy Solution, Siladryl® SA, Total Allergy) 12.5 mg/5 mL oral solution Diphenhydramine (Naramin®) 12.5 mg/5 mL oral liquid in packet Diphenhydramine (Diphen®) 12.5 mg/5 mL oral elixir Diphenhydramine 50 mg/mL IV syringe	

Medication	Warnings/Precautions
Hydroxyzine 25 mg/mL, 50 mg/mL IM solution Hydroxyzine 10 mg/5 mL Hydroxyzine 10, 25, 50 mg oral tablet Hydroxyzine pamoate (Vistaril®) 25, 50, 100 mg oral capsule	• **Concerns related to adverse effects:** acute generalized exanthematous pustolosis; CNS depression; QT prolongation/torsades de pointes • **Disease-related concerns:** use caution in patients with increased intraocular pressure/glaucoma, prostatic hyperplasia/urinary obstruction, respiratory disease • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist • **Dose form specific issues:** some dosage forms may benzyl alcohol; large amounts of benzyl alcohol have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated hyperosmolality, lactic acidosis, seizures, and respiratory depression • **Other warnings/precautions:** appropriate administration (IM use only; no SQ, IA, or IV); Severe injection-site reactions have been reported with IM administration (eg, extensive tissue damage, necrosis, gangrene) requiring surgical intervention; the effectiveness of hydroxyzine for long-term use (>4 months) has not been assessed
Carbinoxamine 4 mg oral tablet Carbinoxamine 4 mg/5 mL oral liquid Carbinoxamine (Karbinal® ER) 4 mg/5 mL extended release oral suspension	• **Concerns related to adverse effects:** may cause CNS depression • **Disease-related concerns:** use caution in patients with asthma, cardiovascular disease, increased intraocular pressure, prostatic hyperplasia/urinary obstruction, pyloroduodenal obstruction, thyroid dysfunction • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist • **Special populations:** use is contraindicated in children <2 years of age • **Dosage form specific issues:** some products may contain sodium metabisulfite, which may cause allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes, in susceptible patients
Promethazine 6.25 mg/5 mL oral syrup Promethazine 12.5, 25, 50 mg oral tablet Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV ampule Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV vial	• **Concerns related to adverse effects:** altered cardiac conduction; anticholinergic effects; CNS depression; extrapyramidal symptoms; neuroleptic malignant syndrome; orthostatic hypotension; photosensitivity; serious tissue injury with injection (boxed warning); impaired core body temperature regulation; • **Disease-related concerns:** use caution in patients with bone marrow suppression, cardiovascular disease, increased intraocular pressure/glaucoma, hepatic impairment, myasthenia gravis, Parkinson disease, respiratory disease, seizure history or risk • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist • **Special populations:** respiratory depression has been reported in children younger than 2 (boxed warning) • **Dosage form specific issues:** some dosage forms may benzyl alcohol; large amounts of benzyl alcohol have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; injection may contain sodium metabisulfite which may cause allergic reaction
Cyproheptadine 4 mg oral tablet Cyproheptadine 2 mg/5 mL, 4 mg/10 mL oral syrup	• **Concerns related to adverse effects:** may cause CNS depression; elderly patients may be more susceptible to adverse effects; may cause excitation in young children • **Disease-related concerns:** use caution in patients with cardiovascular disease, increased intraocular pressure, respiratory disease, thyroid dysfunction • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist • **Special populations:** elderly patients may be more susceptible to adverse effects; antihistamines may cause excitation in young children
Chlorcyclizine (Ahist®) 25 mg oral tablet	• Do not take this product unless directed by a doctor if you have a breathing problem such as emphysema or chronic bronchitis, glaucoma, difficulty in urination due to enlargement of the prostate gland • Ask a doctor before use if you are taking sedatives or tranquilizers • When using this product excitability may occur, especially in children, may cause drowsiness, alcohol, sedatives and tranquilizers may increase drowsiness effect • Use caution when driving a motor vehicle or operating machinery.

Medication	Warnings/Precautions
Dexbrompheniramine (Ala-Hist® IR) 2 mg oral tablet Dexbrompheniramine (Pediavent®) 1 mg chewable tablet Dexbrompheniramine (Pediavent®) 2 mg/5 mL oral liquid Dexchlorpheniramine (Ryclora®) 2 mg/5 mL oral solution	• **Concerns related to adverse effects:** may cause CNS depression, which may impair physical or mental abilities • **Disease related concerns:** use with caution in patients with cardiovascular disease (including hypertension), diabetes, increased intraocular pressure/glaucoma, prostatic hyperplasia/urinary obstruction, respiratory disease, and thyroid dysfunction • **Concurrent drug therapy issues:** potentially significant drug interactions may exist • **Special populations:** use with caution in the elderly and pediatric patients • **Other warnings/precautions:** when used for self-medication (OTC), discontinue use and contact health care provider if symptoms do not improve within 7 days or are accompanied by fever, new symptoms appear, or if nervousness, dizziness or sleeplessness occur
Triprolidine (Dr Manzanilla Infant, Histex® PD, Histex® PDX, M-Hist PD, PediaClear®, PediaClear® PD Allergy, Vanaclear PD) 0.313 mg/mL, 0.625 mg/mL, 0.938 mg/mL, 1.25 mg/mL oral drops Triprolidine (Miclara® LQ) 1.25 mg/5 mL, 2.5 mg/5 mL oral syrup Dr Manzanilla Pediatric, Histex® (triprolidine) 2.5 mg/5 mL oral syrup Histex® (triprolidine) 1.25 mg chewable tablet	• **Concerns related to adverse effects:** ay cause CNS depression, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (e.g. operating machinery, driving) • **Concurrent drug therapy issues:** potentially significant drug interactions may exist • **Special populations:** may cause excitation in children • **Dosage form specific issues:** Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated with hyperosmolality, lactic acidosis, seizures, and respiratory depression • **Other warnings/precautions:** Prior to self-medication (OTC use), contact health care provider if you have breathing problems (e.g. chronic bronchitis, emphysema), glaucoma, or difficulty urinating because of enlarged prostate
Chlorpheniramine (Aller-Chlor, Allergy, Allergy Relief, Allergy-Time, ChlorHist®, Chlor-Trimeton®, Pharbechlor®, Wal-Finate) 4 mg oral tablet Chlorpheniramine (Allergy Relief, Chlor-Trimeton Allergy, Chlorphen SR) 12 mg oral tablet Chlorpheniramine (Chlor-Trimeton, Ed Chlorped® Jr) 2 mg/5 mL oral syrup	• **Concerns related to adverse effects:** may cause CNS depression • **Disease-related concerns:** use caution in patients with cardiovascular disease, increased intraocular pressure, prostatic hyperplasia/urinary obstruction, respiratory disease, thyroid dysfunction • **Concurrent drug therapy issues:** Effects may be potentiated when used with other sedative drugs or ethanol • **Special populations:** Antihistamines may cause excitation in young children; not for OTC use in children <2 years of age • **Dosage form specific issues:** some dosage forms may contain sodium benzoate/benzoic acid, a metabolite of benzyl alcohol; large amounts of benzyl alcohol have been associated with a potentially fatal toxicity (“gasping syndrome”) in neonates
Clemastine (Allergy Relief, Dayhist® Allergy) 1.34, 2.68 mg oral tablet Clemastine 0.5 mg/5 mL oral syrup	• **Concerns related to adverse effects:** may cause CNS depression • **Disease-related concerns:** use caution in patients with asthma, cardiovascular disease, increased intraocular pressure, prostatic hyperplasia/urinary obstruction, pyloroduodenal obstruction, thyroid dysfunction • **Concurrent drug therapy issues:** Potentially significant drug interactions may exist
Pyrilamine (PediaClear®-8) 12.5 mg/15 mL oral syrup	• Ask a doctor before use if the child has a breathing problem such as emphysema or chronic bronchitis, glaucoma • Ask a doctor before use if the child is taking sedatives or tranquilizers • When using this product marked drowsiness may occur, sedatives and tranquilizers may increase drowsiness, excitability may occur, especially in children

Medication	Warnings/Precautions
Prescription-Only First Generation Antihistamine Combination Products	
Promethazine/ phenylephrine/ codeine (promethazine VC-codeine) 6.25 mg-5 mg-10 mg/5 mL oral syrup	• **Concerns related to adverse effects:** Altered cardiac conduction, anticholinergic effects, CNS depression, constipation, extrapyramidal symptoms, hypotension, neuroleptic malignant syndrome (NMS), phenanthrene hypersensitivity, photosensitivity, respiratory depression [US Boxed Warning], temperature regulation • **Disease-related concerns:** Abdominal conditions, adrenal insufficiency, biliary tract impairment, bone marrow suppression, Cardiovascular disease, Delirium tremens, head trauma, hepatic impairment, myasthenia gravis, obesity, Parkinson disease, prostatic hyperplasia/urinary stricture, psychosis, renal impairment, respiratory disease, seizures, sleep-related disorders, thyroid disease • **Concurrent drug therapy issues:** Benzodiazepines or other CNS depressants: [US Boxed Warning], cytochrome P450 interactions: [US Boxed Warning] • **Special populations:** CYP2D6 "ultrarapid metabolizers", cachectic or debilitated patients: Avoid use caution in cachectic or debilitated patients; there is a greater potential for critical respiratory depression, even at therapeutic dosages, elderly, Neonatal withdrawal syndrome: [US Boxed Warning], pediatrics • **Dosage forms related issues:** Benzyl alcohol and derivatives, propylene glycol • **Other warnings/precautions:** Abrupt discontinuation/withdrawal, abuse/misuse/diversion: [US Boxed Warning], accidental ingestion: [US Boxed Warning], appropriate use, medication errors: [US Boxed Warning], naloxone access, surgery
Brompheniramine/ pseudoephedrine/ dextromethorphan (Bromfed® DM) 2 mg-30 mg-10 mg/5 mL oral syrup	• **Concerns related to adverse effects:** CNS depression • **Disease-related concerns:** Cardiovascular disease, GI obstruction, GU dysfunction, Increased intraocular pressure, respiratory disease, seizures, thyroid dysfunction • **Concurrent drug therapy issues:** Sedatives • **Special populations:** CYP2D6 poor metabolizers, pediatric • **Other warnings/precautions:** cough, self-medication (OTC use)
Promethazine/dextromethorphan (promethazine-DM) 6.25 mg-15 mg/5 mL oral syrup	• **Concerns related to adverse effects:** altered cardiac conduction, anticholinergic effects, CNS depression, extrapyramidal symptoms, neuroleptic malignant syndrome, orthostatic hypotension, temperature regulation • **Disease-related concerns:** Bone marrow suppression, cardiovascular disease, glaucoma, hepatic impairment, myasthenia gravis, Parkinson disease, respiratory disease, seizures • **Special populations:** CYP2D6 poor metabolizers, debilitated patients, pediatric • Other warnings/precautions: Abuse/Misuse
Promethazine/phenylephrine (promethazine VC) 6.25 mg-5 mg/5 mL oral syrup	• **Concerns related to adverse effects:** Altered cardiac conduction, anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome (NMS), orthostatic hypotension, sedation, temperature regulation • **Disease-related concerns:** Bone marrow suppression, cardiovascular disease, diabetes, glaucoma, hepatic impairment, hyperthyroidism, myasthenia gravis, Parkinson disease, prostatic hyperplasia, respiratory disease • **Concurrent drug therapy issues:** antiemetic effects, sedatives • **Special populations:** Elderly, pediatric: [US Boxed Warning]

PRACTICE GUIDELINES

Allergic Rhinitis

American College of Allergy, Asthma & Immunology Guidelines (2020 Update)
Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020;146(4):721-767.

- Should routinely prescribe monotherapy with an intranasal corticosteroid rather than a combination of an intranasal corticosteroid with an oral antihistamine
- Should recommend an intranasal corticosteroid over a leukotriene receptor antagonist (for 15 years of age)
- For moderate to severe symptoms, may recommend the combination of an intranasal corticosteroid and an intranasal antihistamine
- Antihistamines target the histamine1 (H1) receptor and relieve the itching, sneezing, and rhinorrhea of AR. Antihistamines are available as oral (first- and second-generation) and intranasal preparations. First-generation antihistamines (eg, diphenhydramine, chlorpheniramine, and hydroxyzine) cross the blood-brain barrier easily and bind central H1-receptors abundantly, which can cause sedation. They also lack specificity because cross-binding also occurs with cholinergic, a-adrenergic, and serotonergic receptors, which can cause dry mouth, dry eyes, urinary retention, constipation, and tachycardia. Cumulative use of first-generation antihistamines with strong anticholinergic properties has been associated with higher risk of dementia. In contrast, second generation antihistamines (eg, fexofenadine, cetirizine, levocetirizine, loratadine, desloratadine, ebastine, epinastine, and bilastine) are more specific for peripheral H1-receptors and have limited penetration of the blood-brain barrier, thus reducing sedation.

Recommendations related to first-generation antihistamines:

- Should not prescribe a first-generation antihistamine and are in favor of a second-generation antihistamine when prescribing an oral antihistamine for the treatment of AR

American Academy of Otolaryngology – Head and Neck Surgery Allergic Rhinitis Guidelines (2015)
Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. American Academy of Otolaryngology – Head and Neck Surgery. 2015; 152(2):197-206.

Recommendation	Grade of Recommendation
Clinicians should recommend oral second-generation/less-sedating antihistamines for patients with allergic rhinitis and primary complaints of sneezing and itching	Strong Recommendation: based on randomized, controlled trials with minor limitations and a preponderance of benefit over harm
Clinicians may offer intranasal antihistamines for patients with seasonal, perennial, or episodic allergic rhinitis	Option: based on randomized, controlled trials with minor limitations and observational studies, with equilibrium of benefit over harm
Clinicians may offer combination pharmacologic therapy in patients with allergic rhinitis who have inadequate response to pharmacologic monotherapy	Option: based on randomized, controlled trials with minor limitations and observational studies, with equilibrium of benefit over harm

Urticaria

American Family Physician (AFP) Acute and Chronic Urticaria: Evaluation and Treatment (2017)
Schaefer P. Acute and Chronic Urticaria: Evaluation and Treatment. Am Fam Physician. 2017;95(11):717-724.

Recommendations:

- Second-generation antihistamines are considered first-line agents in the management of chronic urticaria
- For patients not responding to monotherapy with a second-generation antihistamine one of the following strategies may be employed:
    - Increase the dose of the second-generation antihistamine

- Add another second-generation antihistamine
- Add a H_2-antagonist
- Add a leukotriene receptor antagonist
- Add a first-generation antihistamine

- For patients still uncontrolled after the second step, a potent antihistamine such as hydroxyzine or doxepin should be utilized.
- Refractory chronic urticaria may be treated with omalizumab, cyclosporine, other anti-inflammatory agents, immunosuppressants, or biologics

Infusion Reaction Prophylaxis

European Society for Medical Oncology (EMSO) Guidelines for the Management of Infusion Reactions to Systemic Anticancer Therapy (2017)

Rosella S, Blasco I, Garcia FL, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Annals of Oncology. 2017; 28(4): 100-118.

Recommendation	Grade of Recommendation
If premedications are to be taken orally, oncology nurses should check that the patient has actually taken them	V, C
In the management of infusion reaction, the combined use of H_1 and H_2 antagonists is superior to the use of either class alone.	I, B
Diphenhydramine (1-2 mg/kg or 25-50 mg) may be given slowly via IV in combination with ranitidine (50 mg in 20 ml diluent) IV over 5 minutes.	V, C
After all symptoms have resolved, rechallenge with a reduced infusion rate and additional premedication (corticosteroids/antihistamines)	V, C

Recommendation definitions

Level of Evidence	Description
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grade of Recommendation	**Description**
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages, optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Extrapyramidal Side Effects Associated With Second-Generation Antipsychotics

Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Group (2011)

Pringsheim T, Doja A, Belanger S, et al. Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth. Pediatric Child Health. 2011; 16(9):590-598.

Recommendation	Level of Evidence
For the treatment of neuroleptic-induced acute dystonia, administer diphenhydramine. The patient and family can be advised that if an acute dystonic reaction occurs, they can self-administer an oral dose of diphenhydramine while seeking medical care. Treatment for two to five days to prevent recurrence may be considered.	High

For the treatment of neuroleptic-induced acute dystonia, an anticholinergic (benztropine) may be administered.	Very low

Insomnia

VA/Dod Clinical Practice Guidelines: The Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea (Insomnia/OSA) (2019)
Va.gov: Veterans Affairs [Internet]. 2019 [cited 2023 Oct 10]. Available from: https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp

- Suggest against the use of diphenhydramine for the treatment of chronic insomnia disorder
- Lack of rigorous data supporting the effectiveness of these antihistamines as nighttime sleep aids for chronic insomnia

American Academy of Sleep Medicine Clinical Practice Guidelines (2017)
Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, and Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2017; 13(2)307-349.

- All patients with chronic insomnia receive cognitive-behavioral therapies for insomnia (CBT-I) as the initial treatment intervention. Strong recommendation, moderate quality evidence
- Shared decision-making approach should be employed by clinicians in determining whether pharmacotherapy should be used for patients who did not achieve adequate response with CBT-I. Weak recommendation, low quality evidence
- Insufficient evidence to draw conclusions regarding the overall efficacy of pharmacotherapy in the insomnia population

Recommendations related to first-generation antihistamines:

- Clinicians should not use diphenhydramine as a treatment for sleep onset and sleep maintenance insomnia (versus no treatment) in adults. Weak recommendation, low quality evidence (benefit is approximately equal to harm). Recommendation is based on trials of 50 mg doses of diphenhydramine.

Antiemetics

American Academy of Family Physicians Antiemetics Guidelines (2015)
Flake ZA, Linn BS, and Hornecker JR. Practical selection of antiemetics in the ambulatory setting. American Academy of Family Physicians. 2015; 91(5):293-296.

- Antihistamines and anticholinergics are the preferred treatments for motion sickness. (Evidence rating C)
- When combined with aspirin, metoclopramide reduces nausea associated with migraine headaches. (Evidence rating B)
- Ondansetron significantly reduces the need for intravenous rehydration in children with gastroenteritis. (Evidence rating B)
- Pyridoxine with or without doxylamine is recommended to reduce pregnancy-induced nausea and vomiting. (Evidence rating C)

Grade of Recommendation	Description
A	Consistent, good-quality, patient-oriented evidence
B	Inconsistent or limited-quality patient-oriented evidence
C	Consensus, disease-oriented evidence, usual practice, expert opinion, or case series

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES*

Citation	Design	Endpoints
Bender BG, Berning S, Dudden R, et al. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. 2003; 111(4): 770-776.	Meta-analysis of 18 articles to compare the sedating and performance-impairing effects of diphenhydramine relative to placebo and second-generation antihistamines. Search using MEDLINE limited to studies that included patients with atopic disease and control subjects, blinded and randomized clinical trials, objective examination of alertness and psychomotor performance, and reported means and variances	Primary endpoint: Alertness and psychomotor performance
Results: Diphenhydramine impaired performance relative to placebo control and second-generation antihistamines, including acrivastine, astemizole, cetirizine, fexofenadine, loratadine, and terfenadine. There was a high variance, the average sedating effect of diphenhydramine was modest, and some tests of performance showed less sedation with diphenhydramine than in the control and second-generation antihistamine groups. There was a significant average effect size indicating a mild sedating effect of second-generation antihistamines compared to placebo. **Conclusion:** Diphenhydramine-induced sedation was not consistently found in the selected studies, with some designs intended to increase the probability of this outcome with higher diphenhydramine doses. Although this sedating effect has been established in the literature, this meta-analysis does not draw a clear distinction between sedating and nonsedating antihistamines.		
Citation	**Design**	**Endpoints**
Cho H, Myung J, Suh HS, et al. Antihistamine use and the risk of injurious falls or fracture in elderly patients: a systematic review and meta-analysis. 2018; 29(1):2163-2170.	Meta-analysis using MEDLINE, EMBASE, and local databases through November 2016 that observed the association between antihistamine use and the risk of injurious falls or fractures among elderly populations. A random effects model was used and heterogeneity was examined based on I-square and Cochran's Q test. Of the 473 identified studies, 5 were included in the analysis.	Primary endpoint: Risk of injurious falls or fractures
Results: First generation antihistamines had an increased risk of injurious falls or fracture (odds ratio [OR] 2.03, 95% confidence interval [CI] 1.49-2.76, heterogeneity: p = 0.41, I2 = 0%). Among studies that included all generations of antihistamines, the association was statistically significant without heterogeneity (OR 2.89, 95% CI 1.71-4.89, heterogeneity: p = 0.42, I2 = 0%). **Conclusion:** First generation antihistamines may considerably increase the risk of injurious falls or fractures among the elderly and should be prescribed with caution in this patient population.		

***Reliable clinical trial data, systematic reviews, and meta-analyses investigating first generation antihistamines are limited due to their conduction prior to digital recording and their general acceptance as being safe and efficacious.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (10/1/2023 - 12/31/2023)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Single-Drug First Generation Antihistamine Products								
Doxylamine (Nighttime Sleep-Aid, Sleep Aid, Ultra Sleep, Unisom®, Wal-Som) 25 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Diphenhydramine (Alka-Seltzer Plus Allergy, Compoz, NightTime Sleep Aid, Nytol®, Rest Simply, Simply Sleep, Sleep Aid, Sleep II, Sleep Tablet, Sleep-Tabs, Sominex®) 25 mg oral tablet, gel cap, caplet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Aler-Tab, Aller-G-Time, Allergy, Allergy Medicine, Allergy Relief, Anti-Hist, Banophen®, Benadryl® Allergy, Complete Allergy, Diphen®, Geri-Dryl®, Total Allergy, Wal-Dryl Allergy) 25 mg oral tablet, ultratab, caplet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (NightTime Sleep Aid, NightTime Sleep Gel, Nytol, Ormir, Sleep Aid, Sleep Time, Unisom® SleepGels, Unisom® SleepMinis, Wal-Sleep, Z-Sleep, ZzzQuil®) 25, 50 mg oral capsule, softgel	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Aler-Caps®, Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Antihistamine Allergy, Banophen®, Benadryl®, Complete Allergy, Diphenhist®, Medi-Phedryl, Pharbedryl®, Wal-Dryl Allergy) 25, 50 mg oral capsule	22	16	$19.30	$0.88	0	0 (0%)	F	No change
Diphenhydramine (Children's Allergy, Children's Allergy Relief, Children's Wal-Dryl Allergy) 12.5 mg orally disintegrating tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Unisom® SleepMelts, Wal-Sleep Z, Wal-Som) 25 mg orally disintegrating tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Children's Allergy Relief, Allergy Relief) 12.5, 25 mg chewable tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (PediaClear® Cough, Vanamine PD) 6.25 mg/mL oral drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Children's Wal-Dryl Allergy) 12.5 mg/5 mL prefilled spoon	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Sleep Aid, Sleep Time, Wal-Sleep, Z-Sleep, ZzzQuil) 50 mg/30 mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change

Diphenhydramine (Allergy, Allergy Medication, Allergy Medicine, Allergy Relief, Children's Allergy, Children's Aurodryl Allergy, Children's Benadryl® Allergy, Children's Diphenhydramine, Children's Wal-Dryl, Diphedryl®, Geri-Dryl®, M-Dryl®, Pediacare Allergy Solution, Siladryl® SA, Total Allergy) 12.5 mg/5 mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Naramin®) 12.5 mg/5 mL oral liquid in packet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine (Diphen®) 12.5 mg/5 mL oral elixir	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Diphenhydramine 50 mg/mL IV syringe	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydroxyzine 25 mg/mL, 50 mg/mL IM solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydroxyzine 10 mg/5 mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Hydroxyzine 10, 25, 50 mg oral tablet	56	44	$240.97	$4.30	0	0 (0%)	F	No change
Hydroxyzine pamoate (Vistaril®) 25, 50, 100 mg oral capsule	6	5	$21.69	$3.62	0	0 (0%)	F	No change
carbinoxamine 4 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Carbinoxamine 4 mg/5 mL oral liquid	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Carbinoxamine (Karbinal® ER) 4 mg/5 mL extended release oral suspension	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
promethazine 6.25 mg/5 mL oral syrup	18	5	$158.24	$8.79	0	0 (0%)	F	No change
Promethazine 12.5, 25, 50 mg oral tablet	6	3	$34.89	$5.82	0	0 (0%)	F	No change
Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV ampule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Promethazine (Phenergan®) 25 mg/mL, 50 mg/mL IV vial	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Cyproheptadine 4 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
cyproheptadine 2 mg/5 mL	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Chlorcyclizine (Ahist®) 25 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexbrompheniramine (Ala-Hist® IR) 2 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexbrompheniramine (Pediavent®) 1 mg chewable tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexbrompheniramine (Pediavent®) 2 mg/5 mL oral liquid	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dexchlorpheniramine (Ryclora®) 2 mg/5 mL oral solution	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Triprolidine (Dr Manzanilla Infant, Histex® PD, Histex® PDX, M-Hist PD, PediaClear®, PediaClear® PD Allergy, Vanaclear PD) 0.313 mg/mL, 0.625 mg/mL, 0.938 mg/mL, 1.25 mg/mL oral drops	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Triprolidine (Miclara® LQ) 1.25 mg/5 mL, 2.5 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Dr Manzanilla Pediatric, Histex® (triprolidine) 2.5 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Histex® (triprolidine) 1.25 mg chewable tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Chlorpheniramine (Aller-Chlor, Allergy, Allergy Relief, Allergy-Time, ChlorHist®, Chlor-Trimeton®, Pharbechlor®, Wal-Finate) 4 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change

Chlorpheniramine (Allergy Relief, Chlor-Trimeton Allergy, Chlorphen SR) 12 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Chlorpheniramine (Chlor-Trimeton, Ed Chlorped® Jr) 2 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Clemastine (Allergy Relief, Dayhist®, Dayhist® Allergy) 1.34, 2.68 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Clemastine 0.67 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Pyrilamine (PediaClear-8®) 12.5 mg/15 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Prescription-Only First Generation Antihistamine Combination Products								
Promethazine/phenylephrine/codeine (promethazine VC-codeine) 6.25 mg-5 mg-10 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	F	No change
brompheniramine/pseudoephedrine/dextromethorphan (Bromfed® DM) 2 mg-30 mg-10 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Promethazine/dextromethorphan (promethazine-DM) 6.25 mg-15 mg/5 mL oral syrup	36	34	$322.93	$8.97	1	1 (100%)	F-QL (240/30)	No change
Promethazine/phenylephrine (promethazine VC) 6.25 mg-5 mg/5 mL oral syrup	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Total	**144**	**107**	**$798.02**	**$5.54**	**1**	**1 (100%)**		

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. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on October 23, 2023.
2. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on October 23, 2023.
3. "DailyMed." DailyMed. N.p., n.d. Web. 11 Nov 2021. Available at https://dailymed.nlm.nih.gov/dailymed/
4. "Micromedex Products." Micromedex Products. N.p., n.d. Web. 11 Nov 2011. Available at http://www.micromedexsolutions.com/micromedex2/librarian/
5. Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: Allergic rhinitis. American Academy of Otolaryngology – Head and Neck Surgery. 2015; 152(2):197-206.
6. Rosella S, Blasco I, Garcia FL, et al. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. Annals of Oncology. 2017; 28(4): 100-118.
7. Pringsheim T, Doja A, Belanger S, et al. Treatment recommendations for extrapyramidal side effects associated with second-generation antipsychotic use in children and youth. Pediatric Child Health. 2011; 16(9):590-598.
8. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, and Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. Journal of Clinical Sleep Medicine. 2017; 13(2)307-349.
9. Flake ZA, Linn BS, and Hornecker JR. Practical selection of antiemetics in the ambulatory setting. American Academy of Family Physicians. 2015; 91(5):293-296.
10. Bender BG, Berning S, Dudden R, et al. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. 2003; 111(4): 770-776.
11. Cho H, Myung J, Suh HS, et al. Antihistamine use and the risk of injurious falls or fracture in elderly patients: a systematic review and meta-analysis. 2018; 29(1):2163-2170.
12. Dykewicz MS, Wallace DV, Amrol DJ, et al. Rhinitis 2020: A practice parameter update. J Allergy Clin Immunol. 2020;146(4):721-767.
13. Schaefer P. Acute and Chronic Urticaria: Evaluation and Treatment. Am Fam Physician. 2017;95(11):717-724.
14. Va.gov: Veterans Affairs [Internet]. 2019 [cited 2023 Oct 10]. Available from: https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp

Opioid Containing Antitussives

Executive Summary

CLASS OVERVIEW

This review covers products labeled as antitussive agents that are opioid containing. Opioids are considered centrally acting cough suppressants. Though the mechanism is not well understood, they are believed to act directly on the cough center in the brain. There are currently two agents in this category, codeine and hydrocodone, but other opioids such as morphine may be used off label in certain settings. These come in a wide variety of products and presentations combined with at least one other agent targeted to common cough and cold symptoms.

The use of opioids as antitussives are generally not recommended for the control of cough associated with mild, self-limiting illnesses such as the common cold due to safety concerns. Non-opioid agents such as benzonatate and dextromethorphan are more commonly used for temporary relief. For patients with chronic cough due to an underlying condition, eliminating the precipitant or treating the underlying cause is an appropriate initial course of action. Opioid-containing cough suppressants are primarily recommended when all other interventions have been exhausted and cough is negatively impacting a patient's quality of life, such as in a palliative setting for cancer patients. The FDA has limited the use of opioid containing cough suppressants in children, as the risks do not outweigh the benefits in those under 18 years of age.

UTILIZATION FINDINGS

There were 11 claims for 8 members, for a total cost of $74, and an average cost per claim of $6. The only two utilized medications were promethazine-codeine (Phenergan with Codeine) 6.25-10 mg/5 ml syrup with 6 claims, followed by guaifenesin-codeine (Cheratussin AC) oral solution 100-10 mg/5 ml with 5 claims. There were no prior authorization requests.

RECOMMENDATIONS

- No changes

CLINICAL SUMMARY

Opioids are considered centrally acting cough suppressants. Though the mechanism is not well understood, they are believed to act directly on the cough center in the brain. There are currently two agents in this category, codeine and hydrocodone, but other opioids such as morphine may be used off label in certain settings. Codeine and hydrocodone are prodrugs which are metabolized to morphine and hydromorphone, respectively, via the CYP2D6 enzyme system. There can be wide variability in the level of activity of this enzyme system due to one's genetic makeup, leading to unintended over or under exposure to morphine or hydromorphone at even standard doses.

Cough is a reflex that can serve to help clear airways of secretions or foreign material. However, cough that is persistent can become detrimental to a patient's quality of life. Cough can also be an important mechanism in the spread of contagious illnesses. It can occur in both acute and chronic settings and be due to a wide variety of acute illnesses, chronic conditions, or medication use. This table provided by the academy of CHEST physicians outlining the spectrum of topics addressed in their guidelines related to cough demonstrates the broad nature of the topic:

TABLE 1] Spectrum of Topics for the Third Edition of the CHEST Cough Guidelines

Section	Topics
Introductory matter	Overview of the management of cough
	Methodologies for the development of the management of cough: CHEST guideline and expert panel report
	Anatomy and neurophysiology of coughing
	Global physiology and pathophysiology of cough
	An assessment of intervention fidelity in studies on the diagnosis and treatment of chronic cough in the adult
	Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report
	Classifying cough as an aid to suggesting differential diagnoses[a]
	Empirical management of cough
Acute cough	Common cold
	Acute bronchitis
	Allergic rhinitis
	Community-acquired pneumonia
Subacute	Postinfectious
	Pertussis
Chronic	Upper airway cough syndrome
	Asthma
	Nonasthmatic eosinophilic bronchitis
	Gastroesophageal reflux disease
	Chronic bronchitis/COPD
	Bronchiectasis
	Bronchiolitis and other nonbronchiectatic suppurative airway disease
	Occupational and environmental factors
	Drug-induced cough
	TB
	Interstitial lung disease
	Lung cancer
	Aspiration
	Cardiac causes
	Psychogenic, habit, and tic cough
	Uncommon causes
	Unexplained (refractory) chronic cough
Special groups	Pediatric age group
	Immunocompromised host
	Athletes
	The elderly
Symptomatic	Cough suppressant
	Pharmacologic protussive therapy

Treatment strategies for cough require an evaluation and assessment of the underlying reason for the cough to determine the most appropriate course of action, if any. Cough due to self-limiting illnesses such as upper respiratory infections often do not require intervention, however some may seek care either through over-the-counter preparations or through a medical provider, depending on the degree of disruption to the patient's life. For patients with chronic cough due to an underlying condition, eliminating the precipitant or treating the underlying cause is an appropriate initial course of action. Opioid-containing cough suppressants are primarily recommended when all other interventions have been exhausted and cough is negatively impacting a patient's quality of life, such as in a palliative setting for cancer patients.

Utilization of opioids as antitussives and pain therapies have been under increased scrutiny due to the ongoing epidemic of abuse, addiction, and overdose deaths associated with these products. While once commonly prescribed and considered the gold standard, warnings and restrictive activities on the part of the FDA in recent decades have sharply reduced the use of opioids as antitussives and analgesics. In 2017, FDA restricted use of codeine cough and pain products and tramadol in children under 12 years with a contraindication warning on the labels of these products. Labeling was again updated in 2018 specifically to codeine- or hydrocodone-containing cough and cold medications, limiting their use to those 18 years of age and older. Ultimately, the FDA concluded that risks including slowed breathing and abuse/misuse did not outweigh benefits in children.

PRACTICE GUIDELINES

Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report (2018)

Summary of Suggestions

1. For adult patients complaining of cough, we suggest that acute cough be defined as being < 3 weeks in duration (Grade 2C).
2. For adult patients complaining of cough, we suggest that subacute cough be defined as being between 3 and 8 weeks in duration (Grade 2C).
3. For adult patients complaining of cough, we suggest that chronic cough be defined as being > 8 weeks in duration (Grade 2C).
4. For adult patients seeking medical care complaining of cough, we suggest that estimating the duration of cough is the first step in narrowing the list of potential diagnoses (Grade 2C).
5. For adult patients around the globe complaining of cough, we suggest that the cough be managed using evidence-based guidelines that are based upon duration of cough (Grade 2C).

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated with the Common Cold: CHEST Expert Panel Report (2017)

Summary of Recommendations and Suggestions

1. For adult and pediatric patients with cough due to the common cold, we suggest against the use of over-the-counter cough and cold medicines until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).
2. In adult patients with cough due to the common cold, we suggest against the use of nonsteroidal anti-inflammatory agents until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).
3. In pediatric patients (aged 1-18 years) with cough due to the common cold, we suggest honey may offer more relief for cough symptoms than no treatment, diphenhydramine, or placebo, but it is not better than dextromethorphan (Ungraded Consensus-Based Statement).
   Remarks: Infants < 1 year of age should not be administered honey, and children < 2 years of age should not be administered dextromethorphan for cough symptoms.
4. In pediatric patients (aged < 18 years) with cough due to the common cold, we suggest avoiding use of codeine-containing medications because of the potential for serious side effects including respiratory distress (Ungraded Consensus-Based Statement).

Symptomatic Treatment of Cough Among Adult Patients with Lung Cancer: CHEST Guideline and Expert Panel Report (2017)

Summary of Recommendations and Suggestions

1. In adult patients with cough associated with lung cancer that persists despite cancer treatment, we suggest, as a first step, that a comprehensive assessment according to a published, evidence-based management guideline be undertaken to identify any co-existing causes linked with cough and initiate treatment accordingly (Ungraded, Consensus Based Statement).
2. In adult patients with lung cancer experiencing cough despite anticancer treatment, we suggest cough suppression exercises as alternative or additional to pharmacological therapy where such services are available (Grade 2C).
3. In adult patients with cough due to localized endobronchial disease for whom surgery, chemotherapy, or external beam radiation are not indicated, we suggest the use of endobronchial brachytherapy where such specialist facilities are available and in suitable patients (Grade 2C).
4. In adult patients with lung cancer who require a pharmacological approach for the treatment of cough, we suggest an initial trial with demulcents such as butamirate linctus (syrup) or simple linctus (syrup) or glycerin-based linctus (syrup) where available (Grade 2C).

5. In adult patients with lung cancer experiencing cough that does not respond to demulcents, we suggest pharmacological management using an opiate-derivative titrated to an acceptable side-effect profile (Grade 2C).
6. In adult patients with lung cancer experiencing opioid-resistant cough, we suggest a peripherally acting antitussive (where available), such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate (Grade 2C).
7. In adult patients with lung cancer experiencing opioid-resistant cough that does not respond to peripheral antitussives, we suggest a trial with local anesthetics, including nebulized lidocaine/ bupivacaine or benzonatate (Ungraded, Consensus Based Statement).
8. In adult patients with intractable cough due to lung cancer in whom surgery, chemotherapy, external beam radiation, brachytherapy and the previously mentioned nonpharmacological and pharmacological approaches are ineffective or not indicated, we suggest that clinicians consider performing N-of-1 randomized controlled trials to determine if any of the following drugs might be of benefit in controlling cough because none have been definitively shown to be effective nor devoid of side effects: diazepam, gabapentin, carbamazepine, baclofen, amitriptyline, thalidomide (Ungraded, Consensus Based Statement).

Treatment of Interstitial Lung Disease Associated Cough CHEST Guideline and Expert Panel Report (2018)

Summary of Recommendations and Suggestions

1. For patients with ILD who present with a troublesome cough, we suggest that patients be assessed for progression of their underlying ILD, or complications from immunosuppressive treatment (eg, drug side effect, pulmonary infection) and also be considered for further investigation/treatment trials for their cough according to guidelines for acute, subacute and chronic cough. (Ungraded Consensus Based Statement)
2. For patients with IPF, chronic cough and a negative workup for acid gastroesophageal reflux, we suggest that proton pump inhibitor therapy should not be prescribed. (Ungraded Consensus-Based Statement)
3. For patients with pulmonary sarcoidosis, we suggest that inhaled corticosteroids should not be routinely prescribed to treat the chronic cough. (Grade 2C).
4. For patients with ILD and refractory chronic cough, we suggest trials of therapies recommended for patients with unexplained chronic cough according to the CHEST guidelines, with treatments such as gabapentin and multimodality speech pathology therapy or entering into clinical trials if available. (Ungraded Consensus-Based Statement)
5. For patients with chronic cough due to ILD, when alternative treatments have failed and the cough is adversely affecting their quality of life, we suggest that opiates be recommended for symptom control in a palliative care setting with reassessment of the benefits and risks at 1 week and then monthly before continuing. (Ungraded Consensus-Based Statement)

Recommendation Definitions

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (10/1/2023 - 12/31/2023)

Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Opioid-Containing Antitussives								
Hydrocodone-homatropine (Hycodan) 5-1.5 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydrocodone-homatropine (Hycodan) 5 mg-1.5 mg/5 ml solution	0	0	$0.00	$0.00	0	0 (0%)	F-QL (240/30)	No change
Codeine poli-chlorpheniramine poli (Tuzista XR) 14.7-2.8 mg/5 ml oral suspension extended release	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Chlorpheniramine-codeine phos (Z-Tuss AC) 2 mg-9 mg/5 ml liquid	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Chlorpheniramine-codeine phos (Tuxarin ER) 8-54.3 mg tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Promethazine-codeine (Phenergan with Codeine) 6.25-10 mg/5 ml syrup	6	3	$49.44	$8.24	0	0 (0%)	F-QL (240/30)	No change
Hydrocodone-chlorpheniramine p-stirex (Tussicaps) 10 mg-8 mg capsule	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydrocodone poli-chlorpheniramine poli (Tussionex Pennkinetic) 10-8 mg/5 ml ER susp	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Promethazine-phenylephrine-codeine (Promethazine VC/Codeine) oral syrup 6.25-5-10 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	F	No change
Phenylephrine-brompheniramine-codeine (M-End PE) oral liquid 3.33-1.33-6.33 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Phenylephrine-brompheniramine-codeine (Poly-Tussin AC) oral liquid 10-4-10 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Phenylephrine-chlorpheniramine-codeine (Maxi-Tuss CD) oral liquid 10-4-10 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Phenylephrine-chlorpheniramine-codeine (Capcof) oral syrup 5-2-10 mg/5ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Phenylephrine-dexchlorphen-codeine (Pro-Red AC) oral syrup 5-1-9 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pseudoephedrine-brompheniramine-codeine (Rydex) oral liquid 10-1.33-6.33 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pseudoephedrine-brompheniramine-codeine (Mar-Cof BP) oral liquid 30-2-7.5 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Phenylephrine-triprolidine-codeine (Histex AC) oral syrup 10-2.5-10 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Hydrocodone-chlorpheniramine-pseudoephedrine (Zutripro) 5-4-60mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guaifenesin-codeine (Ninjacof-XG) oral liquid 200-8 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guaifenesin-codeine (Coditussin AC) oral liquid 200-10 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guaifenesin-codeine (Mar-Cof CG) oral liquid 225-7.5 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guaifenesin-codeine (M-Clear WC) oral solution 100-6.33 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Guaifenesin-codeine (Cheratussin AC) oral solution 100-10 mg/5 ml	5	5	$24.85	$4.97	0	0 (0%)	F-QL (480/30)	No change
Pseudoephedrine-codeine-guaifenesin (Lortuss EX) oral liquid 30-10-100 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change

Pseudoephedrine-codeine-guaifenesin (Coditussin DAC) oral liquid 30-10-200 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pseudoephedrine-codeine-guaifenesin (Tusnel C) oral syrup 30-10-100 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Pseudoephedrine-codeine-guaifenesin (Cheratussin DAC) oral solution 30-10-100 mg/5 ml	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**11**	**8**	**$74.29**	**$6.75**	**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. Irwin RS. Introduction to the diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. Chest. 2006 Jan;129(1 Suppl):25S-27S. doi: 10.1378/chest.129.1_suppl.25S. PMID: 16428688. Accessed on 11/4/2021.
2. Ambizas, EM. Acute Cough—Does Anything Help? US Pharm. 2019;(1):8-12. Available at https://www.uspharmacist.com/article/acute-coughdoes-anything-help. Accessed on 10/19/2023.
3. "DailyMed." DailyMed. N.p., n.d. Web. Available at https://dailymed.nlm.nih.gov/dailymed/. Accessed on 10/19/2023.
4. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on 10/19/2023.
5. Irwin RS, French CL, Chang AB, Altman KW; CHEST Expert Cough Panel*. Classification of Cough as a Symptom in Adults and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2018 Jan;153(1):196-209. doi: 10.1016/j.chest.2017.10.016. Epub 2017 Nov 10. PMID: 29080708; PMCID: PMC6689094.
6. US Food and Drug Administration. Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Published 4/20/2017. Available at https://www.fda.gov/media/104268/download
7. US Food and Drug Administration. Drug Safety Communication: FDA Drug Safety Communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older. Published 1/11/2018. Available at https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-labeling-changes-prescription-opioid-cough-and-cold
8. Joseph D. Tobias, Thomas P. Green, Charles J. Coté, SECTION ON ANESTHESIOLOGY AND PAIN MEDICINE, COMMITTEE ON DRUGS, Rita Agarwal, Corrie T.M. Anderson, Courtney Alan Hardy, Anita Honkanen, Mohamed A. Rehman, Kathleen Neville, Constance S. Houck, Bridgette Jones, Ian M. Paul, Janice E. Sullivan, John N. Van Den Anker; Codeine: Time to Say "No". *Pediatrics* October 2016; 138 (4): e20162396. 10.1542/peds.2016-2396.
9. Malesker MA, Callahan-Lyon P, Ireland B, Irwin RS; CHEST Expert Cough Panel. Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold: CHEST Expert Panel Report. *Chest*. 2017;152(5):1021-1037. doi:10.1016/j.chest.2017.08.009.
10. Molassiotis A, Smith JA, Mazzone P, Blackhall F, Irwin RS; CHEST Expert Cough Panel. Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report [published correction appears in Chest. 2017 Nov;152(5):1095]. *Chest*. 2017;151(4):861-874. doi:10.1016/j.chest.2016.12.028.
11. Birring SS, Kavanagh JE, Irwin RS, et al. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. *Chest*. 2018;154(4):904-917. doi:10.1016/j.chest.2018.06.038.

Name: Zepbound (tirzepatide)

Manufacturer: Eli Lilly & Company

Approval Date: 11/8/2023

Marketing Date: 11/10/2023

Recommendation

- No changes

Prescribing Information

Indication

Zepbound™ is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of:

- 30 kg/m2 or greater (obesity) or
- 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease)

Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is an amino acid sequence including a C20 fatty diacid moiety that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Dosage and Administration

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. After 4 weeks, increase to 5 mg injected subcutaneously once weekly. Increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. Consider treatment response and tolerability when selecting the maintenance dosage.
- The maximum dosage is 15 mg subcutaneously once weekly.

Black Box Warning

Risk of Thyroid C-Cell Tumors

In rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Zepbound™ causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

Zepbound™ is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Zepbound™.

Adverse Reactions

Most common (≥5%): Nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, and gastroesophageal reflux disease

Serious: Risk of thyroid C-cell tumor, severe gastrointestinal disease, acute kidney injury, acute gallbladder disease, acute pancreatitis, hypersensitivity reactions, hypoglycemia, diabetic retinopathy, and suicidal behavior and ideation

Use in Specific Populations, Pregnancy

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue Zepbound™ when a pregnancy is recognized. Available data with tirzepatide in pregnant patients are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy.

Drug Interactions

Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

- Zepbound™ lowers blood glucose. When initiating Zepbound™, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia.

Oral Medications

- Zepbound™ delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with Zepbound™.
- Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with Zepbound™.
- Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with Zepbound™ and for 4 weeks after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected.

How Supplied

Subcutaneous Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen

Price

$1,060/28 days

(Per month, based on WAC.)

Clinical Studies

Completed

Title	Tirzepatide Once Weekly for the Treatment of Obesity (SURMOUNT-1) NCT: 04184622 PMID: 35658024
Design	Phase 3, randomized, double-blind, placebo-controlled
Population	N=2539 Mean age of 44.9 years at baseline and a mean duration of obesity of 14 years. Female population accounted for 67.5% while 71% of the participants were white, 11% were Asian, 8% were Black, 9% were American Indian or Alaskan Native, and 7% were of Hispanic or Latino ethnicity. Mean body weight was 104.8 kg, the mean BMI was 38, the mean waist circumference was 114.1 cm, and 94.5% of participants had a BMI of 30 or greater. 40.6% had prediabetes, mean glycated hemoglobin was 5.6%, mean fasting glucose was 95.5 mg/dL, and mean SF-36 physical function score was 49.6.

Arms	Randomized (1:1:1:1)
	• Once weekly tirzepatide for 72 weeks
	  ○ 5 mg (N=630)
	  ○ 10 mg (N=636)
	  ○ 15 mg (N=630)
	• Matching placebo for 72 weeks (N=643)

Endpoint(s)	Co-Primary:
	
	• Percent change from baseline to week 72 in body weight
	• Percentage of participants who achieve ≥5% body weight reduction at week 72
	
	Secondary:
	
	• Participants who after 72 weeks achieved a weight reduction of at least:
	  ○ ≥10% or more
	  ○ ≥15% or more
	  ○ ≥20% or more
	• Change in weight from baseline to week 20
	• Change from baseline to week 72 in waist circumference

Inclusion Criteria	• Male or female, age ≥18 years • Body mass index (BMI) ≥30 kilograms per square meter (kg/m²), or ≥27 kg/m² and previous diagnosis with at least one of the following comorbidities: hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease • History of at least one unsuccessful dietary effort to lose body weight

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

Diabetes mellitus
Change in body weight greater than 5 kg within 3 months prior to starting study
Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
History of pancreatitis
Family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN-2)
History of significant active or unstable major depressive disorder (MDD) or other severe psychiatric disorder within the last 2 years
Any lifetime history of a suicide attempt

</td></tr>
<tr><td>Results</td><td>
Primary:

All changes are from baseline to week 72 → Least squares mean (95% confidence interval [CI]); p<0.001 for all comparisons with placebo

<table>
<tr><th>End Points</th><th>Tirzepatide 5 mg</th><th>Tirzepatide 10 mg</th><th>Tirzepatide 15 mg</th><th>Placebo</th></tr>
<tr><td>% change in body weight</td><td>-15.0
(-15.9 to -14.2)</td><td>-19.5
(-20.4 to -18.5)</td><td>-20.9
(-21.8 to -19.9)</td><td>-3.1
(-4.3 to -1.9)</td></tr>
<tr><td>Difference from placebo in % change</td><td>-11.9
(-13.4 to -10.4)</td><td>-16.4
(-17.9 to -14.8)</td><td>-17.8
(-19.3 to -16.3)</td><td>X</td></tr>
<tr><td>% of participants with ≥5% weight reduction</td><td>85.1
(81.6 to 88.6)</td><td>88.9
(85.9 to 91.9)</td><td>90.9
(88.0 to 93.8)</td><td>34.5
(29.8 to 39.2)</td></tr>
</table>
Secondary:

All changes are from baseline to week 72 → Least squares mean (95% CI); p<0.001 for all comparisons with placebo

<table>
<tr><th>End Points</th><th>Tirzepatide 5 mg</th><th>Tirzepatide 10 mg</th><th>Tirzepatide 15 mg</th><th>Placebo</th></tr>
<tr><td>% of participants with ≥10% weight reduction</td><td>68.5
(64.5 to 72.5)</td><td>78.1
(74.4 to 81.7)</td><td>83.5
(80.0 to 86.9)</td><td>18.8
(14.9 to 22.7)</td></tr>
<tr><td>% of participants with ≥15% weight reduction</td><td>48.0
(43.9 to 52.1)</td><td>66.6
(62.6 to 70.6)</td><td>70.6
(66.7 to 74.5)</td><td>8.8
(5.9 to 11.7)</td></tr>
<tr><td>% of participants with ≥20% weight reduction</td><td>30.0
(26.4 to 33.6)</td><td>50.1
(46.0 to 54.2)</td><td>56.7
(52.6 to 60.8)</td><td>3.1
(1.1 to 5.1)</td></tr>
<tr><td>Change in waist circumference (cm)</td><td>-14.0
(-14.9 to -13.1)</td><td>-17.7
(-18.7 to -16.8)</td><td>-18.5
(-19.3 to -17.6)</td><td>-4.0
(-5.1 to -2.8)</td></tr>
</table>
</td></tr>
</table>

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

All changes are from baseline to week 20 → Least squares mean (95% CI); p<0.001 for all comparisons with placebo

<table>
<tr><th>Endpoint</th><th>Pooled Tirzepatide Groups</th><th>Placebo</th><th>Estimated Treatment Difference from Placebo</th></tr>
<tr><td>Change from baseline to week 20 in body weight</td><td>-12.8
(-13.1 to -12.5)</td><td>-2.7
(-3.2 to -2.2)</td><td>-10.1
(-10.7 to -9.6)</td></tr>
</table>
</td></tr>
<tr><td>Conclusion</td><td>The author concluded, “In this 72-week trial in participants with obesity, 5 mg, 10 mg, or 15 mg of tirzepatide once weekly provided substantial and sustained reductions in body weight.”</td></tr>
<tr><td>Interpretation</td><td>The SURMOUNT-1 study demonstrated efficacious results of tirzepatide for patients with obesity or those who are overweight with weight-related comorbidities. All primary and secondary outcomes provided statistically significant results in the mean percentage change in body weight at week 72, as well as the percentage of participants who had weight reductions of at least 5%, 10% or 15% or more with all strengths of tirzepatide. The substantial degree of weight reduction seen is this trial was significant with about 90% of participants achieving a body weight reduction of 5% or more, which is something that not many other phase 3 trials have achieved. When looking at limitations of the study, the enrolled participants with obesity and overweight may only represent a small subpopulation that have a greater commitment to managing their weight than the general population with obesity. This may lead to a greater reduction in body weight if participants are actively managing their weight with other lifestyle interventions more efficiently than others. Furthermore, only 5.5% of enrolled participants were overweight which may be challenging to generalize these findings across this specific population of patients.</td></tr>
</table>

Title	Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial (SURMOUNT-2) NCT: 04657003 PMID: 37385275
Design	Phase 3, randomized, double-blind, placebo-controlled
Population	N=938 Mean age of 54.2 years at baseline and a mean duration of obesity of 18 years. Female population accounted for 51% while 76% of the participants were white, 13% were Asian, 8% were Black, and 60% were of Hispanic or Latino ethnicity. Mean body weight was 100.7 kg, the mean BMI was 36, the mean waist circumference was 114.9 cm, and 33% of participants had a BMI of 30 or greater. The mean duration of diabetes was 8.5 years, mean glycated hemoglobin (HbA1c) was 8.0%, mean fasting glucose was 159.3 mg/dL, and 89% were treated with biguanides while 27% were treated with sulfonylureas.

<table>
<tr><td>Arms</td><td>Randomized (1:1:1)
Once weekly tirzepatide for 72 weeks
10 mg (N=312)
15 mg (N=311)
Matching placebo for 72 weeks (N=315)</td></tr>
<tr><td>Endpoint(s)</td><td>Co-Primary:
Percent change from baseline to week 72 in body weight
Percentage of participants who achieve ≥5% body weight reduction at week 72
Secondary:
Participants who after 72 weeks achieved a weight reduction of at least:
≥10% or more
≥15% or more
≥20% or more
Change in HbA1c from baseline to week 72
Change from baseline to week 72 in fasting glucose
Change from baseline to week 72 in waist circumference</td></tr>
<tr><td>Inclusion Criteria</td><td>Male or female, age ≥18 years
Type 2 diabetes with HbA1c ≥7% to ≥10% at screening, on stable therapy for the last 3 months prior to screening
BMI of ≥27 kg/m²
Are overweight or have obesity
History of at least one self-reported unsuccessful dietary effort to lose body weight</td></tr>
<tr><td>Exclusion Criteria</td><td>Type 1 diabetes mellitus, history of ketoacidosis or hyperosmolar state/come or any other types of diabetes except T2DM
Have at least 2 confirmed fasting self-monitoring blood glucose (SMBG) values >270 mg/dL (on 2 nonconsecutive days) prior to visit 3
Have proliferative diabetic retinopathy OR diabetic macular edema OR non-proliferative diabetic retinopathy that requires acute treatment
Self-reported change in body weight greater than 5 kg within 3 months prior to starting study
Obesity induced by other endocrinologic disorders or monogenetic or syndromic forms of obesity
History of chronic or acute pancreatitis
Family or personal history of MTC or MEN-2
History of significant active or unstable MDD or other severe psychiatric disorder within the last 2 years
Any lifetime history of a suicide attempt</td></tr>
<tr><td>Results</td><td>Primary:
All changes are from baseline to week 72 → Least squares mean (95% CI); p<0.001 for all comparisons to placebo
<table><tr><th>End Points</th><th>Tirzepatide 10 mg</th><th>Tirzepatide 15 mg</th><th>Placebo</th></tr></table></td></tr>
</table>

Percent change in body weight, %	-12.8	-14.7	-3.2
Difference from placebo in % change	-9.6 (-11.1 to -8.1)	-11.6 (-13.0 to -10.1)	X
Participants with ≥5% weight reduction	79%	83%	32%

Secondary:

- All changes are from baseline to week 72 → Least squares mean (95% CI); p<0.001 for all comparisons to placebo

End Points	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
% of participants with ≥10% weight reduction	61	65	9
% of participants with ≥15% weight reduction	40	48	3
% of participants with ≥20% weight reduction	22	31	1
Change in waist circumference (cm)	-10.8	-13.1	-3.3
Change in HbA1c, %	-2.07	-2.08	-0.51
Change in fasting glucose, mg/dL	-48.9	-48.9	-11.0

Conclusion	The author concluded, "In adults with a BMI of 27 kg/m² or higher and type 2 diabetes, once-weekly treatment with tirzepatide demonstrated substantial, clinically meaningful bodyweight reductions of up to 15%, with weight reduction of 20% or higher reached by up to nearly one-third of tirzepatide-treated participants. Additionally, tirzepatide improved cardiometabolic risk factors and glycemic control, with almost half of tirzepatide-treated participants reaching an HbA1c less than 7.5%."
Interpretation	The SURMOUNT-2 study demonstrated efficacious results of tirzepatide for patients with obesity and type 2 diabetes. All primary and secondary outcomes provided statistically significant results in the mean percentage change in body weight at week 72, as well as the percentage of participants who had weight reductions of at least 5%, 10% or 15% or more with both strengths of tirzepatide. The substantial degree of weight reduction is more challenging in people with obesity and type 2 diabetes compared to those without type 2 diabetes, therefore, in this trial we see only about 83% of participants achieving a body weight reduction of 5% or more compared to the SURMOUNT-1 trial. When looking at limitations of the study, an approved dose for treating type 2 diabetes (tirzepatide 5 mg) that provided significant weight reduction in previous studies, was not included in this trial. Also, GI events were self-reported in this trial which may correspond with reporting bias, although this approach has usually been standard practice in other clinical trials. Furthermore, the trial duration was appropriate to study the efficacy of tirzepatide at 72 weeks, however, even longer-term trials may be

	appropriate to study the long-term safety and efficacy of this medication, especially after treatment cessation.

Ongoing

Title	A Phase 3b, Randomized Controlled Study to Evaluate the Efficacy and Safety of Tirzepatide Compared to Semaglutide in Adults Who Have Obesity or Overweight with Weight Related Comorbidities (SURMOUNT-5) NCT: 05822830
Design	Phase 3b, randomized, controlled trial to evaluate the efficacy and safety of tirzepatide compared with semaglutide in adult participants who have obesity or overweight with weight related comorbidities without type 2 diabetes
Completion Date	November 6, 2024

Title	Efficacy, Safety, and Pharmacokinetics of Tirzepatide Once Weekly Versus Placebo in Adolescent Participants Who Have Obesity, or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind Trial (SURMOUNT-ADOLESCENTS) NCT: 06075667
Design	Phase 3, randomized, double-blind trial to evaluate the safety and efficacy of tirzepatide in adolescents that have obesity or overweight with at least one weight-related comorbidity
Completion Date	December 1, 2026

Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Tirzepatide on the Reduction of Morbidity and Mortality in Adults with Obesity (SURMOUNT-MMO) NCT: 05556512
Design	Phase 3, randomized, double-blind, placebo-controlled trial to investigate the effect of tirzepatide on the reduction of morbidity and mortality in adults living with obesity
Completion Date	October 7, 2027

Title	A Phase 3b, Randomized Controlled Study to Evaluate the Efficacy and Safety of Tirzepatide Once Weekly 5mg and/or Maximum Tolerated Dose Versus Placebo for Maintenance of Body Weight

	Reduction in Participants Who Have Obesity or Overweight with Weight-Related Comorbidities (SURMOUNT-MAINTAIN) NCT: 06047548
Design	Phase 3b, randomized, controlled trial to evaluate the efficacy and safety of tirzepatide for the maintenance of body weight reduction
Completion Date	May 22, 2026

Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide Versus Placebo in Patient with Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT) NCT: 04847557
Design	Phase 3, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of tirzepatide in participants with heart failure with preserved ejection fraction and obesity
Completion Date	July 30, 2024

Guidelines

Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. Gastroenterology. 2022;163(5):1198-1225.

Recommendations on Pharmacological Interventions for Management of Obesity

- In adults with obesity or overweight with weight-related complications, who have had an inadequate response to lifestyle interventions, the AGA recommends adding pharmacological agents to lifestyle interventions over continuing lifestyle interventions alone (Strong recommendation, moderate certainty).
- In adults with obesity or overweight with weight-related complications, the AGA suggests using semaglutide 2.4 mg with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, moderate certainty).
- In adults with obesity or overweight with weight-related complications, the AGA suggests using liraglutide 3.0 mg with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, moderate certainty).
- In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine-topiramate ER with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, moderate certainty).
- In adults with obesity or overweight with weight-related complications, the AGA suggests using naltrexone-bupropion ER with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, moderate certainty).

- In adults with obesity or overweight with weight-related complications, AGA suggests against the use of orlistat (Conditional recommendation, moderate certainty). Comment: Patients who place a high value on the potential small weight loss benefit and low value on GI adverse effects may reasonably choose treatment with orlistat.
- In adults with obesity or overweight with weight-related complications, the AGA suggests using phentermine with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, low certainty).
- In adults with obesity or overweight with weight-related complications, the AGA suggests using diethylpropion with lifestyle modifications, compared with lifestyle modifications alone (Conditional recommendation, low certainty).
- In adults with BMI between 25 and 40 kg/m^2, the AGA recommends using Gelesis100 oral superabsorbent hydrogel only in the context of a clinical trial (Knowledge gap).

Recommendation Definitions

Certainty	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision making. Decision aids may be useful in helping patient make decisions consistent with their individual risks, values, and preferences.
For policy makers	The recommendation can be adapted as policy or performance measure in most situations.	Policy making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision making is appropriate.

Clinical Opinions

Obesity is the most prevalent chronic disease state with a prevalence of nearly 43% of adult patients, including both male and female. There are multiple classifications of obesity based on BMI, but most studies include those with a BMI of 30 kg/m^2 or greater, or 27 kg/m^2 or greater with comorbidities. Ensuing complications such as type 2 diabetes and cardiovascular disease are associated with significant morbidity and mortality. The cornerstone of weight management includes lifestyle interventions such as diet and exercise, but maintaining weight can be challenging. Clinical guidelines suggest adjunctive pharmacotherapy to help produce greater weight loss and weight loss maintenance in combination with lifestyle interventions. Selecting the optimal weight loss medication for patients can be challenging and should be carefully selected by considering efficacy, safety profile, and cost.

Zepbound™ (tirzepatide) is a dual GLP-1 and GIP agonist that works by increasing insulin secretion, decreasing glucagon secretion, decreasing food intake and delaying gastric emptying. Tirzepatide was first approved in 2022 for the treatment of type 2 diabetes under the brand name Mounjaro™. Wegovy® (semaglutide), the market leader in weight loss, only targets GLP-1, while Zepbound™ also targets GIP. GIP which is a nutrient-stimulated hormone that may ultimately help lead to a greater reduction in body weight. While there is currently no direct head-to-head evidence comparing the two, there is some evidence that suggests Zepbound™ is more efficacious than Wegovy®. In the SURMOUNT-1 trial, patients who received the highest dose of Zepbound™ experienced an average weight loss of 20.9%. In a clinical trial evaluating Wegovy® in a similar population, patients experienced an average weight loss of 14.9% at the recommended maintenance dose.

There are currently ongoing clinical trials that are studying Zepbound™ directly with Wegovy® in obese or overweight patients, as well as studying Zepbound™ in the adolescent population. It should be noted that payer coverage of drugs for chronic weight management is currently limited, due to it being considered lifestyle or cosmetic. However, the superior efficacy and lower cost of Zepbound™, combined with the healthcare industry evolving in its recognition of obesity as a disease and not a lifestyle choice, may encourage more payers to provide coverage.

Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Wegovy® (semaglutide)	F-PA	0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL, 2.4 mg/0.75 mL subcutaneous auto-injector	$1,349
Saxenda® (liraglutide)	F-PA	18 mg/3 mL subcutaneous auto-injector	$1,349
Orlistat (Xenical®)	F-PA	120 mg oral capsules	$650
Contrave® (naltrexone/bupropion)	F-PA	8 mg-90 mg ER oral tablets	$625

**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).*

References

1. Zepbound™ [prescribing information]. Eli Lilly & Company. Indianapolis, IN; November 2023.
2. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on November 21, 2023.
3. Facts & Comparisons eAnswers, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on November 21, 2023.
4. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on November 21, 2023.
5. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on November 21, 2023.
6. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Available at: http://www.fda.gov/. Accessed on November 21, 2023.
7. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on November 21, 2023.
8. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205-216.
9. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2023;402(10402):613-626.
10. Grunvald E, Shah R, Hernaez R, et al. AGA clinical practice guideline on pharmacological interventions for adults with obesity. Gastroenterology. 2022;163(5):1198-1225.
11. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus semaglutide once weekly in patients with type 2 diabetes. N Engl J Med. 2021;385(6):503-515.

Drug Name: Methylergonovine maleate (Methergine) **Manufacturer:** Novel Laboratories

Approval Date: November 19, 1946

Recommendation

- No changes
  - The current formulary status is F
  - There was no utilization of this medication and no prior authorizations requests from 10/1/2023 to 12/31/2023

Prescribing Information

Indication

Following delivery of placenta, for routine management of uterine atony, hemorrhage and subinvolution of the uterus. For control of uterine hemorrhage in the second stage of labor following delivery of the anterior shoulder.

Mechanism of Action

Methergine acts directly on the smooth muscle of the uterus and increases the tone, rate, and amplitude of rhythmic contractions. Thus, it induces a rapid and sustained tetanic uterotonic effect which shortens the third stage of labor and reduces blood loss.

Dosage and Administration

Oral dosing: 0.2 mg 3 or 4 times daily in the puerperium for a maximum of 1 week.

Black Box Warning

None

Adverse Reactions

Most common: Hypertension, headache, abdominal pain, nausea, and vomiting

Serious: Myocardial infarction and seizure

Use in Specific Populations, Pregnancy

Animal reproductive studies have not been conducted with methylergonovine. It is also not known whether methylergonovine maleate can cause fetal harm or can affect reproductive capacity. Use of methylergonovine is contraindicated during pregnancy because of its uterotonic effects.

Drug Interactions

CYP 3A4 Inhibitors (e.g., Macrolide Antibiotics and Protease Inhibitors): There have been rare reports of serious adverse events in connection with the coadministration of certain ergot alkaloid drugs (e.g., dihydroergotamine and ergotamine)

and potent CYP 3A4 inhibitors, resulting in vasospasm leading to cerebral ischemia and/or ischemia of the extremities. Potent CYP 3A4 inhibitors should not be coadministered with Methergine.

CYP3A4 Inducers: Drugs (e.g., nevirapine, rifampicin) that are strong inducers of CYP3A4 are likely to decrease the pharmacological action of Methergine.

Beta-Blockers: Caution should be exercised when Methergine is used concurrently with beta-blockers. Concomitant administration with beta-blockers may enhance the vasoconstrictive action of ergot alkaloids.

Anesthetics: Anesthetics like halothan and methoxyfluran may reduce the oxytocic potency of Methergine.

Glyceryl Trinitrate and Other Antianginal Drugs: Methylergonovine maleate produces vasoconstriction and can be expected to reduce the effect of glyceryl trinitrate and other antianginal drugs.

How Supplied

Oral Tablets: 0.2 mg

Price

$408

(Per 1 week treatment course, based on NADAC)

Clinical Studies

Completed

Title	Reduction of Endometritis After Cesarean Section With the Routine Use of Methergine NCT: 00858832
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Prevention
Population	N=80, patients 18 and older having singleton pregnancies without evidence of intra-amniotic infection that are undergoing a non-elective cesarean delivery with a normal blood pressure.
Arms	Patient were randomized to receive either: • Methergine 0.2 mg orally every 6 hours for two days, plus routine postpartum care • Routine postpartum care
Endpoint(s)	Number of participants who developed endometritis
Inclusion Criteria	• Female singleton gravidas • Patients receiving non-elective cesarean deliveries after trial of labor • No evidence of chorioamnionitis

Exclusion Criteria	• Diagnosis of chorioamnionitis • Elective cesarean section • Immunocompromised patients and those on antiretroviral drugs • Patients with known infection • Hypertension (two blood pressure readings greater than 140/90, six hours apart), including those with a past history, gestational or preeclampsia • Allergic to ergot alkaloids, including migraine medicine
Results	Fourteen patients (36%) in the control group and four patients (10%) in the Methergine group were diagnosed with endometritis (P<0.005; odds ratio, 5.2; 95% confidence interval, 1.5 to 17.5). Additionally, while the preoperative hemoglobin (Hb) values between the two groups were similar, the mean postoperative Hb level was 10.2 gm/dL in the control group and -11.2 gm/dL in the study group (P<0.001), showing that Methergine reduced postoperative blood loss. There were no significant demographic differences between the two groups.
Conclusion	N/A
Interpretation	While this was on open-label trial design which can introduce bias, Methergine appears to be a successful intervention as a preventative measure for endometritis. It also appears to conserve appropriate Hb levels postoperatively.

Title	The Effect of the Combined Use of Methylergonovine and Oxytocin during Caesarean Section in the Prevention of Post-partum Hemorrhage NCT: N/A PMID: 26449959
Design	Randomized, prospective trial
Population	N=1210, patients 18 to 40 years of age with gestation greater than 34 weeks, with gravida 1 to 3. The mean age of patients was about 31 years.
Arms	Two groups of patients undergoing caesarean section at the same clinic were randomized to receive either: • A combination of methylergonovine (given 0.2 mg IM in the first minute after delivery and post-operatively after 3 hours) and oxytocin (per IV infusion) during the intra-operative and post-operative periods (N=295) • Only oxytocin infusion in the intra-operative and post-operative periods (N=915)
Endpoint(s)	Mean reduction rates of Hb levels in the post-partum period
Inclusion Criteria	• Age 18–40 years • Gestation ≥34 weeks • Gravida 1–3; and all with indications for Caesarean

Exclusion Criteria	• Those with known pre-eclampsia, eclampsia and hypertensive disease • Patients with coagulation disorder • Patients who had been given blood transfusion • Those diagnosed with severe anemia (Hb<7 gr/dL) and polycythemia vera (Hb>16 gr/dL) • Patients with known ischemic heart disease, cerebrovascular disease or peripheral vascular disease, and with no post-partum uterine atony which would require additional medical therapy or blood transfusion due to change in Hb levels
Results	When pre-operative and post-operative Hb values of the patients administered and not administered with methylergonovine maleate were compared, no significant difference was found between the mean pre-operative Hb values of both groups (P=0.687). However, the mean post-operative Hb values of the group which received methylergonovine maleate were found to be statistically significantly higher (P=0.005). In the group administered with methylergonovine maleate, the mean reduction in Hb level of 0.85 ± 0.97 units, between the pre-operative and post-operative readings, was determined to be statistically significant (P=0.001). In the group not administered with methylergonovine maleate, the mean reduction in Hb level of 1.05 ± 0.95 units, between the pre-operative and post-operative readings, was also found to be statistically significant (P=0.001). It was determined that the extent of the reduction in postoperative Hb values compared to pre-operative Hb values demonstrated a highly significant difference between the two groups (P=0.002). The extent of the reduction in post-operative Hb values compared to pre-operative Hb values was found to be significantly greater in the group receiving oxytocin only, as compared with the group receiving the combined treatment.
Conclusion	Uterotonic treatment plays an important role in post-partum hemorrhage. Prophylactic methylergonovine treatments with oxytocin combination treatments were significantly more successful than treatments with oxytocin only for the patients in this study, without any evidence of adverse side effects. The authors call for larger scale studies for determination of a consensus in approach to post-partum hemorrhage prophylaxis.
Interpretation	Only healthy patients (with low cardiovascular risk) were included in the study, therefore potentially providing biased safety results in terms of the methylergonovine intervention.

Ongoing

There are no ongoing studies for oral Methergine currently. The following study is underway regarding IM/IV formulations of methylergonovine.

Title	Second-Line Uterotonics in Postpartum Hemorrhage: A Randomized Clinical Trial NCT: 03584854
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Double (Participant, Outcomes Assessor) • Primary Purpose: Treatment

	This study will evaluate in a randomized fashion the comparative efficacy of methylergonovine and carboprost for treating atonic primary postpartum hemorrhage.
Completion Date	2023

Title	Prophylactic Methylergonovine for Twin Cesarean NCT: 05772156
Design	• Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: Double (Participant, Care Provider) • Primary Purpose: Treatment This study will compare maternal blood loss associated with prophylactic methylergonovine during cesarean delivery among patients with twins.
Completion Date	2023

Guidelines

American College of Obstetrics and Gynecologists (ACOG) Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186.

ACOG does not make recommendations for oral use of Methergine for control of postpartum hemorrhage, but rather the use of IM methylergonovine. Uterotonic agents are considered first-line therapy, but specific agents are not given rank or preference due to a lack of data showing any one product's superiority over another.

Clinical Opinions

Methergine appears to have benefit as a second line agent for appropriately selected candidates for use in treatment of post-partum hemorrhage and in a prophylactic setting. Due to the fact that this medication has been on the market for several years, well-controlled clinical data (in particular pivotal data) is unavailable or potentially non-existent, and new research is scarce. Use of the IM formulation of the product is common in most settings where emergent control of bleeding is needed, as its desired effects are realized much more quickly than when taken orally. Oral use of Methergine should be limited, as less expensive options exist for management.

Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Misoprostol (Cytotec)	F	100 mcg, 200 mcg oral tablets	$3 (for one-time 600 mcg dose)
Methylergonovine maleate injection	NF	0.2 mg/1 mL injection solution	$30 (per 1 mL vial)
Carboprost tromethamine (Hemabate)	NF	250 mcg/1 mL intramuscular solution	$319 (per 1 mL ampule)
Tranexamic acid (Cyklokapron)	NF	1000 mg/10 mL intravenous solution	$12 (per 10 mL vial)

**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).*

References

1. Methergine [prescribing information]. Novel Laboratories, Somerset, NJ; January, 2016.
2. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on November 22, 2023.
3. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on November 22, 2023.
4. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Available at: http://www.fda.gov/. Accessed on November 22, 2023.
5. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on November 22, 2023.
6. American College of Obstetrics and Gynecologists (ACOG) Practice Bulletin No. 183: Postpartum Hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186.
7. Şentürk Ş, Kağıtçı M, Balık G, Arslan H, Kır Şahin F. The Effect of the Combined Use of Methylergonovine and Oxytocin during Caesarean Section in the Prevention of Post-partum Hemorrhage. Basic Clin Pharmacol Toxicol. 2016 May;118(5):338-43.

Alameda MRGs for review Q1 2024 P&T Consent Agenda

Recommendation:

- Minor formatting updates

Oxbryta (voxelotor)	
Therapeutic Classes (AHFS)	BLOOD FORM.,COAG,THROMBOSIS AGENTS MISC.
Medications	Formulary, PA required Preferred: Oxbryta (voxelotor) 300mg tablets NDC 72786-0102-03 Oxbryta (voxelotor) 500mg tablets NDC 72786-0101-01 Oxbryta (voxelotor) 300mg tablets for suspension NDC 72786-0111-03 Non-Preferred: Oxbryta (voxelotor) 300mg tablets NDC 72786-0102-02 Oxbryta (voxelotor) 300mg tablets for suspension NDC 72786-0111-02
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
Coverage Duration	**Initial Approval** If the criteria are met, the initial request may be approved for up to a 6-month duration. **Reauthorization** Reauthorization requests may be approved for 12 months. If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Initial Authorization:**
	• Member has a confirmed diagnosis of sickle cell disease
	• Baseline labs have been submitted for the following:
	  ○ Hemoglobin (Hb)
	  ○ Indirect bilirubin
	  ○ Reticulocytes
	• Documentation was provided that the member has had 1 or more vaso-occlusive pain crises in the last 12 months
	• Member has a baseline Hb level less than or equal to 10.5 g/dL
	• Documentation was provided that the member has been taking hydroxyurea at the maximum tolerated dose and was compliant within the last 6 months as evidenced by paid claims (or a medical reason was provided why the patient is unable to use hydroxyurea)
	• If the request is for a non-preferred NDC, there is a documented medical reason why a preferred NDC cannot be used
	• Request is for an FDA-approved dose
	
	Reauthorization:
	• Documentation submitted indicates clinical benefit at 6 months from initiation, and continued clinical benefit at subsequent 12-month intervals defined as the following:
	• Documentation of one of the following:

	○ Hb increase from baseline (at 6 months from initiation) or maintenance of such Hb increase (at 12-month intervals thereafter) ○ ~~Or documentation of a~~A reduced (from baseline) number of vaso-occlusive/pain crises since Oxbryta was started ~~AND~~ • Documentation of one of the following: ○ Decrease in indirect bilirubin from baseline ○ Or decrease in percentage of reticulocytes from baseline • ~~AND d~~Documentation of consistent fills since the previous authorization
Criteria Statement	Oxbryta is reserved for members with sickle cell disease with baseline hemoglobin levels less than or equal to 10.5g/dL, with one or more pain crises during a 12 month period, and who have used (or cannot/should not use) hydroxyurea.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Remove eprosartan and Tekturna from policy. Off market.

Angiotensin II Receptor Blockers and Renin Inhibitors	
Therapeutic Classes (AHFS)	Angiotensin II Receptor Inhibitors and Renin Inhibitors
Medications	**FORMULARY STATUS: Formulary, Pays at Point-of-Sale (first line)** Losartan (Cozaar) Tablets: 25 mg, 50 mg, 100 mg Losartan/Hydrochlorothiazide (Hyzaar) Tablets: 50mg/12.5mg, 100mg/12.5mg, 100mg/25mg Valsartan/Hydrochlorothiazide (Diovan-HCT) Tablets: 80mg/12.5mg, 160mg/12.5mg,160mg/25mg,320mg/12.5mg, 320mg/25mg Valsartan (Diovan) Tablets: 40 mg, 80mg, 160mg, 320mg Irbesartan (Avapro) Tablets: 75mg, 150mg, 300mg Irbesartan/Hydrochlorothiazide (Avalide) Tablets: 150mg/12.5mg, 300mg/12.5mg Telmisartan (Micardis) Tablets: 20mg, 40mg, 80mg Olmesartan Medoxomil (Benicar) Tablets: 5mg, 20mg, 40mg Olmesartan Medoxomil/ Hydrochlorothiazide (Benicar HCT) Tablets: 20mg/12.5mg, 40mg/12.5mg, 40mg/25mg Amlodipine Besylate/Valsartan (Exforge) Tablets: 5mg/160mg, 5mg/320mg, 10mg/160mg, 10mg/320mg **FORMULARY STATUS: Formulary, Requires Prior Authorization (second line)** Amlodipine Besylate/Olmesartan Medoxomil (Azor) Tablets: 5mg/20mg, 5mg/40mg, 10mg/20mg,10mg/40mg ~~Eprosartan Mesylate (Teveten) Tablets: 600mg~~ Telmisartan/Hydrochlorothiazide (Micardis-HCT) Tablets: 40mg/12.5mg, 80mg/12.5mg, 80mg/25mg Candesartan Cilexetil/ Hydrochlorothiazide (Atacand HCT) Tablets: 16mg/12.5mg, 32mg/12.5mg, 32mg/25mg Candesartan Cilexetil (Atacand) Tablets: 4mg, 8mg, 16mg, 32mg **FORMULARY STATUS: Formulary, Requires Prior Authorization (third line)** Edarbi (Azilsartan) Tablets: 40mg, 80mg Edarbyclor (Azilsartan/ Chlorthalidone) Tablets: 40mg/12.5mg, 40mg/25mg Aliskiren (Tekturna) Tablets: 150mg, 300mg ~~Tekturna HCT (Aliskiren/Hydrochlorothiazide) Tablets: 150mg/12.5mg, 150mg/25mg, 300mg/12.5mg, 300mg/25mg~~ Amlodipine/Valsartan/Hydrochlorothiazide (Exforge HCT) Tablets: 5mg/160mg/12.5mg, 5mg/160mg/25 mg, 10mg/160mg/12.5mg, 10mg/160mg/25mg, 10mg/320mg/25mg Olmesartan Medoxomil/Amlodipine/Hydrochlorothiazide (Tribenzor) Tablets: 20mg/5mg/12.5mg, 40mg/5mg/12.5mg, 40mg/5mg/25mg, 40mg/10mg/12.5mg, 40mg/10mg/25mg Telmisartan/Amlodipine (Twynsta) Tablets: 40mg/5mg, 40mg/10mg, 80mg/5mg, 80mg/10mg 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	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A

Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**PA Criteria for approval (2nd line):** • Documented trial and failure or intolerance of two first line agents for at least 15 days of therapy within the previous 90 days. **PA Criteria for approval (3rd line):** • Documented trial and failure or intolerance of two first line agents for at least 15 days of therapy within the previous 90 days AND documented trial and failure or intolerance of one second line agent for at least 15 days of therapy within the previous 90 days
Criteria Statement	Second line medications are reserved for members who have used (or cannot/should not use) two first line medications. Third line medications are reserved for members who have used (or cannot/should not use) two first line medications and one second line medication.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Cimetidine 300 mg/5 ml oral solution is discontinued. Remove from policy.

Histamine H2 Receptor Antagonists	
Therapeutic Classes (AHFS)	Histamine H2 Receptor Antagonists
Medications	Formulary, step therapy required Cimetidine 200, 300, 400, 800 mg tablets ~~Cimetidine 300 mg/5 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 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: Cimetidine tablets ~~or solution~~ are approved when the following criteria is met: • Documentation of a trial and failure, intolerance, contraindication, or inability to use famotidine tablets.
Criteria Statement	Cimetidine tablets ~~or solution~~ are reserved for members who have used (or cannot/should not use) famotidine tablets.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Ophthalmic Antihistamines	
Therapeutic Classes (AHFS)	Antiallergic Agents (EENT)
Medications	Formulary, with restrictions ((quantity limit may apply) • Azelastine 0.05% drops • Ketotifen (Zaditor) 0.025% drops (QL 10/30) • Olopatadine 0.1% (Pataday Twice Daily) (QL 5/30) • Olopatadine 0.2% (Pataday Once Daily) (QL 2.5/30) Formulary, PA required • Lastacaft (alcaftadine) • Bepotastine (Bepreve) • Pataday Once Daily (olopatadine) 0.7% • Zerviate (cetirizine) 0.24% • Epinastine (Elestat) Any newly marketed ophthalmic antihistamine agent
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	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 the criteria are met, the request will be approved for 1 bottle per 30 days for up to a 12 month duration; **Later Approvals** If the criteria are met, the request will be approved for 1 bottle per 30 days for up to a 12 month duration 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** Formulary, prior authorization required medications are approved when the following criteria are met: • Documented trial and failure, contraindication, or intolerance to at least 3 alternatives: ketotifen, azelastine, olopatadine 0.1%, olopatadine 0.2% for at least 2 weeks (14 days) of therapy. **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.
Criteria Statement	**Pataday Once Daily 0.7%, bepotastine (Bepreve), Lastacaft, epinastine (Elestat), and Zerviate:** Pataday Once Daily 0.7%, bepotastine (Bepreve), Lastacaft, epinastine (Elestat), and Zerviate are reserved for members who have used (or cannot/should not use) at least 3 of the following eye drops: ketotifen, azelastine, olopatadine 0.1%, or olopatadine 0.2%.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Verquvo	
Therapeutic Classes (AHFS)	VASODILATING AGENTS, MISCELLANEOUS
Medications	Formulary, PA required Verquvo (vericiguat)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Patients must be 18 years age or older Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a cardiologist (or in consultation with cardiologist)
Coverage Duration	**Initial Approval** 12 months **Reauthorization** 12 months. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.

PA Review Criteria	**Criteria For Authorization**
	• Medication is prescribed at an FDA approved dose
	• The medication is being used for the treatment of symptomatic chronic heart failure with reduced ejection fraction (less than 45%)
	• Documentation that the patient has had a previous hospitalization for heart failure or has required outpatient IV diuretics
	• Member is currently being prescribed, or will be prescribed, at least one of the following treatment regimens, or documentation has been provided that the member is not able to tolerate these agents:
	  ○ Angiotensin-converting enzyme (ACE) inhibitor OR angiotensin receptor blocker (ARB) OR angiotensin receptor/neprilysin inhibitor (ARNI)
	  ○ Mineralocorticoid receptor antagonist (e.g. spironolactone)
	  ○ Beta-blocker
	  ○ Sodium glucose cotransport 2 (SGLT-2) inhibitor (e.g. Steglatro)
	• Patient is not concomitantly using a long-acting nitrate (e.g. isosorbide mononitrate, transdermal nitroglycerin) or a phosphodiesterase-5 (PDE-5) enzyme inhibitor (e.g sildenafil)
	• Negative pregnancy test (for females of reproductive age; as indicated) within 30 days of request.
	• Prescriber attests to discussing with females of reproductive potential the need to use effective forms of contraception during treatment and for one month after stopping treatment.

	Verquvo is reserved for members with a diagnosis of symptomatic chronic heart failure with reduced ejection fraction (less than 45%) who have had a previous hospitalization for heart failure or have required outpatient IV diuretics, and is currently taking (or cannot/should not take) an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) or angiotensin receptor/neprilysin inhibitor, OR a mineralocorticoid receptor antagonist (e.g. spironolactone) OR a beta-blocker OR a sodium glucose cotransport 2 (SGLT-2) inhibitor (e.g. Steglatro); who is not using a long-acting nitrate and has a negative pregnancy test within the last 30 days (as appropriate).
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Siklos (hydroxyurea)	
Therapeutic Classes (AHFS)	BLOOD FORM.,COAG,THROMBOSIS AGENTS MISC.
Medications	Formulary, PA required Siklos (hydroxyurea) tablets
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a hematologist or other specialist with expertise in the diagnosis and management of sickle cell disease
Coverage Duration	**Initial Approval** If the criteria are met, the initial request may be approved for up to a 12-month duration. **Reauthorization** Reauthorization requests may be approved for 12 months. If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Initial authorization:** • Diagnosis of sickle cell disease • Request is for an FDA approved dose • Documented trial and failure or intolerance to hydroxyurea capsules at a maximum tolerated dose OR • Medical reason why patient is unable to use hydroxyurea capsules **Reauthorization:** • Prescriber attests member experienced a reduction in number of sickle cell crises or their condition is stable as a result of Siklos therapy • Request is for an FDA approved dose
Criteria Statement	Siklos is reserved for members with sickle cell disease who have used (or cannot/should not use) hydroxyurea capsules.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

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	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) a combination of alfuzosin, terazosin, doxazosin, or tamsulosin AND finasteride or dutasteride.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Altoprev (lovastatin ER) and Fluvastatin, Fluvastatin ER	
Therapeutic Classes (AHFS)	Antihyperlipidemic – HMG CoA reductase inhibitors
Medications	Non-formulary (non-preferred, requires prior authorization): Altoprev (lovastatin ER) 20, 40, 60 mg capsules Fluvastatin 20, 40 mg capsule Fluvastatin ER 80 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	**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	Altoprev, fluvastatin, or fluvastatin ER are approved when the following criteria are met: • Documentation of a trial and failure, intolerance, contraindication, or inability to use ALL formulary alternative statins at maximally tolerated doses: simvastatin, lovastatin, pravastatin, atorvastatin, and rosuvastatin.
Criteria Statement	Altoprev, fluvastatin, or fluvastatin ER are reserved for members who have used (or cannot/should not use) ALL formulary alternative statins at highest allowed doses: simvastatin, lovastatin, pravastatin, atorvastatin, and rosuvastatin.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Arikayce (amikacin)	
Therapeutic Classes (AHFS)	AMINOGLYCOSIDE ANTIBIOTICS
Medications	Formulary, PA required Arikayce (amikacin liposome) inhalation suspension
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), 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 pulmonologist, or specialist in the treatment of infectious disease or cystic fibrosis
Coverage Duration	**Initial/ Re-Approval** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Initial criteria for the use of Arikayce (amikacin liposome) inhalation suspension • Refractory MAC lung disease: defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy AND • The medication is being prescribed at a dose that is within FDA approved guidelines
Criteria Statement	For the treatment of mycobacterium avium complex (MAC), Arikayce is reserved for members who do not have negative lung cultures after 6 months of using multiple treatments for this condition.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Long-Acting Muscarinic /Long-Acting Beta Agonist/ Corticosteroid inhaled Triple Combination Products	
Therapeutic Classes (AHFS)	Asthma/COPD Tx - Beta-adrenergic-Anticholinergic-Glucocorticoid combinations
Medications	Formulary, PA required Trelegy Ellipta (fluticasone/ umeclidinium/ vilanterol) Breztri Aerosphere (budesonide/ glycopyrrolate/ formoterol)
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: • Used for an FDA-approved dose and indication • The patient has been well controlled, for at least 3 months, on a regimen consisting of formulary/ preferred single/ combo agents of: an inhaled long-acting beta-agonist (LABA), AND inhaled long-acting antimuscarinic agent (LAMA), AND inhaled corticosteroid (ICS), or combinations thereof, however has compliance issues with multiple inhalers OR • The patient has tried and failed a regimen consisting of formulary/ preferred single/ combo agents consisting of: an inhaled long-acting beta-agonist (LABA), AND inhaled long-acting antimuscarinic agent (LAMA), AND inhaled corticosteroid (ICS), or combinations thereof
Criteria Statement	Trelegy Ellipta and Breztri Aerosphere are reserved for patients with a diagnosis of COPD or asthma who have been stable for at least 3 months on a regimen consisting of an inhaled long-acting beta-agonist (LABA), AND inhaled long-acting antimuscarinic agent (LAMA), AND inhaled corticosteroid (ICS) or combinations thereof, but has a compliance issue OR has used (or cannot/ should not use) a combination on a regimen consisting of multiple inhaled long-acting beta-agonist (LABA), AND inhaled long-acting antimuscarinic agent (LAMA), AND inhaled corticosteroid (ICS) or combinations thereof.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Savella (milnacipran) tablet	
Therapeutic Classes (AHFS)	Fibromyalgia Agents
Medications	Formulary, step therapy required Savella (milnacipran)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	**Initial Approval** 12 months **Reauthorization** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Savella tablet step therapy criteria: • Documentation of a trial and failure or intolerance to duloxetine required.
	Savella tablet is reserved for members who have used (or cannot/should not use) duloxetine.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Fexofenadine-pseudoephedrine	
Therapeutic Classes (AHFS)	Second generation antihistamines
Medications	Formulary, step therapy required Fexofenadine-pseudoephedrine tablet extended release
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Reauthorization** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Fexofenadine-pseudoephedrine tablet extended release step therapy criteria: • Documentation of a trial and failure or intolerance to loratadine, cetirizine, OR levocetirizine required.
	Fexofenadine-pseudoephedrine tablet extended release is reserved for members who have used (or cannot/should not use) loratadine, cetirizine, OR levocetirizine.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Injectable Anticoagulants	
Therapeutic Classes (AHFS)	Anticoagulants
Medications	**Preferred:** Formulary, with quantity limits Enoxaparin is formulary with quantity limits and will be approved automatically within these limits, the below criteria applies to those requests that exceed these limits. **Non-Preferred:** Non-formulary fondaparinux (Arixtra) Fragmin (dalteparin) Any newly marketed injectable anticoagulant
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	Member's current weight
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** For the use in venous thromboembolism (VTE):- up to a 31-day duration (unless greater duration of therapy is requested and medically necessary then will be approved for up to a 6 month duration). For use in pregnant members: up to 6 weeks past the patient's expected due date. For use in members with cancer: 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	If the request is for fondaparinux or Fragmin, documentation must be provided of trial and failure, intolerance, contraindication, or inability to use enoxaparin AND the following criteria must be met. PA CRITERIA FOR APPROVAL FOR USE IN VENOUS THROMBOEMBOLISM (VTE): • The medication is being prescribed for the prevention and/or treatment of VTE • The medication is being prescribed at a dose that is within FDA approved guidelines and/or is supported by the medical compendia. • The prescriber must provide a medical reason why the member cannot be treated with a preferred formulary oral anticoagulant (e.g. Eliquis). PA CRITERIA FOR APPROVAL FOR USE IN A PREGNANT MEMBER: • The medication is being prescribed for the prevention or treatment of a VTE while the member is pregnant. • Documentation of the expected due date (EDD). • The medication is being recommended and prescribed by an obstetrician or a hematologist at a dose that is within FDA approved guidelines and/or is supported by the medical compendia.

Injectable Anticoagulants	
	PA CRITERIA FOR APPROVAL FOR USE IN MEMBER WITH CANCER: • The medication is being prescribed for the prevention or treatment of a VTEfor a member with cancer. • The medication is being prescribed at a dose that is within FDA approved guidelines and/or is supported by the medical compendium as defined by the Social Security Act and/or per the National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) standard of care guidelines. • The medication is being prescribed by an oncologist/hematologist • The prescriber must provide a medical reason why the member cannot be treated with a preferred formulary oral anti-coagulant (e.g. Eliquis). REAUTHORIZATION CRITERIA FOR APPROVAL FOR USE IN MEMBER WITH CANCER: • The medication is being used for the prevention and/or treatment of a VTE for a member with cancer. • The prescriber must provide a valid medical reason as to why the member needs to continue treatment and cannot be treated with a preferred formulary oral anticoagulant. • The medication is being prescribed an oncologist/hematologist The medication is being prescribed at a dose that is within FDA approved guidelines or is supported by the medical compendium as defined by the Social Security Act and/or per the National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) standard of care guidelines.
Criteria Statement	For venous thromboembolism (VTE) treatment or prevention, enoxaparin is reserved for members who have used (or cannot/should not use) a preferred formularyoral anticoagulant (e.g. Eliquis). For pregnant members, enoxaparin is reserved for members who need treatment or prevention of venous thromboembolism (VTE) For members with cancer, enoxaparin is reserved for members who need treatment or prevention of venous thromboembolism (VTE) who have used (or cannot/should not use) a preferred formulary oral anticoagulant (e.g. Eliquis). Fragmin or fondaparinux are reserved for members who cannot/should not use enoxaparin.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Atovaquone (Mepron)	
Therapeutic Classes (AHFS)	Antiprotozoals, Miscellaneous
Medications	Formulary, PA required Atovaquone (Mepron)
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: • For prophylaxis or acute oral treatment of mild to moderate Pneumocystis jiroveci pneumonia (PCP) AND • Documented trial and failure, intolerance, inability to use, or contraindication to therapeutic doses of trimethoprim-sulfamethoxazole (TMP/SMX) (first-line therapy)
Criteria Statement	Atovaquone is reserved for members that have used (or cannot/should not use) trimethoprim-sulfamethoxazole (TMP/SMX)
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Thrombocytopenia Agents	
Therapeutic Classes (AHFS)	Hematopoietic agents
Medications	Formulary, PA required Promacta (eltrombopag) tablets Mulpleta (lusutrombopag) Nplate (romiplostim) Doptelet (avatrombopag) Non-Formulary Promacta (eltrombopag) powder packets Tavalisse (fostamatinib)
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 a hematology specialist or working in consultation with a hematologist
Coverage Duration	**Initial Approval** If the criteria are met, the request will be approved for 12 months for Promacta, Nplate, Doptelet (for the indication of chronic immune thrombocytopenia), and Tavalisse. Doptelet will be approved for a maximum of 5 days (for the indication of chronic liver disease-associated thrombocytopenia) Mulpleta will be approved for a maximum of 7 days. If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	For all indications below, the medication is prescribed at an FDA-approved dose for indication and age **Chronic immune (idiopathic) thrombocytopenia (ITP):** • Platelet count < 30,000 cells/microL • Documented trial and failure, intolerance, or contraindication to use ONE of the following: glucocorticoids, intravenous immune globulin (IVIG), rituximab or splenectomy • For Doptelet, Nplate or Tavalisse, the member must also have a documented trial and failure, intolerance, or contraindication to Promacta **Severe aplastic anemia:** Promacta only: • Documented trial and failure, intolerance or contraindication to at least one immunosuppressive agent **OR** is being prescribed in conjunction with at least one immunosuppressive agent **AND** • Platelet count < 20,000 cells/microL OR < 30,000 cells/microL with bleeding OR reticulocyte count < 20,000 cells/microL OR absolute neutrophil count < 500 cells/microL **Thrombocytopenia in patients with Hepatitis C infection:**

	Promacta only: • Diagnosis of chronic hepatitis C **AND** • Documented treatment with interferon-based therapy **AND** • Patient's degree of thrombocytopenia prevents the initiation or limits the ability to maintain interferon-based therapy **AND** • Medical reason for why patient needs to be treated with interferon over new DAA medication **AND** • Platelet count < 50,000 cells/microL **Thrombocytopenia associated with chronic liver disease in adult patients requiring elective surgery** <u>Doptelet and Mulpleta only</u>: • Patient has a diagnosis of chronic liver disease and is scheduled to undergo a procedure **AND** • Platelet count < 50,000 cells/microL **AND** • For Mulpleta, approve if there is documentation of trial and failure, intolerance, or contraindication to use Doptelet For Promacta powder, approve if there is a documentation of trial and failure, intolerance or contraindication to use Promacta tablets, and all other Promacta criteria above are met.
Criteria Statement	Promacta is reserved for members with chronic immune (idiopathic) thrombocytopenia (ITP), who have used (or cannot/ should not use) one of the following: glucocorticoids, intravenous immune globulin (IVIG), rituximab, or splenectomy. Doptelet, Nplate, and Tavalisse are reserved for members with chronic immune (idiopathic) thrombocytopenia (ITP), who have used (or cannot/ should not use) Promacta. Promacta is reserved for members with severe aplastic anemia who have used (or cannot/ should not use) an immunosuppressive agent or is being used in conjunction with an immunosuppressive agent. Promacta is reserved for members with hepatitis C infection in patients who must be treated with interferon-based therapy. Doptelet is reserved for members who have thrombocytopenia associated with chronic liver disease in adult patients requiring elective surgery. Mulpleta is reserved for members who have thrombocytopenia associated with chronic liver disease in adult patients requiring elective surgery and who have used (or cannot/ should not use) Doptelet.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Travoprost (Travatan Z) ophthalmic drops	
Therapeutic Classes (AHFS)	Prostaglandin analogs
Medications	Formulary, step therapy required Travoprost (Travatan Z) ophthalmic drops 0.004 %
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Reauthorization** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Travoprost (Travatan Z) ophthalmic drops step therapy criteria: • Documentation of a trial and failure or intolerance to latanoprost eye drops required.
	Travoprost (Travatan Z) ophthalmic drops are reserved for members who have used (or cannot/should not use) latanoprost eye drops.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Pyridostigmine (Mestinon)	
Therapeutic Classes (AHFS)	Parasympathomimetic (cholinergic) agents
Medications	Formulary, PA required Pyridostigmine (Mestinon) (Regonol)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	None
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Criteria for initial authorization: • Used for the treatment of myasthenia gravis at FDA-approved doses. Criteria for re-authorization: • Patient is stable and continuing the medication AND • Medication is used for appropriate indication and at appropriate dose
Criteria Statement	Mestinon is reserved for members who have a diagnosis of myasthenia gravis and are using it at the recommended doses.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Antifibrotic Respiratory Tract Agents	
Therapeutic Classes (AHFS)	Antifibrotic Agents
Medications	Formulary, PA required Ofev (nintedanib) Esbriet (pirfenidone)
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 a pulmonologist or lung transplant specialist
Coverage Duration	**Initial Approval** 6 months **Later Approval** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**INITIAL CRITERIA FOR ALL DIAGNOSES:** • Patient is 18 years of age or older • Provider attests that they have reviewed the patient's other medications, and addressed all potential drug interactions • Documentation has been provided that the patient does not smoke **INITIAL CRITERIA FOR IDIOPATHIC PULMONARY FIBROSIS:** • Confirmed diagnosis of Idiopathic Pulmonary Fibrosis attested to by prescriber • Pulmonary function test indicate patient has Forced Vital Capacity (FVC) greater than or equal to 50% within 30 days of request **INITIAL CRITERIA FOR SYSTEMIC SCLEROSIS-ASSOCIATED INTERSTITIAL LUNG DISEASE (ILD) (SSc-ILD):** • The request is for Ofev (nintedanib). • Confirmed diagnosis of SSc-ILD attested to by prescriber • FVC ≥ 40% within 30 days of request • Trial and failure of mycophenolate mofetil (MMF), cyclophosphamide or azathioprine. **INITIAL CRITERIA FOR CHRONIC FIBROSING INTERSTITIAL LUNG DISEASE (ILDS) WITH A PROGRESSIVE PHENOTYPE:** • The request is for Ofev (nintedanib). • Diagnosis of chronic fibrosing ILD (e.g. connective tissue disease [CTD]-associated ILD, chronic fibrosing hypersensitivity pneumonitis [HP], idiopathic non-specific interstitial pneumonia [iNSIP], unclassifiable idiopathic interstitial pneumonia [IIP], environmental/occupational lung disease or sarcoidosis) with a progressive phenotype attested to by prescriber • Recent (12 month) history of treatment with at least one medication to treat ILDs (e.g. a corticosteroid, azathioprine, mycophenolate mofetil (MMF), n-acetylcysteine (NAC), rituximab, cyclophosphamide, cyclosporine, or tacrolimus) • FVC ≥ 45% predicted within 30 days of request **REAUTHORIZATION CRITERIA:**

	• Documentation submitted indicates that the member has obtained clinical benefit from the medication • Documentation has been provided that the patient does not smoke
Criteria Statement	Ofev and Esbriet are reserved for members with a diagnosis of pulmonary fibrosis have pulmonary function tests with FVC over 50%, and have documentation of non-smoking status. Ofev is reserved for members with a diagnosis of systemic sclerosis-associated interstitial lung disease, pulmonary function tests with FVC greater than or equal to 40%, and who has used (or cannot/should not use) mycophenolate mofetil, cyclophosphamide, or azathioprine, and have documentation of non-smoking status. Ofev is reserved for members with a diagnosis of chronic fibrosing interstitial lung disease with a progressive phenotype, pulmonary function tests with FVC greater than or equal to 45% predicted, who has used (or cannot/should not use)) at least one medication to treat ILDs (e.g. a corticosteroid, azathioprine, mycophenolate mofetil, n-acetylcysteine (NAC), rituximab, cyclophosphamide, cyclosporine, or tacrolimus), and have documentation of non-smoking status.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Cystic Fibrosis Agents	
Therapeutic Classes (AHFS)	Cystic Fibrosis (CFTR) Potentiators, Misc. Beta-lactam antibiotics, Mucolytic agents
Medications	Formulary, PA required Kalydeco (ivacaftor) oral granules, tablet Orkambi (lumacaftor/ivacaftor) tablet, granule packet Symdeko (tezacaftor/ivacaftor) tablets Trikafta (elexacaftor/tezacaftor/ivacaftor) tablets Cayston (aztreonam lysine) vial for nebulization TOBI Podhaler (tobramycin) capsule, capsule with inhalation device tobramycin (TOBI) ampule for nebulization tobramycin (Kitabis Pak) ampule for nebulization tobramycin (Bethkis) ampule for nebulization Pulmozyme (dornase alfa) inhalation solution Bronchitol (mannitol) *Or any other newly marketed dosage form, strength, or medication used to treat cystic fibrosis
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 pulmonologist, or specialist in the treatment of cystic fibrosis
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	Initial criteria for the use of Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor) or Trikafta (elexacaftor/tezacaftor/ivacaftor) • Documentation provided includes a copy of the FDA-cleared cystic fibrosis (CF) mutation test OR documentation from the National Cystic Fibrosis Registry (e.g. screen shot) with member's genetic mutations. • The request is appropriate for member (e.g. age/weight/degree of liver function) per package insert or standard of care guidelines • Baseline liver transaminase levels were submitted with request (within 90 days of request) • The request is for an FDA approved indication for the member's genotype and within dosing guidelines Re-authorization criteria for the use of Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor) or Trikafta (elexacaftor/tezacaftor/ivacaftor) • Documentation has been submitted that patient has obtained clinical benefit from medication (i.e. improvement in FEV1, BMI, decrease in number or frequency of pulmonary exacerbations, or improvement in quality of life) • MD attests that liver function testing/monitoring has been completed per the package labeling • The medication is being prescribed at a dose that is within FDA approved guidelines.

	Initial criteria for the use of inhaled tobramycin (Bethkis,Tobi, Kitabis Pak), Pulmozyme (dornase alfa), Tobi Podhaler • The request is appropriate for member (e.g. age/weight) • If the request is for a brand name tobramycin product, documentation has been provided why member is unable to use generic tobramycin • The medication is being prescribed at a dose that is within FDA approved guidelines. Re-authorization criteria for the use of inhaled tobramycin (Bethkis,Tobi, Kitabis Pak), Pulmozyme (dornase alfa), Tobi Podhaler • The request is appropriate for member (e.g. age/weight) • The medication is being prescribed at a dose that is within FDA approved guidelines. • Documentation has been submitted that patient has obtained clinical benefit from medication Initial criteria for the use of Cayston (aztreonam lysine) • The medication is being prescribed for a cystic fibrosis patient colonized with P. aeruginosa • Documentation has been provided why member is unable to use generic tobramycin • The medication is being prescribed at a dose that is within FDA approved guidelines Re-authorization criteria for the use of Cayston (aztreonam lysine) • The medication is being prescribed for a cystic fibrosis patient colonized with P. aeruginosa • The medication is being prescribed at a dose that is within FDA approved guidelines • Documentation has been submitted that patient has obtained clinical benefit from medication (i.e. improvement in FEV1, decrease in number or frequency of pulmonary exacerbations) Initial criteria for the use of Bronchitol • The medication is being prescribed at a dose that is within FDA approved guidelines • The prescriber attests that the patient has not had an episode of hemoptysis (>60 mL) in the 3 months prior to beginning therapy • The prescriber attests that the Bronchitol Tolerance Test (BTT) will be administered and performed under the supervision of a qualified healthcare practitioner Re-authorization criteria for the use of Bronchitol • The medication is being prescribed at a dose that is within FDA approved guidelines • Documentation has been submitted that patient has obtained clinical benefit from medication (i.e. decrease in number or frequency of pulmonary exacerbations)
Criteria Statement	For the treatment of cystic fibrosis, Kalydeco, Orkambi, Symdeko, or Trikafta are reserved for members with documented genetic mutations and who have documented baseline liver transaminase levels within 90 days of request. For the treatment of cystic fibrosis, inhaled tobramycin (Bethkis, Tobi, Kitabis Pak), Pulmozyme (dornase alfa), and Tobi Podhaler are reserved for members of

	appropriate age, indication, and dosing who have used (or cannot/should not use) generic tobramycin . For the treatment of cystic fibrosis in members colonized with P. aeruginosa Cayston is reserved for members who have used (or cannot/should not use) generic tobramycin. For the treatment of Bronchitol is reserved for members of appropriate age, indication, and dosing, who have or will have had the Bronchitol Tolerance Test (BTT) performed, and who have not had an episode of hemoptysis (>60 mL) in the 3 months prior to beginning therapy.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Elmiron (pentosane polysulfate sodium)	
Therapeutic Classes (AHFS)	Protective agents
Medications	Formulary, limited to members age 16 years or older, #90 capsules per 30 days, and 6 fills per year Elmiron 100 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	N/A
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	For requests exceeding 6 months of therapy, the following criteria must be met: • Documentation of medical necessity for therapy beyond 6 months is required. ○ Efficacy and safety of continued treatment after 6 months of therapy is unknown. • The medication is being prescribed at a dose that is within FDA approved guidelines.
Criteria Statement	Using Elmiron for more than 6 months is reserved for members who have a medical reason for using Elmiron for longer than 6 months.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Linezolid	
Therapeutic Classes (AHFS)	Oxazolidinone antibiotics
Medications	Formulary, Step Therapy Linezolid ****Please Note: If the request is for linezolid 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 up 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, linezolid is the only treatment option.
Criteria Statement	Linezolid is reserved for members who have used (or cannot/should not use) up to two formulary medications with the same mechanism of action (if available) or that are used to treat the documented diagnosis based on patient-specific factors.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Symlin (pramlintide)	
Therapeutic Classes (AHFS)	Amylinomimetics
Medications	Formulary, PA required Symlin (pramlintide)
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	None
Prescriber Restrictions	Prescriber is an endocrinologist
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 must be met: • Diagnosis of Type I or Type II diabetes • Patient requires the use of mealtime insulin (e.g. Humulin/Novolin, Apidra/Humalog/Novolog) • Patient unable to achieve blood glucose control despite optimal insulin therapy • Documentation patient's A1C is ≤ 9%
Criteria Statement	SymlinPen is reserved for members with uncontrolled type 1 or type 2 diabetes using mealtime insulin and A1C is 9% or lower.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Corticosteroid Preparations to Treat Hemorrhoids	
Therapeutic Classes (AHFS)	Corticosteroids (skin, mucous membrane)
Medications	Formulary Hydrocortisone acetate (Anucort-HC) rectal suppository 25 Mg Hydrocortisone (Proctozone-HC) topical cream with perineal applicator 2.5 % Formulary, PA required Proctofoam HC (hydrocortisone/pramoxine) 1%-1% rectal foam Hydrocortisone acetate (Proctocort) rectal suppository 30mg
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** 7 days If all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	Initial criteria for authorization for formulary, PA-required medications: • Documented trial and failure, intolerance, inability to use, or contraindication to one preferred formulary medication Re-approval criteria for formulary, PA-required medications • For requests greater than 7 days of treatment, the provider must submit a medical reason of necessity for treatment longer than 7 days
	Proctofoam HC 1%-1% rectal foam and hydrocortisone acetate (Proctocort) rectal suppository 30mg are reserved for members are using the medications for 7 days or less and who have used (or cannot/ should not use) hydrocortisone acetate (Anucort-HC) rectal suppository 25 Mg or hydrocortisone (Proctozone-HC) topical cream with perineal applicator 2.5 %.
Last P&T Review Date	~~3/2023~~3/2024

Alameda PADs for review Q1 2024 P&T Consent Agenda

Recommendation:

- Add in formulation check for appropriateness

Emergency Use Authorization (EUA) Drugs/Products for COVID-19	
Medications	Any approved drug/product by EUA for COVID-19
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	As outlined within current FDA Emergency Use Authorization (EUA) guidelines
Prescriber Restrictions	N/A
Coverage Duration	As outlined within current FDA Emergency Use Authorization (EUA) guideline
Maximum Billable Units	Variable
Other Criteria	Emergency Use Authorization for COVID-19 related drugs/products (all must apply): • The requested drug/product has a currently active Emergency Use Authorization as issued by the U.S. Food and Drug Administration. • Use of the requested drug/product is consistent with the current terms and conditions of the emergency use authorization (such as appropriate age/weight, formulation, disease severity, concurrent use with other medications or medical interventions, etc.). • Attestation that the requested drug/product was purchased by the entity seeking payment (not provided at no charge/reimbursed by the U.S. government). If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review.
Last Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Tzield	
Medications	Tzield (teplizumab-mzwv)
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	Type 2 diabetes (T2D)
Required Clinical Information	See "other criteria"
Age Restrictions	According to package insert
Prescriber Restrictions	Prescriber must be an endocrinologist
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
	• Diagnosis of stage 2 type 1 diabetes (T1D) confirmed by presence of at least two of the following autoantibodies:
	  ○ Glutamic acid decarboxylase 65 (GAD) autoantibody
	  ○ Insulin autoantibody (IAA)
	  ○ Insulinoma-associated antigen 2 autoantibody (IA-2A)
	  ○ Zinc transporter 8 autoantibody (ZnT8A)
	  ○ Islet cell autoantibody (ICA)
	• Abnormal glucose on an oral glucose-tolerance test (or alternative glycemic test if an oral glucose-tolerance test is not available)
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review

Last Review Date	~~3/2023~~3/2024

Recommendation:

- No changes

Ophthalmic indications for bevacizumab	
Medications	Avastin (bevacizumab) Mvasi (bevacizumab-awwb) - biosimilar Zirabev (bevacizumab-bvzr) - biosimilar
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 an ophthalmologist
Coverage Duration	A 3 month duration for initial approval and 12 months for renewal
Maximum Billable Units	Variable

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, in addition to meeting all applicable criteria below unless 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.**
	
	• Member must have a diagnosis for an ophthalmic indication accepted in a nationally recognized compendia
	  ○ Age related macular degeneration - Choroidal retinal neovascularization
	  ○ Branch retinal vein occlusion with macular edema
	  ○ Central retinal vein occlusion with macular edema
	  ○ Choroidal retinal neovascularization, secondary to pathologic myopia
	  ○ Macular edema due to diabetes mellitus
	• Must be prescribed at a dose that is consistent with nationally recognized compendia
	
	If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review

Last Review Date	~~3/2023~~3/2024

Alameda Alliance for Health (IHSS)

Q1 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
Humira Pediatric Crohns Start Subcutaneous Prefilled Syringe Kit 80 MG/0.8ML	F-PA to NF
Humira Pediatric Crohns Start Subcutaneous Prefilled Syringe Kit 80 MG/0.8ML & 40MG/0.4ML	F-PA to NF
Humira Pen Subcutaneous Pen-injector Kit 40 MG/0.4ML	F-PA to NF
Humira Pen Subcutaneous Pen-injector Kit 40 MG/0.8ML	F-PA to NF
Humira Pen Subcutaneous Pen-injector Kit 80 MG/0.8ML	F-PA to NF
Humira Pen-CD/UC/HS Starter Subcutaneous Pen-injector Kit 40 MG/0.8ML	F-PA to NF
Humira Pen-CD/UC/HS Starter Subcutaneous Pen-injector Kit 80 MG/0.8ML	F-PA to NF
Humira Pen-Pediatric UC Start Subcutaneous Pen-injector Kit 80 MG/0.8ML	F-PA to NF
Humira Pen-Ps/UV/Adol HS Start Subcutaneous Pen-injector Kit 40 MG/0.8ML	F-PA to NF
Humira Pen-Psor/Uveit Starter Subcutaneous Pen-injector Kit 80 MG/0.8ML & 40MG/0.4ML	F-PA to NF
Humira Subcutaneous Prefilled Syringe Kit 10 MG/0.1ML	F-PA to NF
Humira Subcutaneous Prefilled Syringe Kit 20 MG/0.2ML	F-PA to NF
Humira Subcutaneous Prefilled Syringe Kit 40 MG/0.4ML	F-PA to NF
Humira Subcutaneous Prefilled Syringe Kit 40 MG/0.8ML	F-PA to NF
Rinvoq Oral Tablet Extended Release 24 Hour 15 MG	F-PA to NF
Rinvoq Oral Tablet Extended Release 24 Hour 30 MG	F-PA to NF
Rinvoq Oral Tablet Extended Release 24 Hour 45 MG	F-PA to NF
Cosentyx (300 MG Dose) Subcutaneous Solution Prefilled Syringe 150 MG/ML	F-PA to NF
Cosentyx Sensoready (300 MG) Subcutaneous Solution Auto-injector 150 MG/ML	F-PA to NF
Cosentyx Sensoready Pen Subcutaneous Solution Auto-injector 150 MG/ML	F-PA to NF
Cosentyx Subcutaneous Solution Auto-injector 300 MG/2ML	F-PA to NF

Medication	Formulary Change
Cosentyx Subcutaneous Solution Prefilled Syringe 150 MG/ML	F-PA to NF
Cosentyx Subcutaneous Solution Prefilled Syringe 75 MG/0.5ML	F-PA to NF
Skyrizi (150 MG Dose) Subcutaneous Prefilled Syringe Kit 75 MG/0.83ML	F-PA to NF
Skyrizi Pen Subcutaneous Solution Auto-injector 150 MG/ML	F-PA to NF
Skyrizi Subcutaneous Solution Prefilled Syringe 150 MG/ML	F-PA to NF
Stelara Subcutaneous Solution 45 MG/0.5ML	F-PA to NF
Stelara Subcutaneous Solution Prefilled Syringe 45 MG/0.5ML	F-PA to NF
Stelara Subcutaneous Solution Prefilled Syringe 90 MG/ML	F-PA to NF
Taltz Subcutaneous Solution Auto-injector 80 MG/ML	F-PA to NF
Taltz Subcutaneous Solution Prefilled Syringe 80 MG/ML	F-PA to NF
Cimzia Starter Kit Subcutaneous Prefilled Syringe Kit 6 X 200 MG/ML	F-PA to NF
Cimzia Subcutaneous Kit 2 X 200 MG	F-PA to NF
Cimzia Subcutaneous Prefilled Syringe Kit 2 X 200 MG/ML	F-PA to NF
Skyrizi Intravenous Solution 600 MG/10ML	F-PA to NF
Skyrizi Subcutaneous Solution Cartridge 180 MG/1.2ML	F-PA to NF
Skyrizi Subcutaneous Solution Cartridge 360 MG/2.4ML	F-PA to NF
Zeposia 7-Day Starter Pack Oral Capsule Therapy Pack 4 x 0.23MG & 3 x 0.46MG	F-PA to NF
Zeposia Oral Capsule 0.92 MG	F-PA to NF
Zeposia Starter Kit Oral Capsule Therapy Pack 0.23MG & 0.46MG & 0.92MG	F-PA to NF
Zeposia Starter Kit Oral Capsule Therapy Pack 0.23MG &0.46MG 0.92MG(21)	F-PA to NF
inFLIXimab Intravenous Solution Reconstituted 100 MG	NF to F-PA
Inflectra Intravenous Solution Reconstituted 100 MG	NF to F-PA
Avsola Intravenous Solution Reconstituted 100 MG	NF to F-PA
Renflexis Intravenous Solution Reconstituted 100 MG	NF to F-PA
Siliq Subcutaneous Solution Prefilled Syringe 210 MG/1.5ML	NF to F-PA
Olumiant Oral Tablet 1 MG	NF to F-PA
Olumiant Oral Tablet 2 MG	NF to F-PA
Olumiant Oral Tablet 4 MG	NF to F-PA

Medication	Formulary Change
Entyvio Intravenous Solution Reconstituted 300 MG	NF to F-PA
Entyvio Subcutaneous Solution Pen-injector 108 MG/0.68ML	NF to F-PA
All claims	Increase in dollar limit per claim pay at point of sale allowance from $1000 to $1500
Zenpep Oral Capsule Delayed Release Particles 60000-189600 UNIT	NF to F-AL (min 21 years)
Penbraya Intramuscular Suspension	NF to F-QL-AL (0.5ml per dose) (2 fills per lifetime) (max age 25 years)
Ibrance capsules and tablets	NF to F-PA
Verzenio tablets	NF to F-PA

Alameda Alliance for Health Q1 2024 PAD Updates

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

HCPCS Code	HCPSC Description	Action
J9258	PACLITAXEL PROTEIN-BOUND PARTICLES (TEVA)	Add PA Requirement
J9072	CYCLOPHOSPHAMIDE	Add PA Requirement
J9286	GLOFITAMAB-GXBM (COLUMVI)	Add PA Requirement
J9321	EPCORITAMAB-BYSP (EPKINLY)	Add PA Requirement
J9324	PEMETREXED (PEMRYDI RTU)	Add PA Requirement
J0217	VELMANASE ALFA-TYCV (LAMZEDE)	Add PA Requirement
J1304	TOFERSEN (QALSODY)	Add PA Requirement
J1413	DELANDISTROGENE MOXEPARVOVEC (ELEVIDYS)	Add PA Requirement
J1412	VALOCTOCOGENE ROXAPARVOVEC-RVOX (ROCTAVIAN)	Add PA Requirement
J2508	PEGUNIGALSIDASE ALFA-IWXJ (ELFABRIO)	Add PA Requirement
J9333	ROZANOLIXIZUMAB-NOLI INJECTION (RYSTIGGO)	Add PA Requirement
J9334	EFGARTIGIMOD ALFA-FCAB AND HYALURONIDASE-QVFC (VYVGART)	Add PA Requirement
J0224	OXLUMO (LUMASIRAN)	Add PA Requirement
J0219	AVALGLUCOSIDASE ALFA-NGPT	Add PA Requirement
J3490	UNCLASSIFIED DRUGS	Remove PA
J0135	HUMIRA (ADALIMUMAB) 20MG	Remove PA
J1325	INJECTION EPOPROSTENOL 0.5 MG	Remove PA
J2941	INJECTION, SOMATROPIN, 1 MG	Remove PA
J7191	FACTOR VIII AHF PORCINE PER IU	Remove PA
J7504	LYMPHCYT GLOB EQUINE PARNTRAL 250MG	Remove PA
J7511	LYMPHCYT GLOB RABBIT PARNTRAL 25MG	Remove PA
J7599	IMMUNOSUPPRESSIVE DRUG NOC	Remove PA
J7685	TOBRAMYCIN INHAL CP THRU DME 300 MG	Remove PA
J9160	ONTAK (DENILEUKIN DIFTITOX) 300 MCG	Remove PA
J9999	NOT OTHWISE CLASS ANTINEOPLSTC DRUG	Remove PA

ALAMEDA Alliance FOR HEALTH

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POLICY AND PROCEDURE

Policy Number	RX-001
Policy Name	Pharmaceutical Operating Processes Summary
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care (IHSS)
Effective Date	04/01/2021
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

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

PROCEDURE

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

I. Pharmacy and Therapeutics (P&T) Committee

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

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

II. Formulary Management

The Alliance has an established process for maintaining, reviewing, and updating its drug

formulary. The Alliance is committed to ensuring that all eligible Alliance members have access to high quality and cost-effective pharmaceutical care. The Alliance's formulary management process complies with the standards set by the Health & Safety Code, Sections 1367.20, 1367.21, 1367.24, 1367.25, and 1367.215.

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

III. Prior Authorization Process

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

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

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

IV. Exception Process

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

V. Generic Substitution

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

VI. Therapeutic Interchange

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

VII. Step Therapy

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

VIII. Limits and Quotas

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

Section 16 *Formulary and Pharmacy Services*.

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

IX. Practitioner Notification of Pharmaceutical Management Procedures

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

X. Member Notification of Pharmaceutical Management Procedures

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

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

XI. Override at the point of service

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

XII. Member Eligibility

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

not available, please contact the Alliance IT Enrollment department to update eligibility.

ii. If current eligibility is NOT found, the Alliance pharmacy personnel will forward case to Business Operation for eligibility update.

XIII. Regulatory Reporting

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

DEFINITIONS / ACRONYMS

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

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

AFFECTED DEPARTMENTS/PARTIES

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

RELATED POLICIES AND PROCEDURES

P&T Charter

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

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

4/1/2018, 3/25/2018, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 3/28/2023, 3/19/2024

REFERENCES

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

- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx

MONITORING

This policy will be reviewed annually to ensure effectiveness.

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	Group Care (IHSS)
Effective Date	12/01/1997
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~9/26/2023~~
Compliance Committee Approval Date	TBD

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 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. 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 a11 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, 3/19/2024

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

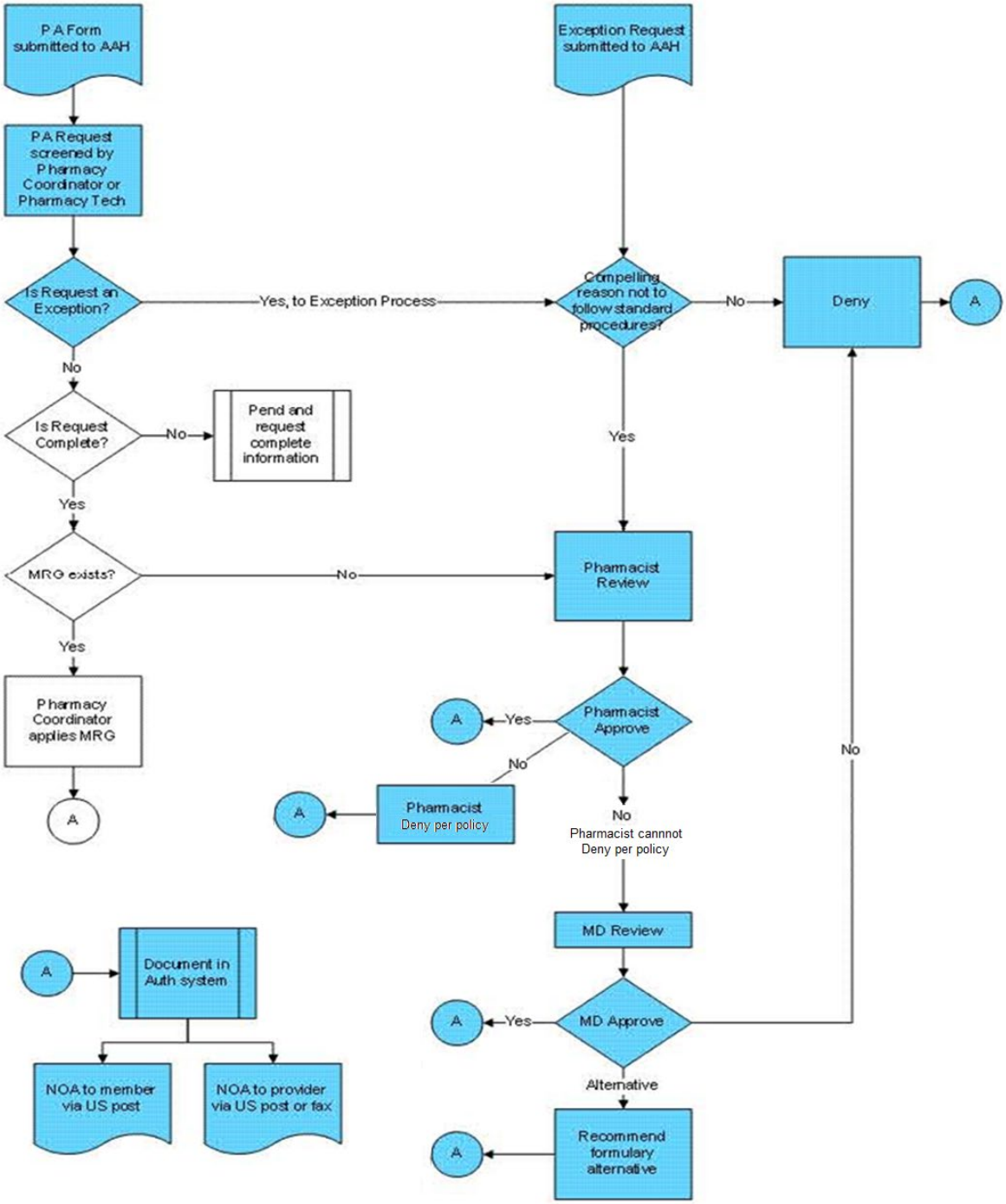
Table 2. Pharmacy Benefit Determination Turnaround Timetable of Different Regulatory Bodies

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~~30~~ hours ~~calendar days~~**

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~~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
Post-service	Approval Modification Denial	A fax is sent to the requesting provider within 72~~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

Pharmaceutical Management Procedures
(Prior Authorization and Exception Process)



POLICY AND PROCEDURE

Policy Number		RX-003
Policy Name		Exception Review Process
Department Name		Pharmacy Services
Department Officer		Chief Medical Officer
Policy Owner		Senior Director, Pharmacy Services
Line(s) of Business		Group Care (IHSS)
Effective Date		6/16/2020
Subcommittee Name	Pharmaceutical and Therapeutics Committee	
Subcommittee Approval Date ~~Approval / Revision Date~~		TBD~~Pending P&T approval on 12/19/2023~~
Compliance Committee Approval Date	TBD	

POLICY STATEMENT

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

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

PROCEDURE

I. Exception Process Guidelines

A. Members and their providers are expected to follow pharmaceutical management procedures set forth by the Alliance. However, in some cases a member or

provider may opt to seek an exception based on medical necessity. Examples of exception requests include (but are not limited to):

1. A request for coverage of a non-formulary item with no existing Medication Review Guidelines (MRG)
2. A request to bypass an implemented formulary management program, such as step therapy
3. A request to authorize a greater supply than standard quantity limits
4. Any request outside the existing pharmaceutical management procedure and authorization process

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

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

II. Exception Review Requirements and Process

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

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

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

15. Information regarding benefits for services or procedures
16. Information regarding the local delivery system
17. Patient characteristics and information

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

1. Quantity Limit (QL) Override

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

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

i. Split dosing for tolerability
ii. One-time dose titration
iii. Requirement of a higher dose for efficacy (must be supported by clinical evidence)

2. Step Therapy (ST) Override

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

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

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

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

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

iv. The required prescription drug is not clinically appropriate for the member because the required drug is expected to do any of the

following, as determined by the member's prescribing provider:

(1) Worsen a comorbid condition.

(2) Decrease the capacity to maintain a reasonable functional ability in performing daily activities.

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

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

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

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

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

(a) Patient name

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

(c) Quantity distributed

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

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

3. Age Limit (AL) Override

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

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

4. Fill Limit (FL) Override

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

b) For override of Fill Limits, the provider must submit documentation for why the member requires additional medication beyond the limit in

place, why formulary alternatives cannot or should not be used in the patient, and any relevant labs results and/or other clinical references, national guidelines, or primary literature to support continued use of the drug requested.

5. Maximum Dose Exceeded Override

a) Maximum doses are set by the prescribing information/package insert for the medication upon FDA approval or by national guidelines for the condition being treated.

b) For use of doses beyond the maximum labeled dose, the provider must submit any relevant labs results, clinical references, national guidelines, and/or primary literature to support the use of a dose beyond the standard dose and justification for why a formulary alternative cannot be used in place of a higher dose of the requested medication.

6. Dose Consolidation Override

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

b) For approval of a doubling (or higher) of the number of tablets/capsules per prescription for a medication that has a higher strength tablet/capsule available, justification must be submitted for why that higher dose tablet/capsule cannot be used.

7. Partial Fill

a) The Alliance has availability of prescription partial fills of approved medically necessary medications.

8. Lost/Stolen Medication Override

a) Requests for non-controlled medications can be approved by Alliance pharmacy technicians upon request by the member, pharmacy, or provider.

b) For Lost/Stolen controlled medications, the member or provider must submit a police report to the plan that documents which medications were taken and the date the event occurred.

c) For more than one loss of controlled medications per 365 days, future approvals will be authorized only in consultation with the prescriber and your pharmacy.

9. Refill-Too-Soon Override

a) Refill-Too-Soon overrides will be handled on a case-by-case basis and by the medical necessity of the situation.

b) Lost/Stolen medication and vacation overrides will be handled by the corresponding exception policies.

10. Vacation Override

a) Vacation Overrides for up to 3 months (90 days) for travel outside California can be approved by the PBM or by the Alliance pharmacy technicians upon request by the member, pharmacy, or provider when documentation of the departure date, destination, and return date are provided for the following:

i. Non-specialty medications
ii. Non-single-source medications, and/or
iii. Non-controlled medications

b) <u>One vacation override per drug</u> per 365 days can be approved by the

PBM and by the Alliance Pharmacy Technicians for medications described in section (C) 10a.

c) For ANY of the following scenarios, providers must submit a standard PA request for review by an Alliance clinical pharmacist with all required information described in section (C) 10a and medical necessity.
   i. Vacation overrides over 90 days outside California or over 30 days within California
   ii. More than one vacation override per drug per 365 days
   iii. Request for specialty, single-source, and/or controlled medications

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

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

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

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

12. Continuation of Therapy Override
   a) The Alliance shall allow continuation of therapy for members using

medically necessary drugs when it can be shown through clinic notes/provider attestation for OTC products or prescription fill history that the member has been taking the medication prior to enrollment.

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

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

d) For transitioning members until the Beneficiary can be seen by a Plan provider to establish a care plan, as required by Welfare & Institutions (W&I) Code, Section 14185(b), the Alliance will allow for continuation of medically necessary medications, including medication samples, if provided clinic notes showing all the following:
   i. Patient name
   ii. Medication name, dose, and route of administration
   iii. Quantity distributed
   iv. Date medication was started and date last given/filled

e) For override of the formulary based on continuation of therapy the provider must submit clinical documentation showing the member has previously tried without success or cannot/should not take formulary alternatives, including any relevant labs.

13. Discharge Medication Override

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

14. Therapeutic Duplication Override

a) If the member is currently taking a medication that is therapeutically equivalent to the medication requested, the reviewing health care provider may deny the request.

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

15. Day Supply Limit

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

D. Exception Requests Based on Medical Necessity:

1. Since exception requests, by definition, do not have a MRG in place, the

Pharmacy Technician will not be able to approve the request.

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

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

E. **External Review**

A request for an external review when the Alliance denies a prior authorization (PA) can be made for a drug that is not covered by the plan or for an investigational drug or therapy. A request for an external review will not prevent the filing of a grievance or Independent Medical Review (IMR) with the California Department of Managed Health Care (DMHC). Requests for external review will be made and completed in the Alliance Grievances and Appeals Department.

III. Pain Medication Requests for the Terminally Ill

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

A. All other medication requests for the terminally ill members

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

determination and provides an explanation of the determination and the reason for the denial or need for more information.

IV. Provision of Drugs during Emergency Circumstances

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

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

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

A. Outpatient services for the purpose of monitoring drug therapy

VII. **Monitoring Process**

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

DEFINITIONS / ACRONYMS

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

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

HCQC: Health Care Quality and Compliance Committee

NCQA: National Committee on Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently PerformRx)

RELATED POLICIES AND PROCEDURES

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

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

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

REVISION HISTORY

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

REFERENCES

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

MONITORING

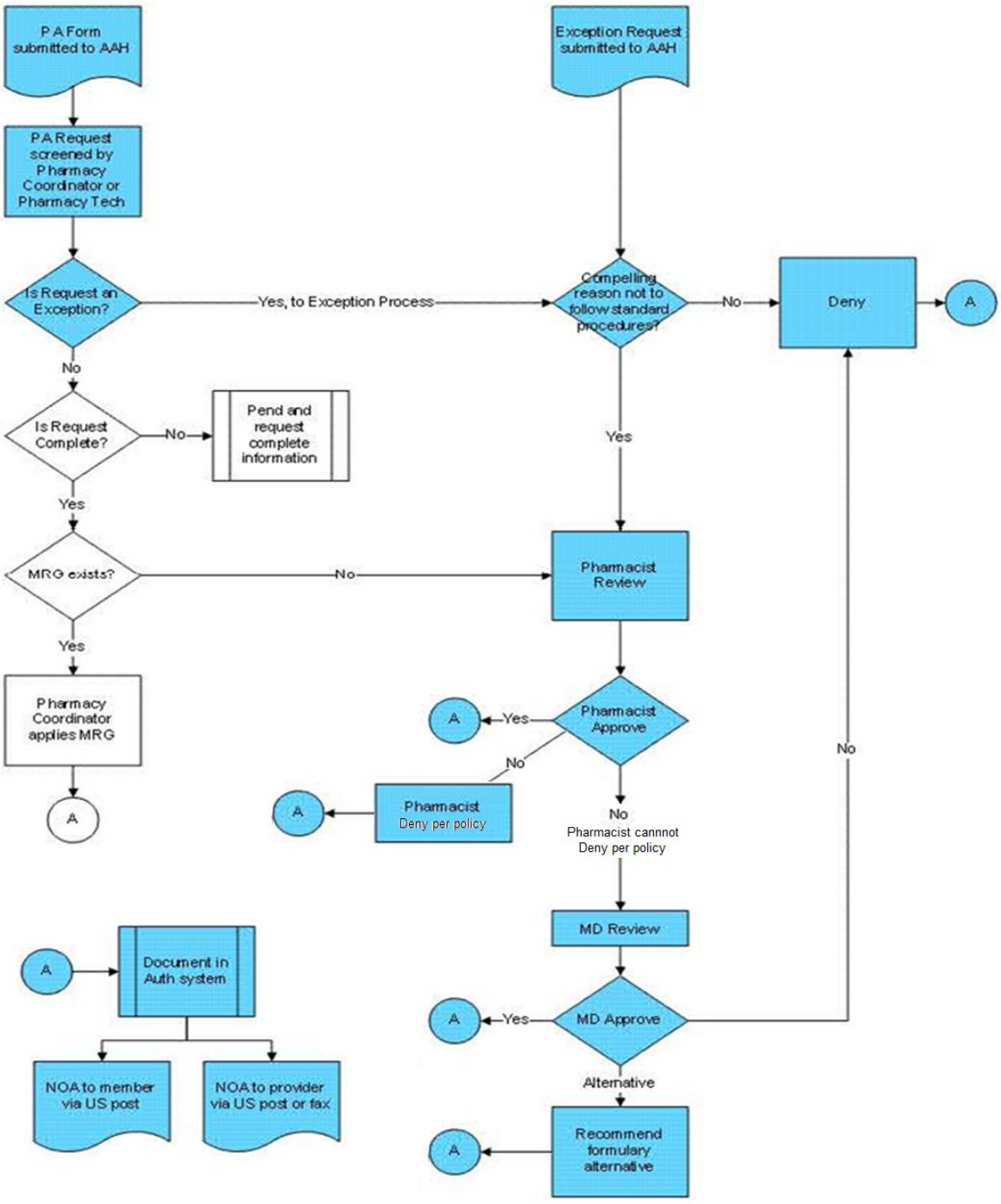
This P&P is reviewed annually to ensure effectiveness.

APPENDIX

Table 1: Decision & Notification Time Frames

Type of Request	Decision	Initial Notification	Written Notification
Prospective, Urgent	Approval	A fax is sent to the requesting provider within 24 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision
	Denial		
Prospective, Non-Urgent	Approval	A fax is sent to the requesting provider within 7224 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision
	Denial		
Post-service	Approval	A fax is sent to the requesting provider within 7224 hours of receipt of the request	NONE
	Modification		Written notification to the member and provider is generated and deposited with the United States Postal Service in time for pick-up within one business day after the decision

Pharmaceutical Management Procedures
(Prior Authorization and Exception Process)



POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-004
Policy Name	Formulary Management
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care (IHSS)
Effective Date	10/01/2007
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

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

PROCEDURE

A. Formulary

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

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

6. The Alliance does not cover drugs within the following categories (<u>unless treating gender dysphoria or alleviating mental health or substance use</u>):
   a. Drugs for the treatment of cosmetic conditions
   b. Investigational or experimental drugs that are under clinical trial
   c. Over the Counter (OTC) drugs, with the following exceptions:
      (i) Certain OTCs are on the formulary based on plan review

7. The Alliance provides coverage for FDA-approved prescription contraceptive methods in accordance with Health & Safety Code, CCR, Section 1367.25.
8. The Alliance's formulary is located on the Alliance's website and is available to Alliance Providers, Pharmacies, and Members upon request.
9. The Alliance provides coverage of standard fertility preservation services when a covered treatment may directly or indirectly cause iatrogenic infertility, and are not within the scope of coverage for treatment infertility.
10. The Alliance provides copayments that will not be higher than the in-network pharmacy's retail price for a prescription drug.
11. The Alliance provides formulary prescription coverage for antiretroviral medications including PrEP without prior authorization/step therapy requirement.

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

1. The P&T Committee's voting membership consists of the Alliance's Chief Medical Officer or designee, the Alliance Senior Director of Pharmacy Services or designee, (4) four licensed practicing physicians and practicing community pharmacists contracted with Alliance (not to exceed 1/3 of the voting membership of the committee or three pharmacists, whichever is greater). The non-voting membership may include a clinical pharmacist from the Alliance's Pharmacy Benefit Manager (PBM), a representative from the Alliance's Quality Improvement Unit, Alliance Operations Unit, and practicing physicians representing a medical specialty as needed in accordance with the agenda and the specific medications or subjects being reviewed.
2. Per the P&T Charter, the P&T Committee is responsible for the following:
    a. Develop and implement effective drug utilization review treatment outcome systems to optimize the quality of the pharmacy services
    b. Review the formulary on a quarterly basis
    c. Ensuring that the formulary review considers all drugs approved by the Federal Drug Administration (FDA)
    d. Ensuring that deletions from the formulary are documented and justified.
3. The following are considered by the P&T Committee when reviewing the formulary:
    a. Alliance Provider recommendations for additions or deletion of drugs to the formulary
    b. Bioavailability data
    c. Cost comparisons against other drugs available to treat the same medical condition(s)
    d. Current therapeutic guidelines
    e. Dosage ranges by route and age
    f. Findings from the following agencies: governmental agencies, medical and pharmaceutical associations, the National Institute of Health, and regulatory body publications
    g. Medical literature and clinical trials
    h. Off-label uses
    i. Patient risk factors relative to contraindications, warnings, and precautions
    j. Patient utilization and experience
    k. Pharmacokinetic data
    l. Pharmacologic considerations (e.g. drug class, similarity to existing drugs, side effect profile, mechanism of action, therapeutic indication, drug-to-drug interaction potential, and clinical advantages over other products in the specific drug class)
    m. Risks versus benefits regarding clinical efficacy and safety of a particular drug relative to other drugs with the same indication
    n. Special monitoring or medication administration requirements

C. Notification of Formulary Changes to Providers and Members

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

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

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

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

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

D. Content Management of Formulary Changes

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

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

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

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

- Drugs used to treat hair loss or hair growth
- Drugs solely used for cosmetic purposes
- Over-the-counter medications (unless approved by the Alliance)
- Non-FDA approved medications (e.g. Medical Foods, herbal remedies, certain supplements, special foods or diet items)
- Nutrition products or household items used for convenience
- Investigational drugs (drugs being studied in clinical trials)
- Comfort or convenience items
- Items used for hygiene (unless criteria have been met. The Alliance will cover incontinence creams and washes when there is a medical need)
- Items used to test blood or other fluids (except blood glucose monitors)
- Drugs used to treat worker's compensation related injury

DEFINITIONS / ACRONYMS

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

AFFECTED DEPARTMENTS/PARTIES

Utilization Management
Pharmacy Services
Member Services
Provider Relations

Communications and Outreach

RELATED POLICIES AND PROCEDURES

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

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

Attachment 1: Request for Formulary Review

REVISION HISTORY

10/1/2007, 3/25/2016, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 9/20/2022, 12/27/2022, 3/28/2023, 3/19/2024

REFERENCES

- NCQA UM 12, Element A, B, D
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-Cal Rx
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx
- DMHC APL 20-001 (OPL): Newly Enacted Statutes Impacting Health Plans
- DMHC APL 19-002 (OPL): Newly Enacted Statutes Impacting Health Plans
- DMHC APL 21-018 Guidance Regarding Preventative Health Services Coverage for HIV Preexposure Prophylaxis (PrEP)

This policy will be reviewed annually to ensure effectiveness.

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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	Group Care (IHSS)
Effective Date	02/01/2012
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~6/20/2023~~
Compliance Committee Approval Date	TBD

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
    f) 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's request 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, 3/19/2024]

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.

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POLICY AND PROCEDURE

Policy Number	RX-006
Policy Name	Pharmacy Services Staff Description
Department Name	Pharmacy
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care
Effective Date	07/15/2012
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance") has an established process for defining the roles for staff involved in the Prior Authorization (PA) and Exception review process. The Alliance is committed to ensuring that staff members involved in the Prior Authorization and Exception review process and are properly licensed and qualified.

This policy and the associated procedures pertain to role assignment for staff members involved in the review process for prior authorization and Exceptions requests.

PROCEDURE

The Alliance employs clinical pharmacists, physicians, pharmacy services specialists, pharmacy technicians, as key staff involved in the prior authorization and exception review process. The qualifications and role of each reviewer in the review process are as follows:

1. The Pharmacy Services Specialists and Pharmacy Technicians are certified clinical assistants. Both positions are tasked with receiving the PA request form, ensuring completeness, and contacting the provider for additional information. He or she can approve a request only if it meets the criteria of the Medical Review Guideline (MRG). He or she must defer requests to the available supervisor (pharmacist or medical director) if the request cannot be approved. Currently, this role is delegated to the Alliance's Pharmacy Benefit Manager (PBM).
2. The PBM's pharmacists will review requests deferred by Pharmacy Services Specialists or Pharmacy Technicians and make determinations on the requests. The PBM's pharmacists can render one (1) decision: approval (with or without MRG).

Any requests that cannot be approved must be escalated to the Alliance Clinical Pharmacist.

3. The Clinical Pharmacist at the Alliance is a currently licensed pharmacist with the California Board of Pharmacy. He or she is tasked with overseeing the review process and daily operations and reviews requests that the PBM's Pharmacy Services Specialists and Coordinators, Pharmacy Technicians, and Clinical Pharmacists cannot approve. The Alliance pharmacist can render three (3) types of decisions: approval (with or without MRG), denial for requests based on Evidence of Coverage (EOC) limitations, and medical necessity denials based on the MRG criteria and/or RX-003 (Exception Review Process). Any requests that cannot be approved, denied based on EOC, or denied based on MRG or RX-003 must be escalated to the Medical Director. A currently licensed, board-certified physician Medical Director may also oversee medical necessity determinations when appropriate or when physician input is needed.

4. The Medical Director is a currently licensed, board-certified physician. He or she is tasked with overseeing the review process and daily operations on an as-needed basis when the pharmacist is not available. He or she is also responsible for reviewing all PA requests for which the pharmacist cannot render a decision.

DEFINITIONS / ACRONYMS

a) Medical Review Guideline: clinical criteria against which requests for prior authorization and exception requests are reviewed; approved by the Pharmacy and Therapeutics (P&T) Committee
b) NCQA: National Committee on Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently PerformRx)

RELATED POLICIES AND PROCEDURES

RX-002 Prior Authorization Review Process
RX-003 Exception Review Process

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

Medical Review Guideline (Excerpt)

REVISION HISTORY

7/15/2012, 5/19/2016, 12/11/2018, 6/25/2019, 3/16/2021, 6/21/2022, 3/28/2023, 3/19/2024

REFERENCES

- NCQA 2016 HP Standards & Guidelines, UM 4 (Appropriate Professionals)
- 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

MONITORING

This policy will be reviewed annually to ensure effectiveness.

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POLICY AND PROCEDURE

Policy Number	RX-007
Policy Name	Pharmaceutical Patient Safety
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care (IHSS)
Effective Date	05/01/2012
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The purpose of this document is to outline the procedure for the functions and scope of the Alameda Alliance for Health (the "Alliance") Pharmacy Department Patient Safety activities.

The Alliance believes in providing appropriate and safe services to its members and works closely with its Pharmacy Benefit Manager (PBM) to ensure proper patient safety protocols are available and practiced to prevent patient safety issues related to pharmaceutical services.

The Alliance has adapted The National Coordinating Council for Medication Error Reporting and Prevention's (NCC MERP) definition of ''medication error," which is:

> ''Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. Such events may be related to professional practice; healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use."

PROCEDURE

I. Recalls and Withdrawals

A. The Food and Drug Administration (FDA) has three (3) different types of recalls, based on the potential severity of harm to the public.

1. Class I: recalls dangerous or defective products that may cause serious health problems or even death
2. Class II: recalls less dangerous products than Class I, that may cause only temporary health problems
3. Class III: recalls products for which use or exposure is not likely to cause adverse health consequences

B. Market withdrawal or voluntary recall is a removal or correction of a marketed product that FDA considers to be in violation of the laws it administers and against which it would initiate legal action (e.g., seizure)

C. The Alliance has a work process set up for Class I, II and voluntary recalls; unless deemed otherwise (e.g. lot level recalls), Class III recalls are not acted upon. In the case of notifications for drug recalls and/or withdrawals, the Alliance's PBM will provide lists of members and prescribers affected. The Alliance will then notify all affected members and/or providers by phone and/or mail of the recall. This notification will take place within 48 hours of notification from the PBM for Class I recalls and within 30 calendar days of FDA notification for Class II recalls and voluntary recalls.

D. The PBM is to generate drug specific reports from their claims data (updated daily) through a variety of data reporting tools. At a minimum, the reports contain the member and prescribing physician information. The Alliance will use these reports in the selection of which members to notify and any additional PBM tools in the notification process. The PBM's Clinical Services staff can assist the Alliance with constructing queries to support the notification process when requested.

E. The process for recalls, at a minimum, will include the following steps (in no specific order):

1. PBM provides the Alliance with a supplemental drug update, which is a specific communication regarding a change to the FDA status of a medication. This recall notice must be received within 48 business hours of initial notice from FDA.
2. All records in National Drug Data File (NDDF) are termed out by setting the recall/withdrawal flag.
3. Product is termed from the Alliance's formularies.
4. Product is termed from all applicable drug management programs.

5. Prior Authorizations for affected product are termed.

F. Drug withdrawal notifications may be provided to members and physicians. These notifications contain background information on the withdrawal, actions taken by the PBM, and recommendations for the Alliance. If the closest therapeutic alternative is a non-formulary item a prior authorization will be entered in the interim. The PBM may notify the Alliance of the action taken regarding the drug that has been recalled/withdrawn within 48 hours for Class I and within 30 days for Class II recalls/withdrawals. The Alliance will not act on limited FDA withdrawal impacting specific lots of products. The PBM does not collect product lot numbers; therefore, it is not possible to identify utilization by members under these circumstances.

II. Medication Error Identification and Reduction (MEIR)

A. The Alliance may receive reports of medication errors from network pharmacies, prescribers, internal staff, and/or members.

B. The Alliance internal staff may include but are not limited to:
1. Clinicians involved in review of prior authorization requests or appeals request
2. Appeals and Grievances staff
3. Member service representatives
4. Quality Improvement Staff
5. Pharmacy Staff

C. The Alliance staff will be trained to identify potential reportable medication errors and understand how to evaluate, resolve, document, and, if necessary, report to the appropriate authority.

D. A report of all received medication errors is presented quarterly to the UM Committee for the purpose of documenting medication errors, identifying trends and patterns, and to determine if further action is necessary (i.e. reporting the medication error to the FDA and/or relevant State Board(s) of Pharmacy).

E. When appropriate, reported medication errors are shared and discussed with downstream providers at the point of dispensing to ensure that corrective actions are implemented and future errors are prevented. These notifications shall be sent by mail with the option to discuss over the phone. This process shall comply with the medication error identification and reduction reporting requirements defined by Centers for Medicare and Medicaid Services (CMS), Utilization Review Accreditation Commission (URAC) and other regulatory and accreditation agencies.

III. Member Communication of Drug Recalls and Withdrawals

A. In addition to notifying members via letter or phone, as detailed above, the Alliance shall make public all drug recall and withdrawal information on the member portal of the plan website. The content can be located under “Safety Resources” within the “Pharmacy & Drug Benefits” section. Each recall and withdrawal shall be made published on the

member portal within 5 business days of receipt of notification from the pharmacy benefit manager.

DEFINITIONS / ACRONYMS

a. FDA: Food and Drug Administration
b. NDDF: National Drug Data File
c. PBM: Pharmacy Benefit Manager (Currently, PerformRx)
d. URAC: Utilization Review Accreditation Commission
e. NCQA: National Committee on Quality Assurance
f. CMS: Centers for Medicare and Medicaid Services
g. NCC MERP: National Coordinating Council for Medication Error Reporting and Prevention.

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Department
Pharmacy Benefit Manager (PerformRx)
Provider Relations
Quality Improvement
Member Services

RELATED POLICIES AND PROCEDURES

P&T Charter

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None.

REVISION HISTORY

5/1/2012, 5/19/2016, 12/11/2018, 11/13/2020, 3/16/2021, 6/21/2022, 3/28/2023, 3/19/2024

- **REFERENCES**CMS Part D Manual, Chapter 7 – Prescription Drug Benefit Manual, section 20.5 – Medication Error Identification and Reduction (MEIR)
- PerformRx Policy, DRUM-1-02 - Internal Medication Error Identification and Reduction Systems
- NCQA, UM 12 Element C
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefit 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 by P&T Committee.

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POLICY AND PROCEDURE

Policy Number	RX-008
Policy Name	PBM Delegated Audit Oversight
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care
Effective Date	3/25/2016
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance) has a contract with its Pharmacy Benefit Manager (PBM) to administer many of the pharmacy services operations. The PBM contract shall indicate that they will comply with all applicable laws and regulations related to providing the Pharmacy Services to the Alliance members.

PROCEDURE

1. An annual audit shall be conducted by the Alliance staff or by a third-party vendor.
2. Audited areas shall be based on the current contract with the PBM. The areas of audit are as listed, but not limited to:
   a. Claims processing
   b. Formulary Management and Benefit Coding
   c. Prior Authorization Process
   d. Pharmacy Credentialing
   e. Pharmacy Encounter File Accuracy
   f. Compliance with the Health Insurance Portability and Accountability Act (HIPAA)
   g. Pharmacy Network Management
   h. Fraud, Waste, and Abuse (FWA) Training
   i. Drug Utilization Monitoring

3. Summary of audit and audit findings will be reviewed by the Pharmacy & Therapeutics (P&T) Committee and the Compliance Committee.
4. Ongoing audits will be conducted when closer and more frequent monitoring is warranted. They are, but not limited to:
   a. Maximum Allowable Cost (MAC) Pricing Management
   b. Turnaround Time for Outpatient Pharmacy Authorization Requests
5. On a quarterly basis, the current PBM will provide the summary of performance measurements as described in the contract.
6. The Alliance Senior Director, Pharmacy Services or designee will review the quarterly performance measures summary report and identify any problems with the completeness and effectiveness or other concerns about the PBM and present them to the P&T Committee.
7. The Alliance Senior Director, Pharmacy Services or designee will manage the audit findings from the annual audit, on-going monthly audits as well as the quarterly performance guarantee reports.
8. The Alliance adopts PerformRx policies for Pharmacy System User Access Review (CORE 1-08) and Utilization Management ("UM") System Controls (DRUM 1-05). These policies are adopted to ensure UM System Controls.
9. The Alliance will also have an NCQA crosswalk audit once a year that will be conducted by Alameda Alliance for Health Pharmacy Services staff.

If deficiencies are found during the audit, the Alliance will request a corrective action plan (CAP) and ensure implementation through a monitoring process as described in policy ADM-CMP-0042 Delegation Oversight.

DEFINITIONS / ACRONYMS

a. PBM: Pharmacy Benefit Manager (Currently, PerformRx)
b. HIPAA: Health Insurance Portability and Accountability Act
c. P&T Committee: Pharmacy and Therapeutics Committee

AFFECTED DEPARTMENTS/PARTIES

PBM

RELATED POLICIES AND PROCEDURES

- CMP-042 Delegation Oversight
- 
  CORE 1-08 Pharmacy System Us
- 
  DRUM 1-05 UM System Controls - 03

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

12/11/2018, 06/25/2019, 3/16/2021, 5/26/2022 – IQIC ad hoc, 6/21/2022 – P&T, 3/28/2023, 3/19/2024

REFERENCES

- Title 22, CCR, Section 53854, 53214
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-cal RX
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out - Medi-Cal Rx

MONITORING

This policy will be reviewed annually to ensure effectiveness.

POLICY AND PROCEDURE

Policy Number	RX-009
Policy Name	Pharmaceutical Emergency Supply Provision
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care
Effective Date	4/1/2016
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Revision / Approval Date~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance") shall arrange for pharmaceutical services to be available during regular business hours. In addition, the Alliance has an existing process to allow a three (3) day emergency fill at any contracted pharmacy to ensure the provision of drugs prescribed in emergency circumstances in amounts sufficient to last until the Member can reasonably be expected to have the full prescription filled California Code of Regulations, Title 22 §53854(1),(2) & (3)).

PROCEDURE

I. Contracted Pharmacies
   A. The Alliance delegates pharmacy contracting to its Pharmacy Benefit Manager (PBM). The PBM provides monthly reports of the pharmacy network in Alameda County. This report shall include the hours of operations of the contracted pharmacies.

II. Provision of Drugs During Emergency Circumstances
   A. "Emergency Circumstances" refer to any of the following situations:
      1. Emergency room (ER) discharge prescriptions
      2. Inpatient discharge prescriptions

3. Any circumstance that involves an imminent and serious threat to the member, including, but not limited to, severe pain, potential loss of life, limb or major bodily function.

B. In emergency circumstances, as defined under Section A, prior authorization is not required for a three (3) day supply of drugs that would otherwise require authorization or exceptions.
C. Alliance providers are informed of this policy via the Alliance's Provider Manual.
D. Alliance providers are responsible for following the prior authorization process or exceptions process for the remainder of the prescription.
E. The Alliance allows for payment of the three (3) day supply of the drugs even in the event that the prior authorization or exceptions 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.

III. Three (3) day Fill Procedure

A. The Alliance has a process in place to allow contracted pharmacies to process a 3-day supply under emergency situations.
B. The 3-day supply process is automated and does not require an authorization from the Alliance or the PBM's staff.
C. The dispensing pharmacist uses his or her clinical judgement to determine the level of emergency. An emergency situation is defined as a condition requiring expedited or urgent processing which includes any condition involving an imminent or serious threat to a member's health.
D. Emergency situations include but are not limited to: A discharge prescriptions from an inpatient stay or an Emergency Room visit, any other conditions that meet the criteria above (Section II. C.)

IV. Monitoring and Audit

A. The Alliance monitors a 3-day emergency override report on a monthly basis to ensure that members have access to a medication in emergency situations.
B. The findings of such monitoring will be reported to the - the P&T Committee.

DEFINITIONS / ACRONYMS

- PBM: Pharmacy Benefit Manager (currently, PerformRx)
- NCQA: National Committee for Quality Assurance

AFFECTED DEPARTMENTS/PARTIES

- Pharmacy Department

RELATED POLICIES AND PROCEDURES

- RX-001 Pharmaceutical Operating Processes Summary

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None

REVISION HISTORY

3/17/20, 03/16/21, 6/21/2022, 3/28/2023, 3/19/2024

REFERENCES

- CCR, Title 22§ 53854(1),(2) & (3)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 - Medi-Cal Rx

MONITORING

This policy will be reviewed annually to ensure effectiveness.

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POLICY AND PROCEDURE

Policy Number	RX-010
Policy Name	Drug Utilization Management
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Medi-Cal, Group Care
Effective Date	10/01/2007
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Revision / Approval Date~~	TBD~~Pending P&T approval on 12/19/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health's (the "Alliance") Pharmacy Services unit has established Drug Utilization Review (DUR) procedures. The objective of DUR is to improve the quality of pharmaceutical care by ensuring that prescriptions are appropriate, medically necessary, and unlikely to result in adverse medical outcomes. The Alliance's DUR procedures comply with the Alliance's contract with the California Department of Health Care Services (DHCS). The Alliance will provide drug utilization encounter data to DHCS monthly.
Unless otherwise indicated, majority of DUR activities will be applicable to GroupCare only.

PROCEDURE

A. Drug Utilization Review (DUR) Overview:

1. DUR promotes patient safety by ensuring that prescriptions are appropriate, medically necessary, and unlikely to result in adverse medical outcomes.
2. All retail, specialty and mail service pharmacies are subject to Concurrent Reviews at point-of-sale and periodic Retrospective Reviews after adjudication.

B. Concurrent DUR:

1. This section does not apply to Medi-Cal line of business after the implementation of Medi-Cal Rx.
2. The Alliance's PBM ensures the safety of dispensed medications by notifying dispensing pharmacies of potential adverse events at the point-of-sale. The online messaging process classifies events at different levels of severity.
3. The PBM provides on-line, concurrent DUR messaging to pharmacies and takes appropriate action. Concurrent DUR includes but is not limited to the following

edits:

(a) Over- and under-utilization
(b) Duplication
(c) Drug-drug or drug-allergy interactions
(d) Drug-disease contraindications
(e) Drug dosage
(f) Drug-age precautions
(g) Drug-gender precaution
(h) Drug-pregnancy precautions

C. Retrospective DUR:

1. The Alliance's PBM will provide a list of on-demand retrospective DUR reports of various topics to monitor fraud, waste, or abuse. These reports are reviewed and may be used by the Alliance to support quality improvement programs (QIPs) and Disease Management programs.
2. The Alliance pharmacy staff or third-party vendor will run these reports as appropriate.
3. For Medi-Cal line of business, the Alliance will participate in Medi-Cal Global DUR Board and other DHCS organized pharmacy committee meetings.
4. For Medi-Cal line of business, the Alliance will receive comprehensive claims and PA history for their members and can use claims data for their own quality improvement, retrospective DUR activities, and coordination of care if needed including but not limited to identifying patterns of:
   (a) Therapeutic appropriateness
   (b) Adverse events
   (c) Incorrect duration of treatment
   (d) Over or under utilization
   (e) Inappropriate or medically unnecessary prescribing
   (f) Gross overprescribing and use
5. For Medi-Cal line of business, the Alliance will provide active and ongoing outreach to educate providers on common drug therapy problems (e.g., asthma medication ratio monitoring, opioid and naloxone co-prescribing, new prescribing guidelines, and advisories) with the goals of improving prescribing and dispensing practices, increasing medication compliance, and improvement of over-all beneficiary health.
6. For Medi-Cal line of business, the Alliance will be required to submit an annual DUR report to include any descriptions of any retro DUR activities and any innovative practices implemented by the plain in the prior federal fiscal year.
7.

For Medi-Cal line of business, the Alliance SIU (Special Investigations Unit) monitors and has a process for identifying and addressing fraud and abuse of controlled substances by the Alliance members and the health care Providers who are prescribing these drugs and pharmacies dispensing these drugs to the Alliance members. The Alliance SIU actively investigates any allegations of fraud, waste or abuse regarding the aforementioned substances.

D. Drug Utilization Data Submission

1. On a regular basis, no less than once monthly, the Alliance's PBM sends the

encounter data in the mutually agreed-upon format to the Alliance.

2. The Alliance's IT team will prepare the data for monthly submission. (See Policy IT Monthly Encounter Data)

E. Monitoring of DUR Process

1. Concurrent DUR reports and Retrospective DUR reports are reviewed by the Alliance pharmacy staff or third-party vendor and Senior Director, Pharmacy Services or designee and reported to the UM Committee and Quality Improvement Health Equity Committee (QIHEC).
2. Pursuant to 42 CFR 438.3(s)(4) and (5), the Alliance is to operate a drug utilization review (DUR) program that complies with the requirements described in Section 1927 (g)of the Social Security Act (the Act) and submit an annual report on the operation of its DUR program activities to DHCS.

F. Preventing Opioid Overutilization

1. This section only applies to Group Care line of business after the implementation of Medi-Cal RX. The Alliance will ensure safe and effective use of opioids which include but are not limited to the following:
   (a) Any long-acting opioid will require a prior authorization (PA)
   (b) Short acting opioids will have quantity and day supply limits
   (c) Members who are receiving above 500 MME (morphine milligram equivalent) will require a PA
   (d) Concurrent use of any opioids and benzodiazepines or opioids and antipsychotics
   (e) The Alliance will ensure that the DUR program meets or exceeds applicable provisions of Section 1004 requirements of the SUPPORT for Patient and Communities Act: A retrospective claims review process that monitors when an individual is concurrently prescribed opioids and benzodiazepines or opioids and antipsychotics.

G. Monitoring Anti-psychotics, Mood stabilizers and Anti-depressants

1. The Alliance will monitor appropriate use of anti-psychotics, mood stabilizers, and anti-depressant medications for all children 18 years of age and under including foster care children enrolled under the California Medicaid State Plan. The Alliance will ensure the following processes:
   (a) Quarterly monitoring of children using anti-psychotics, mood stabilizers and anti-depressants.
   (b) Quarterly monitoring of providers with children using anti-psychotics, mood stabilizers and anti-depressants.

DEFINITIONS / ACRONYMS

- PBM: Pharmacy Benefit Manager (Currently, PerformRx)
- IT: Information Technology Department
- MME: Morphine Milligram Equivalent
- PA: Prior Authorization

AFFECTED DEPARTMENTS/PARTIES

- PBM

- IT

RELATED POLICIES AND PROCEDURES

- PerformRx P&P: DRUM-3-01 Concurrent Drug Utilization Management Program
- Policy IT Monthly Encounter Data

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

None.

REVISION HISTORY

10/7/2007, 8/24/2017, 12/11/2018, 6/25/2019, 3/17/2020, 3/16/2021, 6/15/2021, 6/21/2022, 3/28/2023, 12/19/2023, 3/19/2024

REFERENCES

- DHCS All Plan Letter 19-012 Federal Drug Utilization Review Requirements Designed to Reduce Opioid Related Fraud, Misuse and Abuse
- DHCS All Plan Letter 20-020 Governor's Executive Order N-01-19, regarding Transitioning Medi-Cal Pharmacy Benefits from Managed Care to Medi-Cal RX
- DMHC APL 20-035 (OPL): Medi-Cal Pharmacy Benefit Carve Out – Medi-Cal Rx
- DMHC APL 23-026 Federal Drug Utilization Review Requirements Designed to Reduce Opioid Related Fraud, Misuse and Abuse
- DHCS Contract #23-30212, Exhibit A – Scope of Work

MONITORING

This P&P will be reviewed annually to ensure effectiveness and compliance with regulatory and contractual requirements.

Utilization data is reviewed for trends and analysis, and any identified potential fraud and abuse concerns are reported to the Compliance department. This includes potential fraud and abuse related to controlled substances by members, health care providers prescribing to the member, and pharmacy dispensing the drugs to members.

POLICY AND PROCEDURE

Policy Number	RX-011
Policy Name	Decision and Notification Requirements
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Group Care (IHSS)
Effective Date	10/12/2017
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision~~	TBD~~3/28/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance") has an established process and timeframes for reviewing requests and sending out notification to the members and providers (Notice of Action). The Alliance is committed to ensuring that all requests for prior authorization or exception requests are reviewed in a timely manner. The Alliance's process for sending notifications to the member and provider regarding approved, modified, or denied authorization requests (also known as the "Pharmacy NOA Policy") complies with the standards set by the California Health & Safety Code, Sections 1367.01; the California Code of Regulations (CCR) Title 28, Section 1300.67.241; and the California Welfare & Institutions Code, Section 14185. Prior authorization is not required for the provision of an emergency three (3) day supply of drugs (see RX-009, Pharmaceutical Emergency Supply Provision).

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

PROCEDURE

I. Decision Review Time Frames (Turn-around times)

A. For all covered outpatient drug Prior Authorization requests, a decision will be rendered (Approved/Modified/Denied) within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases.

B. In all cases and for all decisions, notice of the decision rendered will be sent to the

requesting provider either by telephone, fax, mail, or other electronic communication within 24 hours from time of receipt for urgent/emergent cases and 72 hours from time of the receipt of non-urgent cases.

II. Decision Notification Time Frames - The Alliance provides notification of the decision within the following time frames:

A. Approvals

1. Notification of approval of Prior Authorization or Exception requests are made via facsimile or phone to the requesting provider and dispensing pharmacy (if the pharmacy is known) within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases.
2. The Alliance Pharmacy Services Department is responsible for ensuring all notifications are sent within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases. If the act of sending of the notifications is delegated to a vendor, The Alliance Pharmacy Services Department shall monitor notification times monthly to ensure compliance with the notification time frame.
3. Approval Notifications shall include at a minimum:
    1) The name of the medication requested
    2) The quantity and duration of treatment being approved.

B. Denials and Modifications

1. Notifications of denial or modification of Prior Authorization or Exception requests are made via facsimile or phone to the requesting provider and dispensing pharmacy (if the pharmacy is known) within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases after decision has been made. The Alliance notifies MEMBERS of a decision to Deny, or Modify requests for exceptions or prior authorization by sending WRITTEN notification to the member within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases after the decision has been made.
2. The Alliance notifies PROVIDERS of a decision to Deny, or Modify requests for exceptions or prior authorization by sending WRITTEN notification to the requesting provider within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases after the decision has been made.
3. Notifications of denied or modified requests shall include:
    1) Clear and concise explanations of the reasons for the denial and clinical reasons as applicable
    2) The name of the medication requested
    3) The quantity and duration of treatment being denied
    4) The name of the Medical criteria, benefit provision, Pharmacy or UM policy, or Medication Review Guideline used to make the decision
4. The notification includes the medication names, the amount requested, and the requested duration of treatment denied.
5. Providers are notified by telephone or fax within 24 hours from time of the receipt for urgent/emergent cases and within 72 hours from time of receipt for non-urgent cases after the decision has been made. The written

notification includes the medication names, the amount requested, and the duration of treatment denied. Written notifications to the physician or other health care provider of a denial, , or modification of a request will include the name and telephone number of the health care professional responsible for the denial, or modification. The telephone number provided is the direct number or an extension, to allow the physician or health care provider easily to contact the professional responsible for the denial, or modification

6. A standardized form is used, and the following information is included:
    1) The name and address of the Alliance and the state toll-free telephone number for obtaining information for legal service organizations for representation.
    2) Requesting providers are notified by telephone or fax within 24 (for urgent requests) or 72 hours (for non-urgent requests) of the final decision of the exception request in accordance with California Health and Safety Code Section 1367.01. The name and phone number of the person responsible for making the decision is included in the written notification. The notification includes the medication names, the amount requested, and the duration of treatment denied.

VI. Monitoring Process

A. The Senior Director of Pharmacy Services or designee reviews a monthly authorization report, which provides statistics on all approvals, denials, and modifications to ensure that providers and members have been notified in accordance within the mandated turnaround times.

B. The Senior Director of Pharmacy Services or designee shall audit at random up to twelve NOA letters per month. This audit shall include the following:
    1. Evaluation of whether the correct determination was made
    2. Evaluation of whether the correct rationale was used
    3. Whether all acronyms and medical terms were defined
    4. If the letter contains a specific reason for denial
    5. If the letter is easy to understand (clear and concise)
    6. If the criteria used to make the decision has been cited

C. If errors are found, they will be immediately addressed (e.g. new PA entered with correct decision, contact PBM, or discussion with the staff member who made the error).

V. Provider Access to the Decision maker

A. All letters shall contain the name of the clinician who made the decision and the phone number where they can be reached.

B. A log of physician calls and subsequent callbacks shall be kept and reviewed monthly for any barriers. Any barriers found will be immediately addressed.

Table 1: Decision & Notification Time Frames

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

Table 2: Determination Turnaround Time~~t T~~able of Different Regulatory Bodies

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

DEFINITIONS / ACRONYMS

- Pharmaceutical Management Procedures: Formulary drugs that have additional requirements or limits on coverage, such as Step Therapy (ST), Quantity Limits (QL) and Age Limits (AL).
- 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)).
- Emergency Circumstances: When the enrollee's condition is such that the enrollee faces an imminent and serious threat to his or her health, including, but not limited to, the potential loss of life, limb, or other major bodily function, it is considered an emergency (Health and Safety Code
- § 1367.01 (h)(2)).

HCQC: Health Care Quality and Compliance

Committee NCQA: National Committee on Quality

Assurance

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Pharmacy Benefit Manager (Currently PerformRx)

RELATED POLICIES AND PROCEDURES

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

RELATED WORKFLOW DOCUMENTS OR OTHER ATTACHMENTS

Attachment 1 – Prescription Drug Prior Authorization Request Form
Attachment 2 – Exception Review Process Flow Chart

REVISION HISTORY

10/12/2017, 12/11/2018, 3/16/2021, 3/15/2022, 3/28/2023, 3/19/2024

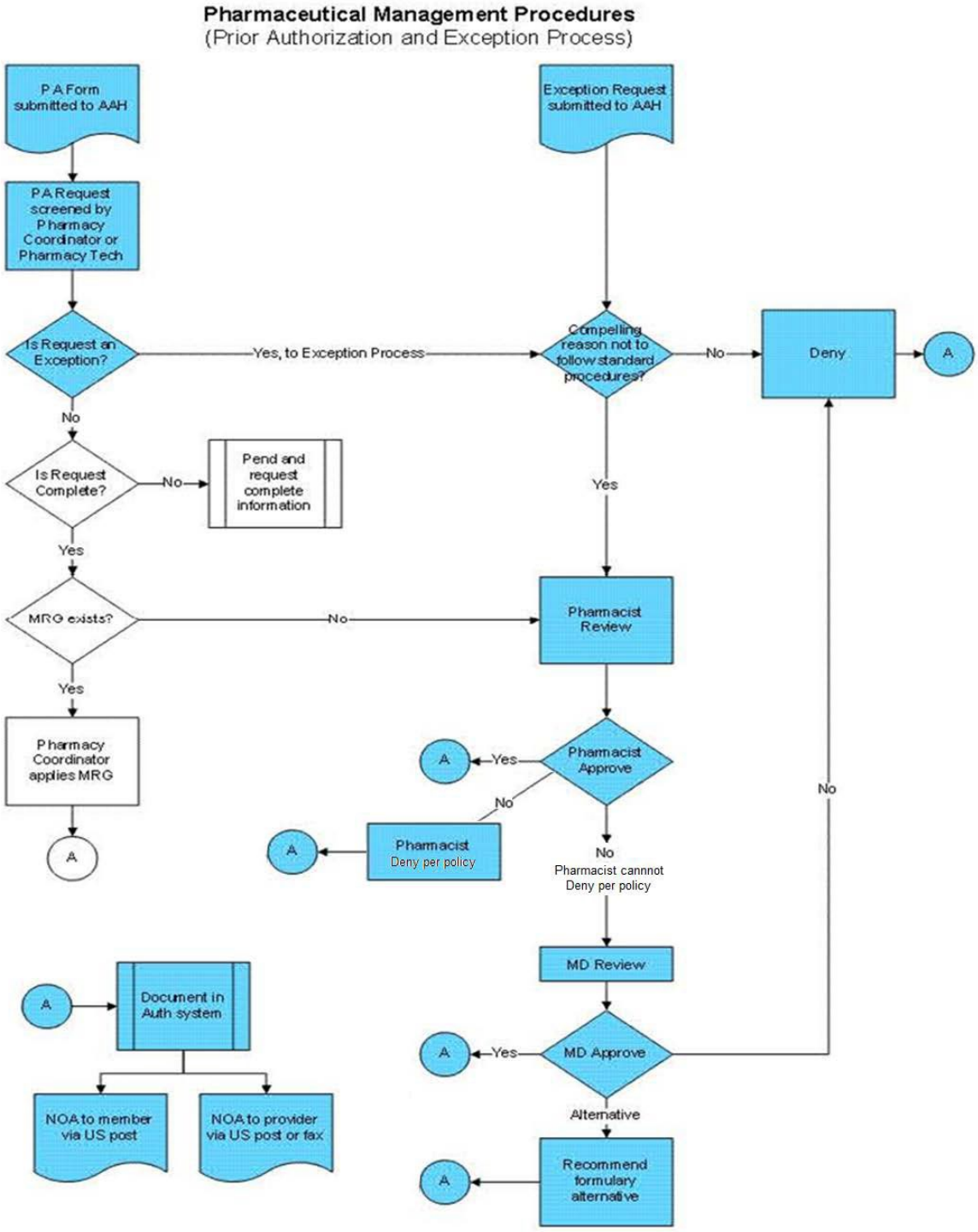
REFERENCES

- California Code of Regulations (CCR), Health & Safety Code, §§1367.01, 1367.21, 1367.22, 1367.24 and 1373.96
- CCR, Welfare & Institutions Code, §14185
- CCR, Title 22, §§51003, 51014.1, 51014.2, 53854 and 53894
- CCR Title 28 §1300.67.24
- MMCD Policy Letter 08-013
- NCQA, 2016 HP Standards & Guidelines, UM 13 (Procedures for Pharmaceutical Management), Element E (Considering Exceptions)
- Welfare and Institutions Code, Section 14185**, 42 CFR 438.3(s)(6), and Section 1927(d)(5)(A) of the Social Security Act**
- 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


Pharmaceutical Management Procedures
(Prior Authorization and Exception Process)
PA Form submitted to AAH
PA Request screened by Pharmacy Coordinator or Pharmacy Tech
Is Request an Exception?
Yes, to Exception Process
No
Is Request Complete?
No
Pend and request complete information
Yes
MRG exists?
No
Yes
Pharmacy Coordinator applies MRG
A
Exception Request submitted to AAH
Compelling reason not to follow standard procedures?
No
Deny
A
Yes
Pharmacist Review
A
Yes
Pharmacist Approve
No
A
Pharmacist Deny per policy
No
Pharmacist cannnot Deny per policy
No
MD Review
A
Document in Auth system
NOA to member via US post
NOA to provider via US post or fax
A
Yes
MD Approve
Alternative
A
Recommend formulary alternative

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POLICY AND PROCEDURE

Policy Number	RX-013
Policy Name	Medical Benefit Physician/Facility-Administered Drugs (PAD) Prior Authorization Review Process
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Medi-Cal, Group Care (IHSS)
Effective Date	7/17/2023
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~Pending P&T approval on 12/19/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health (the "Alliance") has an established process for reviewing and processing medical necessity-based physician/facility-administered drugs (PAD) 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, 1373.96; the California Code of Regulations (CCR) Title 28, Sections 1363.5, 1367.01,; . The Alliance covers medications for treating gender dysphoria or alleviating mental health or substance use. The Alliance ensures parity in coverage of pharmaceuticals used to treat medical/surgical, mental health, and substance abuse disorders.

PROCEDURE

I. Prior Authorization Process Guidelines

A. Prior authorization review and approval hierarchal criteria are utilized and required as outlined in UM-001 (or with PAD Medication Review Guidelines) for the appropriate pharmacy authorizations.

B. The Alliance utilizes evidence-based prior authorization criteria approved by the P&T Committee. Prior authorization criteria are developed and reviewed annually and are based established by organizations such as Medi-Cal guidelines (if for Medi-Cal line of business),

Milliman Care Guidelines, Food and Drug Administration (FDA), National Comprehensive Cancer Network (NCCN), UpToDate, and National Institutes of Health (NIH). The Alliance covers pharmaceuticals in accordance with 42 CFR section 438.900 et seq, to ensure parity in medical/surgical, mental health, and substance abuse benefits and treatment.

II. Prior Authorization Procedures

A. All providers are required to submit prior authorization for Healthcare Common Procedure Coding System (HCPCS) / National Drug Code (NDC) codes that are listed and in alignment with P&T committee approved PA criteria as appropriate.

B. Required information provided on all requests should include:

a) Member demographic information
b) Practitioner demographic information
c) Requested service/procedure to include specific Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS) code(s)
d) Member diagnosis (Specific International Classification of Disease (ICD) Code/Description)
e) Clinical indications necessitating service
f) Pertinent medical history, treatment, or clinical data
g) Location of service to be provided
h) Requested/anticipated duration of therapy
i) Proposed date(s) of services

C. Prior authorization requests must be submitted electronically or by fax to the Alliance UM Department.

a) Pharmacy department will manage the end-to-end process when providers send a PAD PA for the Alliance members. This entails some of the following duties below:
    i. Verify eligibility, coverage, and network
    ii. Check if there are benefit restrictions
    iii. Generate letter of notifications for approval, partial approval, and denial

A. Retro Requests: The Alliance does not accept post-service or retrospective authorization requests for nonemergent or non-urgent services that would require prior authorization more than 90 days past the date of service.

The exception criteria under which a post service / retrospective request greater than 90 days after the date of service may be considered are:

1. Member eligibility issues, i.e., unable to validate eligibility at time of service, incorrect eligibility information at time of service.
2. In-patient services where the facility is unable to confirm enrollment with the Alliance.

B. Pre-Service/Post-Service Review for Pharmacy Technician (PT)
    A. Upon receipt of the authorization request, the PT will review the request for:
        (1) Member eligibility
        (2) Completeness of the request
            (a) Presence of medical codes,
            (b) Presence of medical records
    B. Once the authorization request review is complete, the PT enters the authorization

request into the clinical information system and routes it to the appropriate UM PT processing queue.

C. Upon selecting authorization request from the queue, the assigned PT reviews the pre-service/post-service authorization request that includes:

(1) The UM PT reviewer performs a review of the pre-service/post-service/DME or pump associated with PAD authorization request and clinical information presented using the appropriate UM criteria, according to UM-001 Utilization Management Policy or UM Program.

(a) The PT Reviewer documents the decision-making process in the clinical information system.

(b) The PT Reviewer workflow includes:

(i) For authorization requests meeting criteria under the scope of the PT, the PT Reviewer approves the request and generates the Member and Provider approval notification.

(ii) For authorization requests not consistent with the request (i.e., conflicting CPT Codes to diagnosis, conflicting HCPCs to documentation, etc.), or otherwise are outside of PT scope, where there is a potential for delay, denial, modification, or termination, and for cases involving benefit exhaustion or benefit termination, the PT Reviewer forwards the request to the Pharmacist Reviewer.

C. Pre-Service/Post-Service Review Pharmacist Reviewer (PR)

A. Pharmacist Reviewer performs a medical necessity review of the authorization request and clinical information presented using the appropriate UM criteria, according to UM-001 Utilization Management Policy or UM Program.

(1) The PR utilizes evidence-based criteria and hierarchical criteria process for approving, modifying, deferring, requested services (as applicable).

(a) The hierarchal criteria process:

(i) Regulatory and contractual requirements

(ii) Evidence based guidelines

(iii) Alliance specific guidelines

(iv) National medical association consensus

(v) Medical necessity/medical judgement

(2) The PT Reviewer documents the clinical decision-making process in the clinical information. The documentation must include a review of the clinical information and application of the appropriate criteria used in the determination.

~~(3) For authorization requests not consistent with the request (i.e. conflicting CPT Codes to diagnosis, conflicting HCPCs to documentation, etc.), not meeting UM Criteria, where there is a potential for delay, denial, modification, or termination, and for cases involving benefit exhaustion or benefit termination, the PR forwards the request to the UM Medical Director/Physician Reviewer for review.~~

III. The Alliance's Pharmacy Department processes pharmacy authorization requests in accordance with the procedures described in UM Policy # 001 – Utilization Management and UM Policy #057 (as it may relate to pharmacy services).

a. Outreach calls (up to 3 attempts) may be made to the requesting provider to request reasonably necessary clinical information when needed to make a PA decision or enter missing required clinical information for medication requests. For each outreach attempt, the reviewer is to document the following:

i. Name and title of person spoken to

ii. Phone number called (if different from one already noted in the PA system)

iii. What specific information was requested

IV. Continuity of Care for Covered Services for Newly Enrolled Medi-Cal and GroupCare Beneficiaries

A. PAD CoC requests are managed using the same mechanisms and processes as UM Policy #036 Continuity of Care for Terminated and Non-Participating Providers, UM Policy #058, Continuity of Care for New Enrollees Transitioned to Managed Care After Receiving A Medical Exemption, and UM Policy#059 Continuity of Care for Medi-Cal Beneficiaries Who Transition into MediCal Managed Care.

V. Continuity of Care for Covered Services for Members Receiving Pharmaceutical Treatment

A. Anthem

1. Member may request up to 6 months for continuity of care service to continue an active course of treatment.
2. Active Course of Treatment is defined as a course of treatment in which a member is actively engaged with a provider prior to January 1, 2024, and following the prescribed or ordered course of treatment as outlined by the provider for a particular medical condition as in DHCS 2024 Medi-Cal Managed Care Plan Transition Policy Guide.

B. Medi-Cal Beneficiaries who newly enroll in Medi-Cal managed care from Medi-Cal fee-for service, on or after January 1, 2024 (i.e.. Adult Expansion)

1. Member may request up to 90 days for continuity of care service following AAH enrollment and until reassessment as in APL 23-022.

C. LTC Members

1. ICF-DD
   A. Member may request up to 90 days for continuity of care service following AAH enrollment and until reassessment as in APL 23-023.
2. Subacute
   A. Member may request up to 6 months for continuity of care service following AAH enrollment and or duration of TAR (which ever duration is shorter) as in APL 23-027.
3. LTC-SNF
   A. Member may request up to 90 days for continuity of care service following AAH enrollment and until reassessment as in APL 23-004.

V. Continuation of Therapy

A. The Alliance shall allow continuation of therapy for members using medically necessary drugs when it can be shown through clinic notes or medication fill history that the member has been taking the medication prior to enrollment.

B. For transitioning members until the Beneficiary can be seen by a Plan provider to establish a

care plan, as required by Welfare & Institutions (W&I) Code, Section 14185(b), the Alliance will allow for continuation of medically necessary medications if provided clinic notes showing all of the following:

1. Patient name
2. Medication name, dose, and route of administration
3. Quantity distributed
4. Date medication was started and date last given/filled

VI. Annual Review of PAD Prior Authorization and UM Criteria

a. All PAD 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.

VII. Monitoring of the PA process

a. Inter-rater Reliability- the Alliance evaluates the consistency of decision making for those health care professionals involved in applying PAD Criteria.

VIII. Pharmacy Department will communicate with Utilization Management (UM), Communications & Outreach, Medical Directors, Provider Services (PR), Member Services (MSR), Claims and Benefit Configuration Departments to implement prior authorization restriction requirements in Heath Suite and outreach to providers and members.

IX. Pharmacy Services will comply with appropriate UM policies as they relate to pharmacy supported authorizations, NOA letters and regulatory requirements (see related policies section for reference).

DEFINITIONS / ACRONYMS

- PAD: Physician/Facility-Administered Drugs
- NCQA: National Committee on Quality Assurance
- UM: Utilization Management

AFFECTED DEPARTMENTS/PARTIES

Pharmacy Services
Utilization Management
Claims
Benefit Configuration
Member Services
Provider Relations
Communications and Outreach

RELATED POLICIES AND PROCEDURES

UM-001 Utilization Management
UM-036 Continuity of Care for Terminated and Non-Participating Providers
UM-051 Timeliness of UM Decision Making and Notification
UM-051 Attachment A UM Timeliness Standards for Medi-Cal and Group Care
UM-054 Notice of Action

UM-057 Authorization Service Request
UM-058 Continuity of Care for New Enrollees Transitioned to Managed Care After Receiving A Medical Exemption
UM-059 Continuity of Care for Medi-Cal Beneficiaries Who Transition into MediCal Managed Care

REVISION HISTORY

6/20/2023, 12/19/2023, 3/19/2024

REFERENCES

- NCQA UM 12, Element A**,** B, D
- Alliance Provider Manual
- Health & Safety Code, Sections 1363.5, 1367.01, 1367.21, 1367.215, 1373.96
- Senate Bill 855 – Mental Health as a Medical Necessity
- DHCS All Plan Letter 22-012 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
- DHCS All Plan Letter 22-032 Continuity of Care for Medi-Cal Beneficiaries Who Newly Enroll in Medi-Cal Managed Care from Medi-Cal FFS, and for Medi-Cal Members who Transition into a New Medi-Cal Managed Care Health Plan on or after January 1, 2023
- DHCS APL 23-004 Skilled Nursing Facilities -- Long Term Care Benefit Standardization And Transition Of Members To Managed Care
- DHCS APL 23-027, Subacute Care Facilities -- Long Term Care Benefit Standardization and Transition of Members to Managed Care
- DHCS APL 23-023 – Intermediate Care Facilities for Individuals with Developments Disabilities – Long Term Care Benefit Standardization and Transition of Members to Managed Care
- DHCS Contract #23-30212, Exhibit A – Scope of Work
- 2024 Medi-Cal Managed Care Plan Transition Policy Guide

MONITORING

This policy will be reviewed annually to ensure effectiveness.

APPENDIX

Table 1: Medical Benefit Determination Turnaround Timetable of Different Regulatory Bodies

Type of Request	NCQA	DHCS	DMHC	**Alliance**
Prospective, Urgent	72 hours	72 hours	72 hours	**72 hours**
Prospective, Non-Urgent	Medi-Cal: 14 calendar days Group Care: 15 calendar days	5 business days	5 business days	**5 business days**
Post-service	30 calendar days	30 calendar days	30 calendar days	**30 calendar days**

ALAMEDA Alliance FOR HEALTH

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

POLICY AND PROCEDURE TEMPLATE

Policy Number	RX-014
Policy Name	Physician/Facility-Administered Drugs (PAD) Prior Authorization List Management
Department Name	Pharmacy Services
Department Officer	Chief Medical Officer
Policy Owner	Senior Director, Pharmacy Services
Line(s) of Business	Medi-Cal, Group Care (IHSS)
Effective Date	12/19/2023
Subcommittee Name	Pharmacy and Therapeutics Committee
Subcommittee Approval Date ~~Approval / Revision Date~~	TBD~~Pending P&T approval on 12/19/2023~~
Compliance Committee Approval Date	TBD

POLICY STATEMENT

The Alameda Alliance for Health ("Alliance") has an established mechanism for maintaining, reviewing, and updating its physician/facility-administered drug prior authorization list. The Alliance is committed to ensuring that all eligible Alliance members have access to high quality and cost-effective pharmaceutical care. The Alliance's Physician/Facility-Administered Drugs (PAD) Prior Authorization List Management process complies with the standards set by the Health and Safety Code, CCR, Section 1363.5, 1367.01, 1367.21, 1367.215. The Alliance covers medications for treating gender dysphoria or alleviating mental health or substance use.

PROCEDURE

A. Physician/Facility-Administered Drugs Prior Authorization List Management

1. The Alliance's PAD PA List Management is managed by the Pharmacy and Therapeutics (P&T) Committee with consultation support from PBM and third-party vendor.
2. The P&T Committee objectively appraises, evaluates, and selects physician administered drugs pharmaceutical products for prior authorization requirements inclusion or exclusion. Products are evaluated based on efficacy, safety, ease of

use, and cost. This is an ongoing process to ensure the optimal use of therapeutic agents.

3. The Alliance's PAD PA List Management is updated on a continuing basis after each meeting of the P&T Committee as well as between P&T Committee meetings when interim changes are implemented by Alliance pharmacy services. Alliance Providers are notified of all prior authorization changes in a timely manner, using Alliance's website and fax.
4. Drugs newly approved by the Food and Drug Administration (FDA) are reviewed by the P&T Committee within six (6) months of FDA approval. The P&T Committee determines whether the newly approved drugs will require prior authorization from the Alliance to be included on the Alliance's PAD PA List for review of medical necessity.
5. In accordance with Health & Safety Code, CCR, Section 1367.21, the Alliance allows for the coverage of any drug that is prescribed for use that is different from the FDA-approved use(s), provided that **all of the following conditions** are met to show medical necessity:
    a. The drug is prescribed by a participating licensed health care professional for the treatment of:
        i. A life-threatening condition; or
        ii. A chronic and seriously debilitating condition, and the drug is medically necessary to treat that condition, and the drug is on the Alliance's PAD PA List.
    c. The drug has been recognized for the treatment of that condition by any of the following:
        i. The American Medical Association Drug Evaluations
        ii. The American Hospital Formulary Service Drug Information
        iii. The United States Pharmacopoeia Dispensing Information, Volume I, "Drug Information for Health Care Professionals"
        iv. Two articles from major peer reviewed medical journals that present data supporting the proposed off-label use(s) as generally safe and effective unless there is clear and convincing contradictory evidence presented in a major peer reviewed medical journal.
        v. It is the prescriber's responsibility to submit the supporting documentation.

6. The Alliance covers pharmaceuticals in accordance with 42 CFR section 438.900 et seq, to ensure parity in medical/surgical, mental health, and substance abuse benefits and treatment.

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

1. The P&T Committee's voting membership consists of the Alliance's Chief Medical Officer or designee, the Alliance Senior Director of Pharmacy Services or designee, (4) four licensed practicing physicians and practicing community pharmacists contracted with Alliance (not to exceed 1/3 of the voting membership of the committee or three pharmacists, whichever is greater). The non-voting membership may include a clinical pharmacist from the Alliance's Pharmacy Benefit Manager (PBM), a representative from the Alliance's Quality

Improvement Unit, Alliance Operations Unit, and practicing physicians representing a medical specialty as needed in accordance with the agenda and the specific medications or subjects being reviewed.

2. Per the P&T Charter, the P&T Committee is responsible for the following:
   a. Develop and implement effective drug utilization review treatment outcome systems to optimize the quality of the pharmacy services
   b. Review the list on a quarterly basis
   c. Ensuring that the PAD PA List review considers all drugs approved by the Federal Drug Administration (FDA)
   d. Ensuring that deletions from the PAD PA List are documented and justified.
3. The following are considered by the P&T Committee when reviewing the PAD PA List:
   a. Alliance Provider recommendations for additions or deletion of drugs to the PAD PA List
   b. Bioavailability data
   c. Cost comparisons against other drugs available to treat the same medical condition(s)
   d. Current therapeutic guidelines
   e. Dosage ranges by route and age
   f. Findings from the following agencies: governmental agencies, medical and pharmaceutical associations, the National Institute of Health, and regulatory body publications
   g. Medical literature and clinical trials
   h. Off-label uses
   i. Patient risk factors relative to contraindications, warnings, and precautions
   j. Patient utilization and experience
   k. Pharmacokinetic data
   l. Pharmacologic considerations (e.g., drug class, similarity to existing drugs, side effect profile, mechanism of action, therapeutic indication, drug-to-drug interaction potential, and clinical advantages over other products in the specific drug class)
   m. Risks versus benefits regarding clinical efficacy and safety of a particular drug relative to other drugs with the same indication
   n. Special monitoring or medication administration requirements

C. Notification of PAD PA List Changes

1. The Alliance notifies its Providers about PAD PA List additions, deletions, and modifications and after each quarterly P&T Committee meeting, or more frequently as needed. Providers are notified through the Alliance website update and provider fax.
2. Utilization Management (UM), Community Outreach Medical Director, Provider Services (PR), Member Services (MSR), Claims and Benefit Configuration Departments are also notified of PAD PA List changes. A copy of the Summary of Prior Authorization Updates will be emailed to the Director of UM, PR, MSR, C &O once available. The Director of UM, PR, and MSR will disseminate the information to UM Medical Director, UM Managers, UM coordinator, Provider Services Representatives, and Member

Services Representatives as of the effective date of the change. In addition, any interim changes will be communicated to the Director on an as-needed basis.

DEFINITIONS / ACRONYMS

- PAD: Physician/Facility-Administered Drugs
- Formulary: list of drugs covered by the Alliance
- NCQA: National Committee on Quality Assurance
- UM: Utilization Management
- PR: Provider Relations
- MSR: Member Services
- C&O: Communications and Outreach

AFFECTED DEPARTMENTS/PARTIES

Utilization Management
Pharmacy Services
Member Services
Provider Relations
Communications and Outreach

RELATED POLICIES AND PROCEDURES

RX-002 Prior Authorization Review Process
RX-005 P&T Committee Roles and Scope P&T Charter
UM-001 Utilization Management
UM-036 Continuity of Care for Terminated and Non-Participating Providers
UM-051 Timeliness of UM Decision Making and Notification
UM-051 Attachment A UM Timeliness Standards for Medi-Cal and Group Care
UM-054 Notice of Action
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UM-058 Continuity of Care for New Enrollees Transitioned to Managed Care After Receiving A Medical Exemption
UM-059 Continuity of Care for Medi-Cal Beneficiaries Who Transition into MediCal Managed Care

REVISION HISTORY

3/19/2024

REFERENCES

- NCQA UM 12, Element A, B, D
- Alliance Provider Manual

- Health & Safety Code, Sections 1363.5, 1367.01, 1367.21, 1367.215
- Senate Bill 855 – Mental Health as a Medical Necessity
- DHCS All Plan Letter 22-012 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

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This policy will be reviewed annually to ensure effectiveness.

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

PHARMACY & THERAPEUTICS COMMITTEE

Record of Committee Meeting Minutes

Tuesday, December 19, 2023 | 5:00pm – 7:00pm

Status	Voting Committee Members	Organization	Initials	Officer / Notes
P	Steve O'Brien, MD	CMO - Alliance	SO	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	Pamela Gumbs, PharmD	United Pharmacy	PG	
P	Ivan Lee, MD	Private Practice	IL	
P	Bao Dao, MD	Epic Care	BD	
P	Donna Carey, MD	Medical Director of Case Management- Alliance	DC	

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	Natalee Felten	PerformRx	Formulary Management & Drug Utilization Review
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
A	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	S. O'Brien	• Agenda Overview	Called to order at 6:05PM	
II) Informational Updates	S. O'Brien H. Lee	Informational Updates Anthem, ICF-DD, Adult Expansion - On January 1st we are getting about 110,000 to 120,000 new members. Most of them are coming from Anthem about 80,000 coming from Anthem, the rest will primarily be undocumented adults between the ages of 26-49 years of age. - We have been doing a lot of work in terms of staffing up across the organization. Getting data from Anthem, working on a new contract. This is all part of us becoming a single plan county. The other thing that will occur at that time is the Kaiser members delegated to Kaiser through us which is about 55,000 members will be directly with Kaiser. Kaiser will no longer be a delegate for us. We are expanding and adding about a third of our volume overall to our current production line. So that is a significant increase in our membership. Nothing else changes about the benefit. The State is still doing Medic-Cal Rx which of course is the large majority of the outpatient meds. We are going to increase our number of physicians administered drugs and those drugs we are having to administer. The pharmacy team is highly involved in that. There will be a lot of working with new providers and new partners as we have a lot of continuity of care rights for those members as they are coming on board. CGM - As you know the State expanded their category for their CGM. So now patients with Diabetes type I and type II are eligible for CGM through the Medi-Cal Rx. We will eventually move all those members who are getting CGM through our UM benefit effective July 1st, 2023. Currently we have about a little over 160 patients who are receiving CGM. - For Anthem patients they are protected by continuity of care and for the first six months they can continue with their existing providers. I noticed there are more than ten providers providing that. It will eventually convert to our pharmacy benefit. We expect about sixty plus Anthem members being impacted by this conversion. Medi-Cal Rx - As of December 18th, the state has processed over 166 million pharmacy claims, occurring over sixteen billion dollars in payments. Since 2022 conversion the state has spent over 32 billion dollars for pharmacy benefits. Serving over 16 million beneficiaries. More drugs are being added to the contract drug list.		

Medi-Cal Rx MCDAC

- The Medi-Cal drug advisory committee request, this time we have four medications being requested for further review. I am recommending the four drugs to be added as formulary with prior authorization based on safety efficacy, essential need, or misuse potential.

MCDAC Drug	Indication	CDL Status	**Recommendation** Based on - Safety, Efficacy, Essential Need, Misuse Potential, etc.
Entyvio (vedolizumab) 108mg/0.68ml single dose prefilled syringe and pen	Ulcerative colitis (UC)	F-PA	Keep F-PA
Olumiant (baricitinib) 1mg, 2mg and 4 mg tablets	Adults with moderately to severe Rheumatoid arthritis (RA); COVID-10 hospitalized adults requiring supplmental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal memberane oxygenation (ECMO); alopecia areata	F-PA	Keep F-PA
Sohonos (palovarotene) 1mg, 1.5mg, 2.5mg, 5mg and 10mg capsules	Reduction in volume of new heterotropic ossification in adults; pediatric fibrodysplasia ossificans progressiva (FOP)	F-PA	Keep F-PA
Ycanth (cantharidin) topical solution 0.7% single use applicator	Molluscum contagiosum	F-PA	Keep F-PA

III) Pharmacy Utilization Reports (Quarter 3, 2023)

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)
  - The top 50 drugs accounted for 987 claims for 513 members and cost $1,127,219, which is a decrease of $100,402 in spend from the previous quarter.
  - Biktarvy has risen from number 2 to number 1, with 20 claims for 8 members.
  - Ozempic has risen to number 2 from number 7, with 70 claims for 36 members. There was an increase of 27 claims and of 10 members from the previous quarter. This is likely due to both guideline placement as well as media sensation.
  - Vemlidy is up to number 3 with 42 claims for 18 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).
  - Tagrisso moved up to number 4 from number 10 in the last quarter. This is an increase of one claim since last quarter. This medication is managed via the Oncology MRG.
  - Verzenio is at number 5 and Humira is at 6, both with 3 claims for one member. Brand Humira will be taken off formulary over the next few months Q4 2023 and the lower cost biosimilars will be preferred instead.
- Top 50 Drugs by Cost (Medi-Cal)

		○ The top 50 drugs accounted for 29,064 claims for 24,900 members and cost $40,105,907.36, which is an increase of $365,050.20 in spend from the previous quarter. ○ Ozempic has risen from the number 5 to number 2, with 1484 claims for 1173 members. This is an increase of 303 claims from last quarter. ○ Humira is down to number 3 from number 2 with 117 claims for 89 members. This is a decrease of 4 claims since last quarter. ○ Stelara has moved down to the number 5 spot from number 3, with 42 claims for 38 members. This is a decrease of 6 claims from last quarter. • Top 50 PA Reviewed Drugs by Volume (IHSS) ○ Top 50 PA requests = 113. There were 168 total PA requests for quarter 3. ○ 55 requests (49%) were approved. This approval rate is higher, by 15%, than what was observed last quarter. ○ 58 requests (51%) were denied or partially approved. ○ Vemlidy 25 mg is new at number one and had a total of 10 requests, from which there were 5 approvals, 2 denials and 3 partial approvals. ○ Vemlidy requires a diagnosis of Hepatitis B, and trial and failure of, intolerance to, or inability to use entecavir tablets. ○ Lidocaine 5% patch is at number 2 and had 8 requests with 1 approval. ○ This medication 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. ○ Jardiance 10mg is at number 3 with 7 requests (along with the 25mg tablet, in total it had 10 requests) with 1 approval. ○ The formulary alternative is Steglatro, with trial and failure of metformin. ○ Ozempic 0.25-0.5mg/dose pen is at number 4 with 6 requests for that strength, which is the starting dose. ○ Ozempic requires a trial and failure of metformin. ○ Wegovy 0.25mg/0.5ml is at number 5 and had a total of 6 requests for that strength, which is the starting dose. ○ There were 10 total requests for this medication in the top 50, for various strengths. ○ Wegovy requires a diagnosis of obesity or history of heart attack, despite diet and exercise, and requires trial and failure of, or reason not to use Qsymia and Contrave. - Top 50 PA Reviewed Drugs by Volume (Medi-Cal) ○ The top 50 drugs accounted for 172,215 claims for 152,634 members and cost $3,731,543.80. ○ Albuterol remains at the number 1 spot with 11,278 claims for 9,383 members. A decrease of 740 claims from last quarter. ○ Ibuprofen moved up to number 3 from number 4 with 7,737 claims for 7,008 members. This is an increase of 95 claims from last quarter. ○ Fluticasone has dropped down to number 4 from number 2 with 7,268 claims for 6,704 members. This is a decrease of 2,238 claims from last quarter. ○ Aspirin has risen from number 3 to number 2 with 7,895 claims for 7,301 members. This is an increase of 245 claims from last quarter. ○ Loratadine remains at the number 5 spot with 5,437 claims for 4,786 members. This is a decrease of 749 claims from last quarter.		

IV) E-Voting Material/Consent Agenda

H. Lee
B. Ochoa

Monographs/Class Reviews	Changes
Urinary tract antispasmodics	• No change
Ketone test strips	• No change
Topical antivirals	• No change
Prenatal vitamins	• No change
Physician Administered Drug (PAD) Guidelines	**Changes**
Oral and Injectable Oncology Medications	• No change
Injectable/Specialty Medications	• No change
Viltepso	• No change
Medication Request Guidelines (MRGs)	**Changes**
Urinary Incontinence Agents (part of Urinary tract antispasmodics class review)	• Change brand/generic status of Toviaz
Growth Hormone	• Add Ngenla & Sogroya
Corticotropin	• No change
Testosterone Agents	• No change
Self-administered Disease Modifying Therapies (DMTs) for Multiple Sclerosis (MS)	• Minor wording clarifications
Fentanyl Citrate	• Remove duplicate medication listing
Proton Pump Inhibitors (PPIs)	• Update product listings to align with brand/ generic availability
Gattex (teduglutide)	• No change
Butorphanol (Stadol NS)	• No change

Approved via e-voting:
Yes: 6
No: 0
Abstained: 2

		Step Therapy Exception	• No change		
		Prior Authorization Exception	• No change		
		Diclofenac sodium (Solaraze) 3% gel	• No change		
		Hepatitis B Drugs	• No change		
		Blood Glucose Testing Supplies	• No change		
		Inhaled Corticosteroids/Long-Acting Beta-Agonists (ICS/LABA) Combinations	• No change		
		Agents for graft versus host disease	• No change		
		Ranolazine (Ranexa, Aspruzyo)	• No change		
		Injectable Methotrexate	• No change		
		Temazepam (Restoril)	• No change		
		Janus Kinase Inhibitors for Nonsegmental Vitiligo	• No change		
		Endari	• No change		
		Thalomid (thalidomide)	• No change		
		Topical Diclofenac	• No change		
		Otezla (apremilast) for Behcet Disease	• No change		
		Korlym (mifepristone)	• No change		
		Rayaldee (calcifediol ER)	• No change		
		Tetracycline Antibiotics	• No change		
		Budesonide Nebulization Solution (Pulmicort Respules)	• No change		
		Ophthalmic Anti-Inflammatory Agents	• No change		
		dalfampridine (Ampyra)	• No change		
		Oral and Injectable Oncology Medications	• No change		
		Interim Formulary Updates			
		• See p. 111 in packet			
		Summary of PAD Updates			
		• See p. 112 in packet			

Pharmacy Policy & Procedure Updates	
• RX-003 – Exception Review Process	• Drug monitoring language update (per DHCS contract)
• RX-005 – PT Committee Roles and Scope	• Evidence-Based Decision Making, language update (per mock NCQA trial recommendation)
• RX-010 – Drug Utilization Management	• FWA (per DHCS APL 23-026) and QIHEC (per DHCS contract) language updates
• RX-013 – Physician Facility-Administered Drugs (PAD) Prior Authorization Review Process	• Policy process updates (e.g., COC)
• RX-014 – Physician Facility-Administered Drugs (PAD) PA List Management	• NEW policy outlining PAD list management
ED Oversight	
• None	
90 Day Maintenance List updates	
• None	
P&T Meeting Minutes	
• P&T Meeting Minutes Q3 September 26, 2023	

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
Pradaxa Oral Capsule 150 MG	T2 F-QL (60/30)
Pradaxa Oral Capsule 75 MG	T2 F-QL (60/30)
Mycozyl (tolnaftate) AC External Cream 1 %	NF
Cosentyx Subcutaneous Solution Auto-injector 300 MG/2ML	T2 F-PA
Naloxone 4mg/0.1mL nasal spray OTC	T1 F
COMIRNATY (COVID-19 Vaccine, mRNA, 2023-2024 Formula)	T2 F
COMIRNATY (COVID-19 Vaccine, mRNA, 2023-2024 Formula)	T2 F
Spikevax COVID-19, mRNA, LNP-S, PF, 50 mcg/0.5 mL	T2 F
Spikevax COVID-19, mRNA, LNP-S, PF, 50 mcg/0.5 mL	T2 F
Arexvy Intramuscular Suspension Reconstituted 120 MCG/0.5ML	T2 F-QL (0.5ml per dose, 1 dose per lifetime)
Abrysvo Intramuscular Solution Reconstituted 120 MCG/0.5ML	T2 F-QL (0.5ml per dose, 1 dose per lifetime)
Lagevrio 200 mg capsule	T2 F-AL-QL (40 per 180 days) (18 years and older)
Paxlovid tablet 150/100 mg	T2 F-QL- QL (20 per 180 days) (12 years and older)
Paxlovid tablet 300/100mg	T2 F-QL- QL (30 per 180 days) (12 years and older)

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

HCPCS Code	Product Name (Generic Name, Brand Name)	PA Action
J2326	NUSINERSEN	Add PA Requirement
J1301	EDARAVONE	Add PA Requirement
Q5126	BEVACIZUMAB-MALY (ALYMSYS) BIOSIMILAR	Add PA Requirement
Q5127	PEGFILGRASTIM-FPGK (STIMUFEND) BIOSIMILAR	Add PA Requirement
Q5128	RANIBIZUMAB-EQRN (CIMERLI), BIOSIMILAR	Add PA Requirement
Q5129	BEVACIZUMAB-ADCD (VEGZELMA), BIOSIMILAR	Add PA Requirement
Q5130	PEGFILGRASTIM-PBBK (FYLNETRA), BIOSIMILAR	Add PA Requirement
J3399	ONASEMNOGENE ABEPAR (ZOLGENSMA)	Add PA Requirement
J9029	NADOFARAGENE FIRADENOVEC-VNCG	Add PA Requirement
J9259	PACLITAXEL	Add PA Requirement
J9322, J9323	PEMETREXED	Add PA Requirement
J9380	TECLISTAMAB-CGYV (TECVAYLI)	Add PA Requirement
J9350	MOSUNETUZUMAB-AXGB (LUNSUMIO)	Add PA Requirement
J9381	TEPLIZUMAB-MZWV (TZIELD)	Add PA Requirement
Q5131	ADALIMUMAB-AACF (IDACIO)	Add PA Requirement
S0013	ESKETAMINE	Add PA Requirement
J1449	ROLVEDON (EFLAPEGRASTIM- XNST)	Add PA Requirement
J0800	Corticotropin	Replace w/ J0801 and J0802
J1726	MAKENA	Remove PA Requirement

		J7639	PULMOZYME (DORNASE ALFA) NON-COMP UNIT	Remove PA Requirement		
		Q5122	PEGFILGRASTIM-APGF (NYVPERIA) BIOSIMILAR	Update Drug Name		
		J7191	FACTOR VIII AHF PORCINE PER IU	Update Not carved out to FFS and add PA Requirement for MCAL		

V) New Business	N. Felten	**New PADs** **Myasthenia Gravis Agents** - Includes Vyvgart (efgartigimod), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase) Rystiggo (rozanolixizumab) Soliris (eculizumab) and Ultomiris (ravulizumab) - We want the prescriber to be a neurologist or rheumatologist. Correct diagnosis and positive antibodies serological tests. - Clinical classification of class II, III, or IV. - The member should have trial and failure or contraindication indications for either two conventional therapies or Failed at least 1 conventional therapy and required chronic plasmapheresis or plasma exchange or intravenous immunoglobulin. No concurrent use of the meds within the policy. - There are additional vaccination and antimicrobial safety checks for Soliris and Ultomiris. - For reauthorization we are looking for documentation of clinical response. **Questions:** PB: Is there a policy for zero negatives patients? NF: No, we don't have a policy. PB: will there be a policy? NF: I will look into that for more detail and get back to AAH and committee via email. **Veopoz** - Cost of this drug is 138,000 per month for maintenance dosing. - Provider must be experienced in treating complement related disorders. Patients must have a diagnosis of the disease and documentation of hypoalbuminemia. Any patients with unresolved meningitis or the use of other compliment inhibitors are excluded. - The initial request will be for 6 months and reauthorization for 12 months if there is documentation of positive clinical response. **Lantidra** - This is a novel type one diabetes therapy indicated for the treatment of adults with type I diabetes who are unable to reach targe A1c. Due to repeated hypoglycemic event despite intensive diabetes management. - Administered as one IV infusions directly into the hepatic portal vein. A second dose can be administered if the patient doesn't receive insulin independence within 1 year of infusion. A third infusion can also be administered with the same criteria. - Each infusion cost $105,000.	Move to approve: 1st: PB 2nd:AB	

		- The prescriber must be an endocrinologist and the patient must be 18years or older. We are asking for confirmation of type I diabetes diagnosis. A1c over target goals and an intensive insulin regimen. The member must have documentation of hypoglycemia or one or more episodes of severe hypoglycemia. - For the inclusion criteria in the trial the HbA1c cannot be higher than 12% - The insulin requirement of no more than 0.7 international units per kg per day. (BMI) less than 27 kg/m2 and Member is not diagnosed with a psychiatric disorder (i.e., schizophrenia, bipolar disorder, or major depression) or history of severe cardiac disease. - Members must also be using immunosuppression. We are limiting authorizations to a single treatment and allowing for up to three infusions per lifetime. For the authorization we would like documentation of lack of insulin independence within one year. **Bleeding Disorder Products** - Prescriber must be a hematologist and the correct diagnosis and type must be confirmed along with the appropriate dose. **New MRGs** **Ocaliva** - This drug is indicated for the diagnosis of primary biliary cholangitis (PBC) with confirmation of diagnosis its an oral tablet taken once daily at the maximum dose. The cost is about $9,000 per month. - The prescriber must be a hepatologist or gastroenterologist. We are looking for the correct diagnosis confirmed by the two listed tests. Ocaliva is being requested in addition to ursodeoxycholic acid (UDCA) due to patient having an inadequate response to UDCA monotherapy for at least 1 year, OR member has a documented medical reason (e.g. contraindication, intolerance, hypersensitivity) why UDCA cannot be used and is taking Ocaliva as monotherapy. - There are safety check attestations for liver function Submission Serum ALP and Total bilirubin within 30 days of the request for base line purposes. - For reauthorization there are safety checks for liver function and required lab results to show liver health and the change from baseline.		

		Non-Formulary/Prior Authorization Required Medications - Replaces the following retired MRG policies: - Injectable/Specialty Medications, Non-Formulary and PA Required Medications without Drug-Specific Criteria, Brand Medications When a Generic or Biosimilar is Available. The reason for replacing these is to streamline the policies and make it clearer operationally for the reviewer that this one policy should be used in these scenarios versus the three previous policies. - Other policies with now be retired. The language in this policy reflects the language in the other policies into one streamlined policy. **Sohonos** - Indicated for rare musculoskeletal condition that effects approximately 400 people in the U.S. Oral capsule taking once daily weight based monthly price is $51,000 although it can vary. - Must be prescribed by an orthopedic specialist or provider who specializes in rare connective tissue diseases. We are looking for the correct diagnosis with document genetic testing. - Attestation that patient is not pregnant and appropriate contraception methods will be used at least 1 month before treatment, during treatment, and 1 month after the last dose (if applicable) - Documentation of weight for patients younger than 14 years old and medication is prescribed at an FDA approved dose. - For reauthorization we are looking for Documentation or provider attestation of clinical benefit, patient is not pregnant, and patient is not 14 years. **Recommendation:** **Comments:**		
VI) Class Reviews, Monographs, and Recommendations	N. Felten	**Jesduvroq monograph + new MRG** **Recommendation:** - Daprodustat is a reversible inhibitor of hypoxia inducible factor prolyl hydroxylase-1 (HIF-PH1), PH2 and PH3 (IC50 in the low nM range).		

		- The labeling is somewhat restricted to adult patients who have been on dialysis for at least 4 months. - What is special about this drug is that it is a once daily tablet. The price is variable and can range from $117 - $2,815 Per month depending on severity of anemia, based on WAC. - On policy the prescriber should be a hematologist or nephrologist. We are looking for the correct diagnosis and documented hemoglobin between 8.0 and 11.5 g/dL - Trial and failure, intolerance, contraindication, or inability to use erythropoietin stimulating agents (ESA) Documentation of the current ESA - Serum ferritin level (> 100ng/mL) and Transferrin saturation (TSAT) (> 20%) levels are at normal value. - Cardiovascular safety check - For reauthorization we are looking for recent lab results demonstrate normal values, Serum ferritin, and Transferrin saturation that are normal. **Comments:** PB: At that price with the range, isn't it cheaper than Procrit and Epogen? NF: It does depend on the dose and there are some barriers that could cause this not to become so widely used. So maybe we would think operationally once daily dosing might make it difficult for dialysis centers to incorporate into practice. As well as it being oral and self-administered it may lower compliance leading to worse outcomes. There are other factors at play. The lowest dose may not be used so frequently so that $117 based on patients' characteristics. PB: Thank you.		
		Lodoco Monograph + new MRG **Recommendation:** - Indicated To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. - Dosed 0.5 mg orally once daily, and costs $495 per month. - Recommending changing to formulary PA status - Prescriber must be a cardiologist. The patient must have an established atherosclerotic disease or multiple risk factors for cardiovascular disease and multiple risk factors. - The patient is currently receiving statin therapy, or documentation has been provided that the member has a medical reason statin therapy is not appropriate. - Documentation is provided that guideline directed medical therapies targeted to patient's specific risk factors are being maximized, such as medications targeted at reduction in cholesterol, blood pressure, antiplatelet therapies, and diabetes. - Patient does not have pre-existing blood dyscrasias (ex. leukopenia, thrombocytopenia)and not taking strong CYP3A4 inhibitors or PGP inhibitors due to contra indications. **Comments:**		
		Insulins **Recommendation:**		

		- There were 155 claims for 86 members, for a total cost of $35,437, and an average cost per claim of $228. - The most highly utilized medication was insulin glargine-yfgn (U-100) 100 unit/mL (3 mL) subcutaneous pen with 64 claims, followed by Admelog SoloStar U-100 Insulin lispro 100 unit/mL subcutaneous pen, with 22 claims, and finally insulin lispro (U-100) 100 unit/mL subcutaneous pen, with 12 claims. - Manufacturers Sanofi, Lilly, and Novo Nordisk have announced upcoming price reductions in their insulin products, which will go into effect sometime in Q4 2023 (Lilly and Novo) and 1/1/2024 (Sanofi) notably on several of their branded products. - There are several developments including major price cuts and some drugs going off the market such as Levemir and most recently in interest of us Biocon a division of Mylan announced they would cut the price on insulin glargine-yfgn on 1/1/2024. So that they would be the cheapest product coming in a few dollars under the new lantus price and same as Rezvoglar. - Recommendation is to Change from NF to F-QL (30/30) due to new favorable pricing reductions comparative to other similar formulations. - Lantus Solostar U-100 Insulin 100 unit/mL (3 mL) subcutaneous pen - Lantus Solostar will be similar in price to generic insulin glargine-yfgn pen and Rezvoglar KwikPen ($92-96 per 15ml). - Lantus U-100 Insulin 100 unit/mL subcutaneous solution - Lantus vial will be similar in pricing to generic insulin glargine-yfgn vial ($63-64 per 10ml) - We are adding lantus as our preferred product. - Policy for rapid acting insulin adding insulin aspart to policy under non-formulary medications and making some minor wording updates. **Comments:**		
		Pneumonia vaccine comparator **Recommendation:** - There were 17 claims for 17 members, for a total of $4,100, and an average cost per claim of $241. The most highly utilized medication was Prevnar 20, with 15 claims. There were no prior authorization requests. - Recommending to remove the age limit minimum of 19 years from all applicable vaccines. This was previously to account for Vaccines for Children (VFC) however not all IHSS Group Care members qualify for VHC. All pneumococcal vaccines are indicated from early childhood and up, thus no age limit is indicated. - Neurotoxins class review we did not have any claims on the pharmacy side or prior authorizations requests. **Comments:**		

		Neurotoxins **Recommendation:** - There were no claims and no prior authorization requests. As for formulary changes, we don't recommend any. - MRG policy we are adding a new agent Daxxify as a non-preferred product. - PAD policy for medical side we are also adding Daxxify and removing language indicating that Xeomin is a preferred product. **Comments:** PB: On page 221 if we needed the more concentrated insulin like Toujeo or Tresiba that is still available with a prior auth? NF: Correct, that's right.		
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): **Injectable/Specialty Medications MRG – RETIRE** Guideline (Changes): **Brand Medications When a Generic or Biosimilar is Available – RETIRE** Guideline (Changes): **Non-Formulary and PA Required Medications without Drug-Specific Criteria- RETIRE** Guideline (Changes): **Movement Disorders** - The first change is renaming the title to be specific to the Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors - Adding the newly marketed agent and we are adding the exclusion criteria to prevent the concurrent use of monoamine oxidase inhibitors (MAOIs) - The next group of changes is in the PA review criteria section first, we have the initial authorization section that we didn't have before. - Criteria as its listed per diagnosis the first is Tardive dyskinesia. The changes here for this section are split into three different updates. - The first can be referenced as the 90-day criteria for members who have the diagnosis of tardive dyskinesia we are looking that they have the appropriate indicated symptoms for at least 90 days and also that they are on antipsychotics, and they are stable for that period of time as well. - Secondly, we are looking to see that they have some sort of approach to reducing their symptoms. - For members on the first-generation antipsychotic, we are looking to see there is a switch to a second generation antipsychotic and also a trial of benzodiazepines. - The other change relates to requests for Ingrezza requests and Austedo. Previously we had Ingrezza preferred over Austedo but considering the dosing response and treatment variation we are going to have them both required treatment failure of tetrabenazine.		

		- Requests for Austedo we want to see there is no signs of hepatic impairment or QT prolongation, prescriber attests a baseline ECG. - For Ingrezza we want to see one capsule per day dose. - Diagnosis use in chorea associated with Huntington's disease changes are short and will be to mirror Austedo and Ingrezza. - Also, in the combined reauthorization section we would be looking for positive clinical response and appropriate dosing. Guideline (Changes): **Isotretinoin capsules** - Change is to expand the look back period for preferred antibiotics. Which would be a year instead of six months. - No other changes. Guideline (Changes): **Gonadotropin Releasing Hormone (GNRH) Agonists** - Adding small change, we added to the list of exceptions for preferred oral contraceptive. - No other changes. Guideline (Changes): **Oral Anti-Fungals** - We are adding four medications to the list to be more inclusive. - PA review criteria addresses each medication individually. We are still looking for invasive pulmonary aspergillus infections or a serious fungal infection caused by these species. Additionally, we can also review and consider for those who have invasive candidiasis in critically ill patients for prophylaxis of aspergillus infections for special populations. For example, lung transplant or AML. - Adding to the policy is for esophageal candidiasis or candidemia in nonneutropenic patients we have preferred agents' fluconazole and nystatin. - Additionally, there is blastomycosis or histoplasmosis the preferred agent would be itraconazole. - For intraconazole change is to take out the oral solution section and we will reference and go over that later. We will also add fluconazole to the preferred agents for those with onychomycosis and removing a specific requirement for specific diagnosing for terbinafine. - For griseofulvin there are no changes. - We are adding Posaconazole tablets, looking to have prophylaxis of invasive aspergillus or candida in high-risk patients. Trial and failure or inability to use voriconazole. Invasive aspergillosis: trial and failure or inability to use voriconazole. - Noxafil suspension we are looking for oropharyngeal candidiasis and they would need to try fluconazole first. - For Cresemba we are looking for Diagnosis of invasive mucormycosis in adults or invasive aspergillosis in adults and they would have to try the voriconazole first. - The last product flucytosine we would look for cryptococcal meningitis or cryptococcosis and also we would take in the candidiasis with CNS involvement, or symptomatic urinary tract infection and endocarditis. - We are grouping the reauthorization section we would look for appropriate response to therapy and medical need to continue. - We also having a grouping area for all of our oral and suspension products. So basically if we get a request for these itraconazole or voriconazole, flucytosine we want to see they have tried the tablet or capsules first		

		- There are no other changes. **Comments/Questions:** PB: For intraconazole the inability to use terbinafine or fluconazole? RN: Yes, one or the other PB: Ok, sounds good. Guideline (Changes): **Immunizations** - With this policy there are a number of changes, but they can be summarized into updating for alignment based on strength. - We are also updating to ensure the appropriate fill limits and age limits are addressed in the entire policy as it relates to our group care population. - Additionally, we are adding two RSV vaccines, Abrysvo and Arexvy are added to our formulary. - There are no other changes to this policy. Guideline (Changes): **Anti-Obesity Medications** - The update here to is to add the newly FDA approved Zepbound that was approved last month. We are adding this to our policy and putting it in line with Saxenda and Wegovy. - There are no other changes. - **Comments/Questions:**		

VIII) Physician Administered Drug (PAD) Policies	N. Felten	**Complement inhibitors** - We are adding new drug Izervay and criteria for review. - Since we have a new policy for generalized Myasthenia Gravis, the new agents that were already reviewed, we are removing that and referring to that policy. - Izervay is indicated for the treatment of Geographic Atrophy secondary to age related macular degeneration. The changes include medication coverage duration of 12 months. This drug gets no reauthorization. - We are updating a separating out Syfovre and Izervay based on age and labeling. **Neuromyelitis Optica Spectrum Disorder (NMOSD) Agents** - Here we are updating the language in the policy so that preferred agents are no longer required. **Healthcare professional (HCP) administered/IV Disease Modifying Therapies (DMTs) for Multiple Sclerosis (MS)** - We are updating the language so that preferred agents are no longer required. Minor changes including the name of the policy that would be used to review Tysabri. **Calcitonin Gene-Related Peptide (CGRP) Antagonists for Headache Prevention** - Also, updating the language so that preferred Emgality is no longer required. **Specialty Biologic Agents for FDA approved indications – RETIRE** - Retired so that there are no longer step 1,2 and 3 agents these will be reviewed via the specialty agent's policy.		
IX) Informational Updates on New Developments in Pharmacy	N. Felten	New Product Review - Adding a new dosage form of Kalydeco to formulary with PA as a line extension all the other updates to the column to the right have already been made at either previous meeting materials or in the interim between P&T meetings covered in the interim updates and the consent agenda.		

BRAND NAME	GENERIC NAME/DOSAGE FORM	RECOMMENDATION
Ycanth	cantharidin 0.7% topical solution	Non-formulary
Elrexfio	elranatamab-bcmm 44 mg/1.1 ml, 76 mg/1.9 ml SQ vial	Non-formulary
Opvee	nalmefene 2.7 mg/0.1 ml nasal spray	Non-formulary
Talvey	talquetamab-tgvs 3 mg/1.5 ml, 40 mg/ml subcutaneous vial	Non-formulary
Iyuzeh	latanoprost 0.005% ophthalmic solution	Non-formulary
Airsupra	albuterol-budesonide inhalation aerosol 90-80 mcg/act	Non-formulary
Veopoz	pozelimab-bbfg 400 mg/2mL injection solution	Non-formulary (See new PAD policy)
Eylea HD	aflibercept 8 mg/0.07 mL intravitreal solution	Non-formulary
Sohonos	palovarotene 1 mg, 1.5 mg, 2.5 mg, 5 mg, 10 mg oral capsules	Non-formulary (See new PAD policy)
Nitrofurantoin	nitrofurantoin 50 mg/5 mL oral suspension	Non-formulary

			Balfaxar	prothrombin complex concentrate, human-lans 500 unit, 1000 unit intravenous vials	Non-formulary			
			Rykindo	risperidone 25 mg, 37.5 mg, 50 mg extended release intramuscular vials	Non-formulary			
			Daxxify	daxibotulinumtoxinA-lanm 100 unit intramuscular vial	Non-formulary (See class review)			
			Lodoco	colchicine 0.5 mg oral tablets	F-PA (See monograph)			
			Jesduvroq	daprodustat 1 mg, 2 mg, 4 mg, 6 mg, 8 mg oral tablets	F-PA (See monograph)			
			Cresemba	isavuconazonium 74.5 mg oral capsule	NF (See MRG policy)			
			Akeega	niraparib/abiraterone 50 mg-500 mg, 100 mg-500 mg oral tablets	Non-formulary			
			Lantidra	donislecel-jujn intravenous cellular suspension	Non-formulary (See new PAD policy)			
			Breo Ellipta	fluticasone furoate-vilanterol 50-25 mcg/inhalation	Non-formulary			
			Ojjaara	momelotinib 100 mg, 150 mg, 200 mg tablet	Non-formulary			
			Aphexda	motixafortide 62 mg SC solution reconstituted	Non-formulary			

			Adalimumab-adbm	adalimumab-adbm 10 mg/0.2 ml, 20 mg/0.4 ml, 40 mg/0.8 ml, subcutaneous syringe; 40 mg/0.8 mL subcutaneous auto-injector	Non-formulary			
			Pokonza	potassium chloride 10 mEQ oral packet	Non-formulary			
			Hyrimoz	adalimumab-adaz 40 mg/0.8 ml subcutaneous syringe; 40 mg/0.8 mL subcutaneous auto-injector	Non-formulary			
			Trientine	trientine 500 mg oral capsules	Non-formulary			
			Kepivance	palifermin 5.16 mg intravenous vial	Non-formulary			
			Pombiliti	cipaglucosidase alfa-atga 105 mg intravenous vial	Non-formulary			
			Opfolda	miglustat 65 mg oral capsules	Non-formulary			
			Motpoly XR	lacosamide 100 mg, 150 mg, 200 mg extended-release oral capsules	Non-formulary			
			Cosentyx	secukinumab 125 mg/5 ml intravenous vial	Non-formulary			

			Kalydeco	ivacaftor 5.8 mg oral granules in packet	Add to T2 F-PA (line extension)			
			Entyvio	vedolizumab 108 mg/0.68 ml subcutaneous auto-injector	Non-formulary			
			First Pantoprazole	pantoprazole 4 mg/ml oral suspension kit	Non-formulary			
			Glipizide	glipizide 2.5 mg oral tablet	Non-formulary			
			Likmez	metronidazole 500 mg/5 ml oral suspension	Non-formulary			
			Velsipity	etrasimod 2 mg oral tablets	Non-formulary			
			Abrilada	adalimumab-afzb 20 mg/0.4 ml, 40 mg/0.8 ml subcutaneous syringe; 40 mg/0.8 mL subcutaneous auto-injector	Non-formulary			
			Bimzelx	bimekizumab-bkzx 160 mg/ml subcutaneous syringe; 160 mg/mL subcutaneous auto-injector	Non-formulary			
			Ozobax DS	baclofen 10 mg/5 ml oral solution	Non-formulary			
			Altuviiio	antihemophilic factor (recombinant), Fc-VWF-XTEN fusion	Non-formulary (see new PAD policy)			

				protein-ehtl 750-unit intravenous vial				
			Omvoh	mirikizumab-mrkz 300 mg/15 ml intravenous via	Non-formulary			
			Omvoh	mirikizumab-mrkz 100 mg/ml subcutaneous auto-injector	Non-formulary			
			Zepbound	tirzepatide	Non-formulary			
			Rozlytrek	entrectinib 50 mg oral pellet packet	Non-formulary			
			Fruzaqla	fruquintinib 1 mg, 5 mg oral capsules	Non-formulary			
			Zurzuvae	zuranolone 20 mg, 25 mg, 30 mg oral capsules	Non-formulary			
			Inpefa	sotagliflozin 400 mg oral tablets	Non-formulary			
			Xphozah	tenapanor 20 mg, 30 mg oral tablets	Non-formulary			
			Voquezna	vonoprazan 10 mg, 20 mg tablets	Non-formulary			
X) Old Business		None						
XI) Public Comment	N. Felten	None						

XII) Adjournment	S. O'Brien	- P&T Committee Member Forms **Meeting adjourned at 6:07PM**	None	

DocuSigned by:
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01/26/2024
Date

New Physician Administered Drug (PAD) Guidelines Alameda Q1 2024 P&T

New:

Pompe Disease Agents	
Medications	Lumizyme (alglucosidase alfa) Nexviazyme (avalglucosidase alfa-ngpt) injection Pombiliti (cipaglucosidase alfa-atga) + Opfolda (miglustat)
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	Prescribed by a specialist in the treatment of Pompe disease, such as a genetic or metabolic specialist, neurologist, cardiologist, or pediatrician.
Coverage Duration	If all of the criteria are met, the request will be approved for 12 months.

Other Criteria	**Initial Authorization:**
	For infantile onset Pompe Disease (Lumizyme only):
	• Patient has a diagnosis of infantile-onset Pompe Disease, confirmed by one of the following:
	  ○ Enzyme assay showing a deficiency of acid alpha-glucosidase (GAA) activity in the blood, skin, or muscle
	  ○ Genetic testing showing a mutation in the GAA gene
	• Requested dose is appropriate per prescribing information (documentation of patient weight must be submitted with request)
	• Requested regimen will not be used in combination with other enzyme replacement therapies
	
	For late onset Pompe Disease (Lumizyme, Nexviazyme, or Pombiliti + Opfolda):
	• Patient has a diagnosis of late-onset (non-infantile) Pompe Disease, confirmed by one of the following:
	  ○ Enzyme assay showing a deficiency of acid alpha-glucosidase (GAA) activity in the blood, skin, or muscle
	  ○ Genetic testing showing a mutation in the GAA gene
	• Documentation patient has measurable signs or symptoms of Pompe disease
	• Results of a baseline 6-minute walk test (6MWT) and percent-predicted forced vital capacity (FVC) are provided (not required for patients who are not old enough to walk)
	• Requested dose is appropriate per prescribing information (documentation of patient weight must be submitted with request)
	• Requested regimen will not be used in combination with other enzyme replacement therapies (Exception: Pombiliti + Opfolda are to be used together)
	• For Pombiliti + Opfolda: Patient must have trial and failure of another enzyme therapy (Lumizyme or Nexviazyme)
	
	Re-Authorization:
	• Documentation or provider attestation of positive clinical response to therapy
	  ○ Infantile onset: provider attestation of member benefit
	  ○ Late onset: improvement, stabilization, or slowing of progression of percent-predicted FVC and/or 6MWT
	• Requested dose is appropriate per prescribing information (documentation of patient weight must be submitted with request)

	• Requested regimen will not be used in combination with other enzyme replacement therapies (Exception: Pombiliti + Opfolda are to be used together) 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	3/2024

New:

Zulresso	
Medications	Zulresso (brexanalone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a psychiatrist or an obstetrician-gynecologist
Coverage Duration	If all of the criteria are met, the initial request will be approved for a one-time administration of Zulresso per postpartum period. Reauthorization will not be permitted
Other Criteria	**Initial Authorization:** • Physician attestation of moderate to severe postpartum depression (PPD) diagnosis and submission of validated screening tool result(s) (e.g. Edinburgh Postnatal Depression Scale, Hamilton Depression Rating Scale) • Onset of a major depressive episode within 6 months of delivery • Medication is prescribed at an FDA approved dose • Healthcare facility and patient must be enrolled in the Zulresso REMS program prior to initiation of medication • Patient's weight has been provided 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	3/2024

New:

Adzynma	
Medications	Adzynma (ADAMTS13, recombinant-krhn)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**Other Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a hematologist, oncologist, intensive care specialist, or specialist in the treatment of rare genetic hematologic diseases
Coverage Duration	On-demand therapy: If all criteria are met, the request will be approved for 1 month. Prophylactic therapy: If all criteria are met, the initial request will be approved for 6 months. Reauthorization requests will be approved for 12 months.

Other Criteria	**Initial Authorization**
	• Diagnosis of congenital thrombotic thrombocytopenic purpura (cTTP) as confirmed by BOTH of the following:
	  ○ Molecular genetic testing
	  ○ ADAMTS13 activity <10%
	• Prescriber attestation that member has not been diagnosed with any other TTP-like disorder (i.e., microangiopathic hemolytic anemia, immune-mediated thrombotic thrombocytopenic purpura [iTTP])
	• If request is for prophylactic therapy, member must also have a history of at least one documented TTP event
	• Member's weight
	• Request is for an FDA-approved dose
	
	Reauthorization
	• Documentation of positive clinical response to therapy (i.e., improvement in acute and subacute TTP events, platelet counts, microangiopathic hemolytic anemia episodes, or clinical symptoms)
	• Member's 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 P&T Review Date	3/2024

New Medication Request Guidelines (MRGs) Alameda Q1 2024 P&T

New:

Presbyopia Agents	
Therapeutic Classes (AHFS)	Miotics
Medications	Vuity (pilocarpine HCl ophthalmic solution) Qlosi (pilocarpine HCl ophthalmic 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 Vuity: 40-55 years Qlosi: 45-64 years
Prescriber Restrictions	Prescribed by an optometrist or ophthalmologist
Coverage Duration	**Initial Approval** 6 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Initial Authorization:** • Diagnosis of presbyopia • Trial and failure or contraindication to corrective lenses (i.e., eye glasses, contact lenses) • Medication is prescribed at an FDA approved dose **Re-Authorization:** • Documentation or provider attestation of positive clinical response • Medication is prescribed at an FDA approved dose
Criteria Statement	Vuity and Qlosi are reserved for members who have used (or cannot/should not use) corrective lenses (i.e., eye glasses, contact lenses).
Last P&T Review Date	3/2024

New:

Zurzuvae	
Therapeutic Classes (AHFS)	Antidepressants, Miscellaneous
Medications	Zurzuvae (zuranolone) 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	Check AAH active CCS cases for members < 21 years of age According to package insert
Prescriber Restrictions	Prescriber must be a psychiatrist or an obstetrician-gynecologist .
Coverage Duration	If all of the criteria are met, the initial request will be approved for one 14-day course of Zurzuvae per postpartum period. Reauthorization will not be permitted.
PA Review Criteria	**Initial Authorization:** • Physician attestation of moderate to severe postpartum depression (PPD) diagnosis and submission of validated screening tool result(s) (e.g. Edinburgh Postnatal Depression Scale, Hamilton Depression Rating Scale) • Onset of a major depressive episode within 6 months of delivery • Medication is prescribed at an FDA approved dose
Criteria Statement	Zurzuvae is reserved for members who have a diagnosis of moderate to severe postpartum depression (PPD) and submission of validated screening tool result(s) (e.g. Edinburgh Postnatal Depression Scale, Hamilton Depression Rating Scale) with onset of a major depressive episode within 6 months of delivery.
Last P&T Review Date	3/2024

New:

Dificid	
Therapeutic Classes (AHFS)	Other Macrolides
Medications	Dificid (fidaxomicin)
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	Prescribed by an infectious disease specialist or gastroenterologist
Coverage Duration	If the criteria are met, the request will be approved for up to a 10-day duration.
PA Review Criteria	**Authorization for initial Clostridium difficile infection:** 1. Documentation provided for intolerance or medical reason why patient is unable to use oral vancomycin 2. Dose requested follows FDA labeling **Authorization for recurrent Clostridium difficile infection:** 1. Documentation provided that patient has tried oral vancomycin for management of Clostridium difficile infection 2. Dose requested follows FDA labeling
Criteria Statement	Dificid is reserved for members who have either an initial or recurrent Clostridium difficile infection who have used (or cannot/should not use) oral vancomycin.
Last P&T Review Date	3/2024

New:

Fabhalta	
Therapeutic Classes (AHFS)	Complement Inhibitors
Medications	Fabhalta (iptacopan) 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	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	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.
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 • Hemoglobin (Hgb) < 10 g/dL **Re-Authorization:** • Provider has submitted documentation of clinical response to therapy (e.g., reduction in disease severity, improvement in quality of life scores, increase in Hgb, reduced need for blood transfusions, etc.) • The request is for a dose that is FDA approved or in nationally recognized compendia in accordance with the patient's diagnosis, age, and concomitant medical condition
Criteria Statement	Fabhalta is reserved for members who have a diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) by high sensitivity flow cytometry with a hemoglobin (Hgb) < 10 g/dL, who have complied with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria.
Last P&T Review Date	3/2024

Drug Name: Casgevy (exagamglogene autotemcel)

Manufacturer: Vertex Pharmaceuticals

Approval Date: 12/8/2023

Marketing Date: 12/14/2023

Prescribing Information

Indication

Treatment of patients aged 12 years and older with:

- Sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs)
- Transfusion-dependent β-thalassemia (TDT)

Mechanism of Action

Casgevy™ is a cellular gene therapy consisting of autologous CD34+ hematopoietic stem cells (HSCs) edited by CRISPR/Cas9-technology at the erythroid specific enhancer region of the BCL11A gene to reduce BCL11A expression in erythroid lineage cells, leading to increased fetal hemoglobin (HbF) protein production.

After Casgevy™ infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells. In patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs.

Dosage and Administration

- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for Casgevy™ manufacturing
- The minimum recommended dose is 3×10^6 CD34+ cells/kg via intravenous infusion
- Full myeloablative conditioning must be administered between 48 hours and 7 days before infusion of Casgevy™
- Prophylaxis for seizures should be considered prior to initiating myeloablative conditioning

Black Box Warning

None

Adverse Reactions

Most common Grade 3 or 4 non-laboratory adverse reactions (incidence ≥ 25%): Mucositis and febrile neutropenia in patients with SCD and TDT, and decreased appetite in patients with SCD

Most common Grade 3 or 4 laboratory abnormalities (≥ 50%): Neutropenia, thrombocytopenia, leukopenia, anemia, and lymphopenia

Serious: Potential neutrophil engraftment failure, prolonged time to platelet engraftment, and hypersensitivity reactions

Use in Specific Populations, Pregnancy

There are no clinical data from the use of exagamglogene autotemcel in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with exagamglogene autotemcel to assess whether it can cause fetal harm when administered to a pregnant woman. Casgevy™ must not be administered during pregnancy because of the risks associated with myeloablative conditioning. Pregnancy after Casgevy™ infusion should be discussed with the treating physician.

Drug Interactions

None

How Supplied

Cell suspension for intravenous infusion

Price

$2.2 million

(Per one-time treatment, based on WAC.)

Clinical Studies

Ongoing

Title	A Safety and Efficacy Study Evaluating CTX001 in Subjects With Severe Sickle Cell Disease NCT: 03745287
Design	Single-arm, open-label, multi-site, single-dose, phase 1/2/3 study to evaluate the safety and efficacy of CTX001 (Casgevy™) in subjects with severe SCD
Population	N=63 At the time of the interim analysis (conducted in June 2023), 58 (92%) patients started mobilization. A total of 44 (76%) patients received Casgevy™ infusion and formed the full analysis set (FAS). Thirty-one patients from the FAS (70%) had adequate follow-up to allow evaluation of the primary efficacy endpoint and formed the primary efficacy set (PES). The key demographics and baseline characteristics for all patients administered Casgevy™ are shown in the table below. The baseline characteristics and demographics are consistent between the PES and the FAS.

	<table><tr><th>Demographics and disease characteristics</th><th>Full Analysis Set (FAS) * (N=44)</th><th>Primary Efficacy Set (PES) *,† (N=31)</th></tr><tr><td>Age, n (%) Adults (≥ 18 and ≤ 35 years) Adolescents (≥ 12 and < 18 years) All ages (≥ 12 and ≤ 35 years) Median (min, max)</td><td> 32 (73%) 12 (27%) 20 (12, 34)</td><td> 24 (77%) 7 (23%) 21 (12, 34)</td></tr><tr><td>Sex, n (%) Female Male</td><td> 20 (45%) 24 (55%)</td><td> 14 (45%) 17 (55%)</td></tr><tr><td>Race, n (%) Black or African American White Other</td><td> 38 (86%) 3 (7%) 3 (7%)</td><td> 27 (87%) 1 (3%) 3 (10%)</td></tr><tr><td>Genotype, n (%) β^S/β^S β^S/β^0 β^S/β^+</td><td> 40 (91%) 3 (7%) 1 (2%)</td><td> 30 (97%) 1 (3%) 0</td></tr><tr><td>Annualized rate of severe VOCs in the 2 years prior to enrollment (events/year) Median (min, max)</td><td> 3.5 (2.0, 18.5)</td><td> 3.5 (2.0, 18.5)</td></tr><tr><td>Annualized rate of hospitalizations due to severe VOCs in the 2 years prior to enrollment (events/year) Median (min, max)</td><td> 2.5 (0.5, 9.5)</td><td> 2.0 (0.5, 8.5)</td></tr></table> * Interim analysis conducted based on June 2023 data cut-off date. † The primary efficacy set (PES), is a subset of the full analysis set (FAS). The PES was defined as all patients who had been followed for at least 16 months after CASGEVY infusion. Patients who had less than 16 months follow-up due to death or discontinuation due to CASGEVY-related adverse events, or continuously received RBC transfusions for more than 10 months after CASGEVY were also included in this set. An additional patient who had less than 16 months of follow-up but was otherwise determined to be a non-responder for the primary efficacy endpoint, was also included in PES.
Arms	Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for Casgevy™ manufacture, followed by myeloablative conditioning and infusion of Casgevy™. Patients were then followed for 24 months after Casgevy™ infusion. Patients who complete or discontinue from the trial are encouraged to enroll in the long-term ongoing follow-up trial (NCT04208529), for additional follow up for a total of 15 years after Casgevy™ infusion.
Endpoint(s)	Primary: • Proportion of VF12 responders, defined as patients who did not experience any protocol-defined severe VOCs for at least 12 consecutive months within the first 24 months after Casgevy™ infusion Secondary: • Proportion of HF12 responders, defined as patients who did not require hospitalization due to severe VOCs for at least 12 consecutive months within the 24-month evaluation period

Inclusion Criteria	• Age between 12 to 35 years
	• Diagnosis of severe sickle cell disease as defined by:
	  ○ Documented severe sickle cell disease genotype
	  ○ History of at least 2 severe VOC events per year for the previous 2 years prior to screening; severe VOC is defined as an occurrence of at least one of the following events:
	  ▪ Acute pain event requiring a visit to a medical facility and administration of pain medications (opioids or intravenous non-steroidal anti-inflammatory drugs [NSAIDs]) or red blood cell (RBC) transfusions
	  ▪ Acute chest syndrome

	▪ Priapism lasting >2 hours and requiring a visit to a medical facility ▪ Splenic sequestration • Eligible for autologous hematopoietic stem cell transplant
Exclusion Criteria	• Advanced liver disease • History of untreated Moyamoya disease or presence of Moyamoya disease that puts the patient at risk of bleeding • Patients with an available 10/10 human leukocyte antigen matched related hematopoietic stem cell donor • More than 10 unplanned hospitalizations or emergency department visits related to chronic pain rather than SCD-related acute pain crises in the year before screening • Prior hematopoietic stem cell transplant
Results	Primary: • The interim analysis occurred at the time when the alpha spending was approximately 0.02 for a one-sided test, when 31 patients were evaluable for VF12 responder status • The VF12 response rate was 29/31 (93.5%; 98% one-sided confidence interval [CI], 77.9% to 100%) • The 29 VF12 responders did not experience protocol defined severe VOCs during the evaluation period with a median duration of 22.2 months at the time of the interim analysis • One VF12 responder, after initially achieving a VF12 response, experienced an acute pain episode meeting the definition of a severe VOC at Month 22.8 requiring a 5-day hospitalization; this patient was reported to have a parvovirus B19 infection at the time. Secondary: • Of the 31 patients evaluable for VF12 response, one patient was not evaluable for HF12 response; the remaining 30 patients (100%; 98% one-sided CI, 87.8% to 100%) achieved the secondary endpoint of HF12
Conclusion	In this trial, treatment with Casgevy™ met the primary and key secondary endpoint, with the elimination of VOCs in 93.5% of patients and elimination of inpatient hospitalization for VOCs in 100% of patients.
Interpretation	One-time administration of Casgevy™ has thus far proven to be an effective treatment option for the elimination of VOCs and inpatient hospitalizations for patients with severe SCD. Limitations of this trial are that it is single-arm and unblinded, opening it up to bias. However, it should be noted that preliminary data shows a clinically meaningful improvement in hemoglobin (Hb) and quality of life measures. As this is an ongoing trial, the full data set for the primary and secondary endpoints are not currently available. Additionally, it is unclear if repeat administration of Casgevy™ will be necessary long-term. A follow-up trial (NCT04208529) is currently following patients for up to 15 years after Casgevy™ administration to evaluate its durability.
Completion Date	October 2024

<table>
<tr><td>Title</td><td>A Safety and Efficacy Study Evaluating CTX001 in Subjects With Transfusion-Dependent β-Thalassemia

NCT: 03655678</td></tr>
<tr><td>Design</td><td>Single-arm, open-label, multi-site, single-dose, phase 1/2/3 study in subjects with TDT</td></tr>
<tr><td>Population</td><td>N=59

At the time of the interim analysis (conducted in January 2023), 59 (100%) patients started mobilization. A total of 52 (88%) patients received Casgevy™ infusion and formed the FAS. Thirty-five patients from the FAS (67%) had adequate follow-up to allow evaluation of the primary efficacy endpoint and formed the PES. The key demographics and baseline characteristics for all patients administered Casgevy™ are shown in the table below. The baseline characteristics and demographics are consistent between the PES and the FAS.
Table 10: Demographics and baseline characteristics of patients treated with CASGEVY at the interim analysis in Trial 2
<table><tr><th>Demographics and disease characteristics</th><th>Full Analysis Set (FAS) [#] (N=52)</th><th>Primary Efficacy Set (PES) (N=35) [#†]</th></tr><tr><td>Age, n (%)
Adults (≥ 18 and ≤ 35 years)
Adolescents (≥ 12 and < 18 years)

All ages (≥ 12 and ≤ 35 years)
Median (min, max)</td><td>
34 (65.4)
18 (34.6)

20 (12, 35)</td><td>
24 (68.6)
11 (31.4)

20 (12, 33)</td></tr><tr><td>Sex, n (%)
Female
Male</td><td>
25 (48.1)
27 (51.9)</td><td>
17 (48.6)
18 (51.4)</td></tr><tr><td>Race, n (%) [‡]
Asian
White
Multiracial
Other</td><td>
22 (42.3)
18 (34.6)
3 (5.8)
2 (3.8)</td><td>
13 (37.1)
15 (42.9)
3 (8.6)
0</td></tr><tr><td>Genotype, n (%)
β⁰/β⁰-like [*]
Non-β⁰/β⁰-like</td><td>
31 (59.6)
21 (40.4)</td><td>
20 (57.1)
15 (42.9)</td></tr><tr><td>Baseline annualized RBC transfusion volume (mL/kg)
Median (min, max)</td><td>
201 (48, 331)</td><td>
205 (115, 331)</td></tr><tr><td>Baseline annualized RBC transfusion episodes
Median (min, max)</td><td>
17 (5, 35)</td><td>
17 (11, 35)</td></tr><tr><td>Spleen intact, n (%)</td><td>36 (69.2)</td><td>26 (74.3)</td></tr><tr><td>Baseline liver iron concentration (mg/g)
Median (min, max)</td><td>
3.5 (1.2, 14.0)</td><td>
4.0 (1.4, 14.0)</td></tr><tr><td>Baseline cardiac iron T2* (msec)
Median (min, max)</td><td>
34.0 (12.4, 61.1)</td><td>
34.8 (19.6, 61.1)</td></tr><tr><td>Baseline serum ferritin (pmol/L)
Median (min, max)</td><td>
2892 (584, 10837)</td><td>
2654 (674, 10741)</td></tr></table>[*] Low to no endogenous β-globin production (β⁰/β⁰, β⁰/IVS-I-110 and IVS-I-110/IVS-I-110).
[#] Interim analysis conducted based on January 2023 data cut-off date.
[†] The primary efficacy set (PES), is a subset of the full analysis set (FAS). The PES was defined as all patients who had been followed for at least 16 months after CASGEVY infusion. Patients who continuously received RBC transfusions for more than 10 months after CASGEVY infusion were also included in this set.
[‡] Race was not collected per regional regulatory requirements in 7 (13.5%) patients in the FAS and 4 (11.4%) patients in the PES.</td></tr>
<tr><td>Arms</td><td>Eligible patients underwent mobilization and apheresis to collect CD34+ stem cells for Casgevy™ manufacture, followed by myeloablative conditioning and infusion of Casgevy™. Patients were then followed for 24 months after Casgevy™ infusion. Patients who complete or discontinue from the trial are encouraged to enroll in the long-term ongoing follow-up trial (NCT04208529), for additional follow up for a total of 15 years after Casgevy™ infusion.</td></tr>
</table>

Endpoint(s)	Primary: • Proportion of patients achieving transfusion independence for 12 consecutive months (TI12), defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months any time within the first 24 months after Casgevy™ infusion Secondary: • Proportion of patients achieving transfusion independence for 6 consecutive months (TI6), defined as maintaining weighted average Hb ≥9 g/dL without RBC transfusions for at least 6 consecutive months any time within the 24-month evaluation period • Safety & adverse events

Inclusion Criteria	• Age between 12 to 35 years
	• Diagnosis of TDT as defined by:
	  ○ Documented homozygous β-thalassemia or compound heterozygous β-thalassemia including β-thalassemia/hemoglobin E (HbE)
	  ○ History of at least 100 mL/kg/year or ≥10 units/year of RBC transfusions in the prior 2 years
	• Eligible for autologous hematopoietic stem cell transplant

Exclusion Criteria	• Severely elevated iron in the heart (i.e., patients with cardiac T2* less than 10 msec by magnetic resonance imaging [MRI] or left ventricular ejection fraction [LVEF] <45% by echocardiogram) • Advanced liver disease (aspartate transaminase [AST] or alanine transaminase [ALT] >3× the upper limit of normal [ULN], or direct bilirubin value >2.5× ULN, or if a liver biopsy demonstrated bridging fibrosis or cirrhosis [liver biopsy was performed if liver iron content was ≥15 mg/g by MRI]) • Patients with an available 10/10 human leukocyte antigen matched related hematopoietic stem cell donor • Prior hematopoietic stem cell transplant • Patients with associated α-thalassemia and >1 alpha deletion or alpha multiplications • Patients with sickle cell beta thalassemia variant • White blood cell (WBC) count $<3 \times 10^9$/L or platelet count $<50 \times 10^9$/L not related to hypersplenism
Results	• The interim analysis occurred at the time when the alpha spending was approximately 0.017 for a one-sided test, when 35 patients were evaluable for TI12 responder status • The TI12 and TI6 responder rate was 32/35 (91.4%; 98.3% one-sided CI, 75.7% to 100%) • All patients who achieved TI12 remained transfusion-independent, with a median (min, max) duration of transfusion-independence of 20.8 (13.3, 45.1) months and normal mean weighted average total Hb levels (mean, 13.1 g/dL) • The median (min, max) time to last RBC transfusion for patients who achieved TI12 was 30 (11, 91) days following Casgevy™ infusion • Three patients did not achieve TI12 or TI6; these patients had reductions in annualized RBC transfusion volume requirements of 79.8%, 83.9% and 97.9%, and reductions in annualized

	transfusion frequency of 78.6%, 67.4% and 94.6%, respectively, compared to baseline requirements • Most common adverse events were febrile neutropenia (61.5%), headache (53.8%), and stomatitis (50.0%); most adverse events and serious adverse events occurred within first 6 months after infusion • Two patients had serious adverse events considered related to Casgevy™: headache, hemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome and idiopathic pneumonia syndrome (latter also considered related to busulfan) all in the context of HLH (N=1) and delayed engraftment and thrombocytopenia (both also considered related to busulfan) (N=1), which all resolved; there were no deaths, discontinuations, or malignancies
Conclusion	In this trial, treatment with Casgevy™ met the primary and key secondary endpoint, with Casgevy™ treatment resulting in early and sustained increases in Hb leading to transfusion independence in >90% of patients with TDT. Safety profile of Casgevy™ was generally consistent with myeloablative busulfan conditioning and autologous transplantation. These results show Casgevy™ has the potential to deliver a one-time functional cure to patients with TDT.
Interpretation	One-time administration of Casgevy™ has thus far proven to be an effective treatment option for the elimination of transfusions in almost all patients with TDT across all genotypes with associated clinically meaningful increases in total Hb that were maintained over time. Limitations of this trial are that it is single-arm and unblinded, opening it up to bias. Additionally, as this is an ongoing trial, the full data set for the primary and secondary endpoints are not currently available. It is also unclear if repeat administration of Casgevy™ will be necessary long-term. A follow-up trial (NCT04208529) is currently following patients for up to 15 years after Casgevy™ administration to evaluate its durability.
Completion Date	August 2024

Title	Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Transfusion-Dependent β-Thalassemia NCT: 05356195
Design	Phase 3, single-dose, open-label study to evaluate the safety and efficacy of a single dose of Casgevy™ in pediatric subjects with TDT
Completion Date	May 2026

Title	Evaluation of Safety and Efficacy of CTX001 in Pediatric Participants With Severe Sickle Cell Disease NCT: 05329649

Design	Phase 3, single-dose, open-label study to evaluate the safety and efficacy of a single dose of Casgevy™ in pediatric subjects with severe SCD
Completion Date	May 2026

Title	Evaluation of Efficacy and Safety of a Single Dose of Exa-cel in Participants With Severe Sickle Cell Disease, βS/βC Genotype NCT: 05951205
Design	Phase 3, single-arm, open-label trial to evaluate the efficacy and safety of exa-cel (Casgevy™) in adolescent and adult participants with severe SCD, βS/βC genotype (HbSC)
Completion Date	December 2029

Title	A Long-term Follow-up Study in Subjects Who Received CTX001 NCT: 04208529
Design	Multi-site, observational study to evaluate the long-term safety and efficacy of Casgevy™ in subjects who received Casgevy™ in previous trials
Completion Date	September 2039

Guidelines

Yawn BP, Buchanan GR, Afenyi-annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-48.

Clinical guidelines and recommendations for the management of sickle cell disease have not been updated since the approval of Casgevy™. Current treatment recommendations for sickle cell disease primarily revolve around management of complications and the use of hydroxyurea or blood transfusions.

- Hydroxyurea therapy is recommended for adults with 3 or more severe vaso-occlusive crises during any 12-month period, with sickle cell disease pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome
- Treatment with hydroxyurea without regard to the presence of symptoms should be offered for infants, children, and adolescents
- In patients with sickle cell anemia, transfuse red blood cells to bring hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia

- In patients with sickle cell anemia who receive transfusions long-term, the goal of transfusion should be to maintain a HbS level of <30% prior to the next transfusion

Farmakis D, Porter J, Taher A, et al. 2021 thalassaemia international federation guidelines for the management of transfusion—dependent thalassemia. HemaSphere. 2022;6(8):732-748.

Blood transfusions:

- The diagnosis of thalassaemia should be confirmed with appropriate clinical and laboratory methods before the onset of transfusions (A)
- Careful donor selection and screening should be used, favoring voluntary, regular, nonremunerated blood donors (A)
- At each transfusion, ABO, Rh(D) compatible blood should be administered; choosing units compatible for ABO, C, c, E, e, and Kell antigens is highly recommended (A)
- Before each transfusion, screening for new antibodies and an indirect antiglobulin test (IAT) cross-match should be performed, or in centers that meet regulatory requirements, an electronic cross-match should be performed where allowed (A)
- Washed red cells should be used for patients who have severe allergic reactions (A)
- Transfusions should be performed every 2–4 weeks, maintaining pretransfusion hemoglobin above 90–105 g/L or up to 110–120 g/L for patients with cardiac complications (A)
- The post-transfusion hemoglobin should be kept below 140–150 g/L (A)

Iron overload and iron 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)
- 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)
- 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 deferoxamine) (B)
- The optimal chelation regime must be tailored for the individual and will vary with their current clinical situation
- 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)

Hematopoietic stem cell transplantation (HSCT):

- HSCT should be offered to thalassemia patients and their parents at an early age, before complications due to iron overload have developed, if an HLA identical sibling is available
- Either bone marrow or cord blood from an HLA identical sibling can be used
- A matched unrelated donor can be used, provided that high compatibility criteria for both HLA class I and II loci are present

- Haploidentical HSCT in thalassemia can be considered in experienced HSCT centers in the context of well-designed clinical trials
- Myeloablative conditioning regimens should always be used for standard transplantation
- Post-transplant care should include all transplant and thalassemia related complications
- In thalassemia patients, HSCT is cost-effective when compared to life-long supportive therapy

Gene therapy:

- Allogeneic HSCT: young patients (≤17-year-old) with a β+ or β0 genotype having an HLA-compatible sibling or a 10/10 matched volunteer donor
- Gene therapy with Zynteglo™: young patients in the 12- to 17-year-old age group with a β+ genotype who do not have an HLA-compatible sibling donor
- Gene therapy with Zynteglo™: patients in the 17- to 55-year-old age group with a β+ genotype who do not have severe comorbidities and are at-risk or ineligible to undergo an allogenic HSCT but can otherwise undergo an autologous gene therapy procedure with an acceptable risk

Luspatercept:

- Luspatercept can be considered for:
  - Patients who require regular red blood cell transfusions,
  - ≥18 years of age
- The recommended starting dose of luspatercept is 1 mg/kg once every 3 weeks by subcutaneous injection
- If the predose hemoglobin level is ≥115 g/L and is not influenced by recent transfusion, consider delaying dosing of luspatercept until the level is ≤110 g/L
- Before administration of luspatercept, hemoglobin level, and liver function tests including ALT and AST levels should be monitored to ensure proper dosing and metabolism of the medication
- If a TDT patient does not achieve a reduction in red-cell transfusion burden after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the luspatercept dose to 1.25 mg
- If a patient experienced a response followed by a lack of or lost response to luspatercept, consider initiating a search for causative factors
- Luspatercept should be discontinued if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time
- It is important to monitor any TDT patient receiving luspatercept for signs and symptoms of thromboembolic events and initiate treatment accordingly
- Blood pressure should be monitored before each administration of luspatercept
- As no data are currently available on luspatercept use in pregnant women, all pregnant women should be advised of the potential risk to a fetus
- Safety and efficacy of luspatercept in pediatric patients has not yet been established and its use in pediatric patients in therefore not currently recommended

Recommendation Definitions

Level of Evidence	Definition
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	Expert consensus or opinion and small studies, retrospective studies, registries.

Clinical Opinions

Sickle cell disease is an inherited red blood cell disorder. Patients with sickle cell disease have an abnormal type of hemoglobin, HbS, referring to the sickle shape of affected cells. Patients with sickle cell disease inherit an HbS gene from one parent and another abnormal hemoglobin gene from the other parent (i.e., hemoglobin S, hemoglobin C, or beta thalassemia). Prevalence of sickle cell disease is estimated to be about 100,000 people in the U.S. and disproportionately affects African-Americans. Sickle cell disease is associated with severe clinical complications with the acute presentation being vascular occlusion, resulting in recurrent pain episodes, life-threatening infections as a result of splenic infarction, acute chest syndrome, pulmonary hypertension, stroke, and cumulative multiorgan damage. These episodes are categorized as vaso-occlusive crises (VOC) and are the primary cause of health care encounters. The vaso-occlusive process is a complex multifactorial process believed to comprise multiple interactions between sickled red cells, activated leukocytes, endothelial cells, platelets, and plasma proteins. Currently, the only curative treatment for sickle cell disease is hematopoietic stem cell transplantation. Blood transfusions are used to treat and prevent complications of sickle cell disease, and pharmacological options are limited and primarily revolve around the use of hydroxyurea. Newer treatments like Oxbryta® (voxelotor) and Adakveo® (crizanlizumab-tmca) are typically reserved for patients who failed treatment with hydroxyurea or cannot tolerate it.

Casgevy™ (exagamglogene autotemcel) is a novel gene therapy that is indicated for the treatment of sickle cell disease in patients 12 years and older with recurrent VOCs. It is the first FDA-approved gene therapy that uses CRISPR/Cas9-editing technology for genetic modification. Approval for Casgevy™ was based on results from an ongoing single-arm, multicenter pivotal trial in adult and adolescent patients 12 to 35 years of age with sickle cell disease. Of the 31 patients with sufficient follow-up time to be evaluable, 29 (93.5%) achieved the primary efficacy outcome, freedom from severe VOC episodes for at least 12 consecutive months during the 24-month follow-up period. In addition, all treated patients achieved successful engraftment with no patients experiencing graft failure or graft rejection. Casgevy™ will compete directly with Lyfgenia® (lovotibeglogene autotemcel), a gene therapy that utilizes a lentiviral vector for genetic modification and was approved on the same day as Casgevy™. Unlike Lyfgenia®, which has a black box warning for hematologic malignancies, Casgevy™ has no black box warning. Additionally, Casgevy™ holds a significant price advantage, as it costs $2.2 million per one-time dose, whereas Lyfgenia® costs $3.1 million per one-time dose. These two factors should heavily favor Casgevy™ in gaining market share. The Institute for Clinical and Economic Review (ICER) released an updated draft evidence report back in July 2023, indicating that gene therapies for sickle cell disease would be cost-effective if priced at up to $2.05 million per treatment. The pricing for Casgevy™ falls in line with ICER's estimate, meaning it could be cost-effective despite its high price tag. It is unknown, however how long the benefits of a one-time dose of Casgevy™ will be sustained, or if repeat administration will be necessary in the future. An ongoing follow-up trial (NCT04208529) is currently following patients for up to 15 years after Casgevy™ administration to evaluate its durability.

In January 2024, just one month after its initial approval, Casgevy™ received a second indication for the treatment of patients 12 years of age and older with transfusion-dependent beta thalassemia. Beta thalassemia, commonly referred to as "Cooley's anemia," is an inherited blood disorder caused by mutations within the β-globin gene that result in reduced hemoglobin leading to reduced oxygen throughout the body. This can lead to complications due to significant iron accumulation in target organs. In younger patients, common complications include an early onset of endocrine disorders including growth failure and hypogonadism with increasing risk as patients age, often resulting in conditions such as hypothyroidism, hypoparathyroidism, diabetes and osteoporosis. More serious complications of the disease include heart failure and arrhythmias as well as hepatic disease such as fibrosis, cirrhosis or hepatocellular carcinoma. Current treatment options have been limited to supportive therapies including, chronic blood transfusions and managing iron overload. Similar to sickle cell disease, the only possible curative treatment is hematopoietic stem cell

transplantation, which only a small number of patients are eligible for. Prior to Casgevy™, the only FDA-approved gene therapy for the treatment of beta thalassemia was Zynteglo™ (betibeglogene autotemcel).

Like Zynteglo™, Casgevy™ is specifically indicated for transfusion-dependent beta-thalassemia, which is the most severe form of beta-thalassemia. These patients experience severe anemia and lifelong dependence on RBC transfusions. It is estimated that there are approximately 1300-1500 individuals within the U.S. with transfusion-dependent beta-thalassemia. In terms of price, Casgevy™ holds an advantage over Zynteglo™, which costs $2.8 million per one-time treatment. Lifetime healthcare costs in the U.S. for a patient with beta thalassemia are estimated to be between $5 and $5.7 million, which means that the $2.2 million for Casgevy™ has the potential to be cost-effective. An ongoing follow-up trial (NCT04208529) is currently following patients for up to 15 years after Casgevy™ administration to evaluate its durability and determine whether or not repeat administration will be necessary. Due to the high cost of Casgevy™ and its specific target population, utilization management techniques will be necessary to facilitate appropriate use and cost-containment.

Alternatives (SCD)

Drug Name^	Formulary Status	Dosage Form	Price*
Lyfgenia® (lovotibeglogene autotemcel)	NF	Intravenous suspension	$3.1 million (per one-time treatment)
Oxbryta® (voxelotor)	F-PA	300 mg, 500 oral tablets; 300 mg tablets for oral suspension	$11,428
Adakveo® (crizanlizumab-tmca)	NF	100 mg/10 intravenous solution	$9,812

Alternatives (TDT)

Drug Name^	Formulary Status	Dosage Form	Price*
Zynteglo™ (betibeglogene autotemcel)	NF	Intravenous suspension	$2.8 million (per one-time treatment)

**Price per month for maintenance dose for a 70 kg adult 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).*

Physician Administered Drugs (PAD) Medication Request Guideline

Recommendation:

- Add new gene therapy approved for this disease state – Casgevy
- Exclude repeat use of the same agent or trial of a different gene therapy agent
- Require no prior stem cell transplant vs not having access to a family matched donor

Gene Therapy for Regular Red Blood Cell (RBC) Transfusion Dependent Beta-Thalassemia	
Medications	Zynteglo (betibeglogene autotemcel), Casgevy (exagamglogene autotemcel)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	Repeat use of same gene therapy agent Trial of a different gene therapy agent after another has been used ~~N/A~~
Required Clinical Information	See "other criteria"
Age Restrictions	Per FDA approved prescribing information~~N/A~~
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
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Medication is prescribed at an FDA approved dose
	• Member has a diagnosis of transfusion dependent beta-thalassemia
	• Member requires regular RBC transfusions defined as ONE of the following:
	  ○ History of ≥100 mL/kg/year of packed red blood cell (pRBCs) in the past 2 years
	  ○ History of ≥8 transfusions of pRBCs per year in the past 2 years
	• Patient has not had a prior HSCT or gene therapy treatment ~~Prescriber attests that the member does not have accessibility to a family matched hematopoietic stem-cell transplantation (HSCT)~~
	• Negative pregnancy test (if applicable)
	
	The safety and effectiveness of repeat administration of Zynteglo or Casgevy 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~~3/2024

References

1. Casgevy™ [prescribing information]. Vertex Pharmaceuticals, Boston, MA; December, 2023.
2. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on January 25, 2024.
3. Facts & Comparisons eAnswers, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on January 25, 2024.
4. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on January 25, 2024.
5. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on January 25, 2024.
6. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Available at: http://www.fda.gov/. Accessed on January 25, 2024.
7. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on January 25, 2024.
8. Frangoul H, Altshuler D, Cappellini MD, et al. Crispr-cas9 gene editing for sickle cell disease and β-thalassemia. N Engl J Med. 2021;384(3):252-260.
9. Yawn BP, Buchanan GR, Afenyi-annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-48.
10. Farmakis D, Porter J, Taher A, et al. 2021 thalassaemia international federation guidelines for the management of transfusion—dependent thalassemia. HemaSphere. 2022;6(8):732-748.

Drug Name: Lyfgenia (lovotibeglogene autotemcel)

Manufacturer: bluebird bio

Approval Date: 12/8/2023

Marketing Date: 12/14/2023

Prescribing Information

Indication

Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events (VOEs)

Limitations of Use

Following treatment with Lyfgenia®, patients with α-thalassemia trait (-α3.7/-α3.7) may experience anemia with erythroid dysplasia that may require chronic red blood cell transfusions. Lyfgenia® has not been studied in patients with more than two α-globin gene deletions.

Mechanism of Action

Lyfgenia® is a $\beta^{A\text{-}T87Q}$-globin gene therapy consisting of autologous CD34+ cells from patients with sickle cell disease containing hematopoietic stem cells (HSCs) transduced with BB305 lentiviral vector (LVV) encoding $\beta^{A\text{-}T87Q}$-globin, suspended in cryopreservation solution. Lyfgenia® is intended for one-time administration to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into the patient's own HSCs.

Lyfgenia® adds functional copies of a modified β^{A}-globin gene (threonine [T] replaced with glutamine [Q] at position 87, T87Q or $\beta^{A\text{-}T87Q}$-globin) into patients' HSCs through transduction of autologous CD34+ cells with BB305 LVV. After Lyfgenia® infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active $\beta^{A\text{-}T87Q}$-globin that will combine with α-globin to produce functional hemoglobin (Hb) containing $\beta^{A\text{-}T87Q}$-globin (HbA^{T87Q}). $\beta^{A\text{-}T87Q}$-globin can be distinguished from wildtype β^{A}-globin and from β^{S}-globin through reverse-phase high-performance liquid chromatography (RPHPLC) or ultra-high performance liquid chromatography (UPLC). HbA^{T87Q} has similar oxygen-binding affinity and oxygen hemoglobin dissociation curve to wild type HbA, reduces intracellular and total hemoglobin S (HbS) levels, and is designed to sterically inhibit polymerization of HbS thereby limiting the sickling of red blood cells.

Dosage and Administration

- Patients are required to undergo HSC mobilization followed by apheresis to obtain CD34+ cells for Lyfgenia® manufacturing
- The minimum recommended dose is 3×10^6 CD34+ cells/kg via intravenous infusion
- Myeloablative conditioning must be administered before infusion of Lyfgenia®
- Following myeloablative conditioning, allow a minimum of 48 hours of washout before Lyfgenia® infusion

Black Box Warning

Hematologic Malignancy: Hematologic malignancy has occurred in patients treated with Lyfgenia®. Patients should be monitored closely for evidence of malignancy through complete blood counts at least every 6 months and through integration site analysis at Months 6, 12, and as warranted.

Adverse Reactions

Most common ≥ Grade 3 (incidence ≥ 20%): Stomatitis, thrombocytopenia, neutropenia, febrile neutropenia, anemia, and leukopenia

Serious: Hematologic malignancy, delayed platelet engraftment, neutrophil engraftment failure, insertional oncogenesis, and hypersensitivity reactions

Use in Specific Populations, Pregnancy

There are no available data on Lyfgenia® administration in pregnant women. No reproductive and developmental toxicity studies in animals have been conducted with Lyfgenia® to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known whether Lyfgenia® has the potential to be transferred to the fetus. Therefore, Lyfgenia® should not be administered to women who are pregnant, and pregnancy after Lyfgenia® infusion should be discussed with the treating physician.

Drug Interactions

Anti-retrovirals: Patients should not take anti-retroviral medications for at least one month prior to mobilization for required and until all cycles of apheresis are completed. There are some long-acting anti-retroviral medications that may require a longer duration of discontinuation for elimination of the medication. Anti-retroviral medications may interfere with manufacturing of Lyfgenia®.

How Supplied

Cell suspension for intravenous infusion

Price

$3.1 million

(Per one-time treatment, based on WAC.)

Clinical Studies

Ongoing

Title	A Study Evaluating the Safety and Efficacy of bb1111 in Severe Sickle Cell Disease NCT: 02140554
Design	Single-arm, 24-month, open-label, multicenter, phase 1/2 study evaluating gene therapy by transplantation of autologous CD34+ stem cells transduced ex vivo with the bb1111 (Lyfgenia®) in patients with severe sickle cell disease
Population	N=43

<table>
<tr><td></td><td>At the time of the interim analysis, 43 subjects underwent apheresis after mobilization with plerixafor of which 36 patients received myeloablative busulfan conditioning. Seven patients did not proceed to conditioning; 2 patients discontinued due to apheresis-related issues and 5 discontinued at patient and/or physician discretion. Thirty-six patients received the intravenous infusion of Lyfgenia® with a median dose of 6.4 × 10^6 CD34+ cells/kg (48 hours after the last dose of busulfan). No patients experienced graft failure or graft rejection. The following table includes the demographics and baseline characteristics for patients in the study.
<table>
<tr><th>Attribute</th><th>Transplant Population
N = 36</th><th>Transplant Population for VOE Efficacy Outcomes
N = 32</th></tr>
<tr><td>β-globin Genotype: β^S/β^S, n (%)</td><td>36 (100)</td><td>32 (100)</td></tr>
<tr><td>α-globin Genotype: αα/αα, n (%)
α-globin Genotype: αα/-α3.7, n (%)
α-globin Genotype: -α3.7/-α3.7, n (%)</td><td>23 (64)
11 (31)
2 (6)</td><td>20 (63)
10 (31)
2 (6)</td></tr>
<tr><td>Age in years, median (min, max)</td><td>24 (12, 38)</td><td>25 (12, 38)</td></tr>
<tr><td>Age in years, n (%)
≥ 18 years
≥ 12 years to < 18</td><td>
28 (78)
8 (22)</td><td>
24 (75)
8 (25)</td></tr>
<tr><td>Sex: Male, n (%)</td><td>22 (61)</td><td>20 (63)</td></tr>
<tr><td>Race: Black/African American n (%)
Race: Not Reported n (%)</td><td>35 (97)
1 (3)</td><td>31 (97)
1 (3)</td></tr>
</table>
</td></tr>
<tr><td>Arms</td><td>Lyfgenia® intravenous infusion</td></tr>
<tr><td>Endpoint(s)</td><td>Primary:

• Complete resolution of vaso-occlusive events (VOE-CR) between 6 months and 18 months after infusion of Lyfgenia®; VOEs were defined as any of the following events requiring evaluation at a medical facility:
  ○ An episode of acute pain with no medically determined cause other than vaso-occlusion, lasting more than 2 hours
  ○ Acute chest syndrome (ACS)
  ○ Acute hepatic sequestration
  ○ Acute splenic sequestration
• Complete resolution of severe vaso-occlusive events (sVOE-CR) between 6 months and 18 months after infusion of Lyfgenia®; sVOEs were defined as either of the following events:
  ○ VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit
  ○ Priapism requiring any level of medical attention

Secondary:

• Globin response (GR), defined as meeting the following criteria for a continuous period of at least 6 months after Lyfgenia® infusion:
  ○ Weighted average hemoglobin A^{T87Q} percentage of non-transfused total Hb ≥30% AND
  ○ Weighted average non-transfused total Hb (HbS + HbF + HbA_2 + HbA^{T87Q}) increase of ≥3 g/dL compared to baseline total Hb OR weighted average non-transfused total Hb ≥10 g/dL</td></tr>
</table>

Inclusion Criteria	• Age between 12 and 50 years • Diagnosis of sickle cell disease, with either βS/βS or βS/β0 or βS/β+ genotype • Experienced at least 4 severe VOEs in the prior 24 months • Karnofsky performance status of ≥60 or a Lansky performance status of ≥60 • Hydroxyurea treatment failure or intolerance
Exclusion Criteria	• Positive for presence of human immunodeficiency virus type 1 or 2 (HIV-1 and HIV-2), hepatitis B virus (HBV), or hepatitis C (HCV) • Clinically significant and active bacterial, viral, fungal, or parasitic infection • Inadequate bone marrow function • History of severe cerebral vasculopathy: defined by overt or hemorrhagic stroke; abnormal transcranial Doppler (≥200 cm/sec) needing chronic transfusion; or occlusion or stenosis in the polygon of Willis; or presence of Moyamoya disease. • Advanced liver disease • Contraindications to the use of plerixafor during the mobilization of hematopoietic stem cells and any contraindications to the use of busulfan and any other medicinal products required during the myeloablative conditioning, including hypersensitivity to the active substances or to any of the excipients • Prior or current malignancy or immunodeficiency disorder, except previously treated, non-life threatening, cured tumors such as squamous cell carcinoma of the skin • Prior hematopoietic stem cell transplant • Pregnancy or breastfeeding in a postpartum female or absence of adequate contraception for fertile participants • Prior receipt of gene therapy
Results	Primary: • Of the 32 patients evaluable for VOE-CR, 28/32 (88%) achieved complete elimination of VOEs between 6 and 18 months post infusion with Lyfgenia® • Of the 32 patients evaluable for sVOE-CR, 30/32 (94%) achieved complete elimination of sVOEs between 6 and 18 months post infusion with Lyfgenia® • After the primary evaluation period to last follow-up, 4/32 patients who achieved VOE-CR experienced VOEs • After the primary evaluation period up to 24 months, 17/35 (49%) patients were prescribed opioids for sickle cell and non-sickle cell-related pain Secondary: • All 36 patients infused in were evaluated for globin response, of which 31/36 (86%) achieved GR; all patients maintained GR once it was achieved
Conclusion	In this trial, treatment with Lyfgenia® met the primary endpoints, with the elimination of VOEs in 88% of patients and elimination of sVOEs in 94% of patients.
Interpretation	One-time administration of Lyfgenia® has thus far proven to be an effective treatment option for the elimination of VOEs and sVOEs for patients with severe sickle cell disease. Lyfgenia® also displayed meaningful improvements in hemoglobin levels. Limitations of this trial are that it is single-arm and

	unblinded, opening it up to bias. As this is an ongoing trial, the full data set for the primary and secondary endpoints are not currently available. Additionally, it is unclear if repeat administration of Lyfgenia® will be necessary long-term. A follow-up trial (NCT04293185) is currently following patients long-term to evaluate its durability.
Completion Date	October 2024

Title	A Study Evaluating Gene Therapy With BB305 Lentiviral Vector in Sickle Cell Disease NCT: 04293185
Design	Non-randomized, open-label, multi-site, single-dose, phase 3 study evaluating gene therapy by transplantation of autologous CD34+ stem cells transduced ex vivo with bb305 (Lyfgenia®)in patients with sickle cell disease
Completion Date	April 2027

Guidelines

Yawn BP, Buchanan GR, Afenyi-annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-48.

Clinical guidelines and recommendations for the management of sickle cell disease have not been updated since the approval of Lyfgenia®. Current treatment recommendations for sickle cell disease primarily revolve around management of complications and the use of hydroxyurea or blood transfusions.

- Hydroxyurea therapy is recommended for adults with 3 or more severe vaso-occlusive crises during any 12-month period, with sickle cell disease pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome
- Treatment with hydroxyurea without regard to the presence of symptoms should be offered for infants, children, and adolescents
- In patients with sickle cell anemia, transfuse red blood cells to bring hemoglobin level to 10 g/dL prior to undergoing a surgical procedure involving general anesthesia
- In patients with sickle cell anemia who receive transfusions long-term, the goal of transfusion should be to maintain a HbS level of <30% prior to the next transfusion

Clinical Opinions

Sickle cell disease is an inherited red blood cell disorder. Patients with sickle cell disease have an abnormal type of hemoglobin, HbS, referring to the sickle shape of affected cells. Patients with sickle cell disease inherit an HbS gene from one parent and another abnormal hemoglobin gene from the other parent (i.e., hemoglobin S, hemoglobin C, or beta thalassemia). Prevalence of sickle cell disease is estimated to be about 100,000 people in the U.S. and disproportionately affects African-Americans. Sickle cell disease is associated with severe clinical complications with the acute presentation

being vascular occlusion, resulting in recurrent pain episodes, life-threatening infections as a result of splenic infarction, acute chest syndrome, pulmonary hypertension, stroke, and cumulative multiorgan damage. These episodes are categorized as vaso-occlusive events (VOEs), and are the primary cause of health care encounters. The vaso-occlusive process is a complex multifactorial process believed to comprise multiple interactions between sickled red cells, activated leukocytes, endothelial cells, platelets, and plasma proteins. Currently, the only curative treatment for sickle cell disease is hematopoietic stem cell transplantation. Blood transfusions are used to treat and prevent complications of sickle cell disease, and pharmacological options are limited and primarily revolve around the use of hydroxyurea. Newer treatments like Oxbryta® (voxelotor) and Adakveo® (crizanlizumab-tmca) are typically reserved for patients who failed treatment with hydroxyurea or cannot tolerate it.

Lyfgenia® (lovotibeglogene autotemcel) is a novel gene therapy that is indicated for the treatment of patients 12 years of age or older with sickle cell disease and a history of VOEs. Lyfgenia® utilizes a lentiviral vector for genetic modification. Approval for Lyfgenia® was based on results from an ongoing single-arm, multicenter pivotal trial in adult and adolescent patients 12 to 50 years of age with sickle cell disease. Effectiveness was evaluated based on complete resolution of VOEs (VOE-CR) between 6 and 18 months after infusion with Lyfgenia®. In the trial, 28 (88%) of 32 patients achieved VOE-CR during this time period. Lyfgenia® will compete directly with Casgevy™ (exagamglogene autotemcel), a gene therapy that utilizes CRISPR/Cas9-editing technology for genetic modification and was approved on the same day as Lyfgenia®. Unlike Casgevy™, which has no black box warning, Lyfgenia® has a black box warning for hematologic malignancies. Patients receiving Lyfgenia® should have lifelong monitoring for these malignancies. Additionally, Casgevy™ holds a significant price advantage, as it costs $2.2 million per one-time dose, whereas Lyfgenia® costs $3.1 million per one-time dose. These two factors should heavily favor Casgevy™ and may make it difficult for Lyfgenia® in gaining market share. The Institute for Clinical and Economic Review (ICER) released an updated draft evidence report back in July 2023, indicating that gene therapies for sickle cell disease would be cost-effective if priced at up to $2.05 million per treatment. The pricing for Lyfgenia® far exceeds ICER's estimate, meaning it could be difficult to justify it as being cost-effectiveness despite its effectiveness at eliminating VOEs. It is also unknown how long the benefits of a one-time dose of Lyfgenia® will be sustained, or if repeat administration will be necessary in the future. An ongoing follow-up trial (NCT04293185) is currently following patients long-term to evaluate its durability. Due to the high cost of Lyfgenia®, its risks for hematologic malignancies, and its specific target population, utilization management techniques will be necessary to facilitate appropriate use and cost-containment.

Alternatives

Drug Name^	Formulary Status	Dosage Form	Price*
Casgevy™ (exagamglogene autotemcel)	NF	Intravenous suspension	$2.2 million (per one-time treatment)
Oxbryta® (voxelotor)	F-PA	300 mg, 500 oral tablets; 300 mg tablets for oral suspension	$11,428
Adakveo® (crizanlizumab-tmca)	NF	100 mg/10 intravenous solution	$9,812

**Price per month for maintenance dose for a 70 kg adult 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).*

Physician Administered Drugs (PAD) Medication Request Guideline

New:

Gene Therapy for Sickle Cell Disease	
Medications	Casgevy (exagamglogene autotemcel), Lyfgenia (lovotibeglogene autotemcel)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), or disease state specific standard of care guidelines.
Exclusion Criteria	Repeat use of same gene therapy agent Trial of a different gene therapy agent after another has been used
Required Clinical Information	See "other criteria"
Age Restrictions	Per FDA approved prescribing information
Prescriber Restrictions	Prescriber must be a hematologist or specialist in the treatment of sickle cell disease
Coverage Duration	If all the criteria are met, the initial request will be approved for a one-time treatment for one gene therapy agent
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization:**
	• Medication is prescribed at an FDA approved dose
	• Member has a diagnosis of sickle cell disease
	• Member has experienced at least 2 severe vaso-occlusive crises/events (VOE) per year in the past 2 years defined as either:
	  ○ VOE requiring a hospitalization or multiple visits to an emergency department/urgent care over 72 hours and receiving intravenous medications at each visit
	  ○ priapism lasting > 2 hours and requiring a visit to a medical facility
	  ○ acute chest syndrome
	  ○ splenic sequestration
	  ○ hepatic sequestration
	• 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)
	• Prescriber attests pregnancy has been ruled out prior to initiation of treatment (if applicable)
	• Patient has not had a prior HSCT or gene therapy treatment
	
	The safety and effectiveness of repeat administration of Casgevy or Lyfgenia 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	3/2024

References

1. Lyfgenia® [prescribing information]. bluebird bio, Inc., Somerville, MA; December, 2023.
2. ClinicalTrials.gov. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov/. Accessed on January 3, 2024.
3. Facts & Comparisons eAnswers, Hudson, Ohio: Wolters Kluwer Clinical Drug Information, Inc.; 2013; Accessed on January 3, 2024.

4. Pubmed.gov. U.S. National Library of Medicine, National Institutes of Health. Available at: https://www.ncbi.nlm.nih.gov/pubmed. Accessed on January 3, 2024.
5. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on January 3, 2024.
6. U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Available at: http://www.fda.gov/. Accessed on January 3, 2024.
7. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on January 3, 2024.
8. Yawn BP, Buchanan GR, Afenyi-annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-48.

Direct Oral Anticoagulants

Executive Summary

CLASS OVERVIEW

The direct oral anticoagulants (DOACs), sometimes referred to as non-vitamin K oral anticoagulants (NOACs), include the factor Xa inhibitors Xarelto® (rivaroxaban), Eliquis® (apixaban), and Savaysa® (edoxaban), along with the direct thrombin inhibitor Pradaxa® (dabigatran). The terms DOAC and NOAC are used interchangeably in this document. The acronym DOAC is used preferentially, but the acronym NOAC is used when it was also used in the related guideline or study. All carry indications for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and reduction in the risk of stroke in non-valvular atrial fibrillation (NVAF). Additionally, rivaroxaban, apixaban, and dabigatran are indicated for the secondary prevention of venous thromboembolism (VTE) and thromboprophylaxis after hip or knee replacement surgery. Rivaroxaban also has additional indications for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding and for the long-term prevention of major adverse cardiovascular events in patients with coronary artery disease (CAD) and peripheral artery disease (PAD). Only rivaroxaban and dabigatran can be used in pediatric patients, specifically for VTE treatment and to reduce the risk of recurrent VTE. Rivaroxaban has an additional pediatric indication for thromboprophylaxis in children ages 2 years and older with congenital heart disease who have undergone the Fontan procedure.

The DOACs do not require bridging or routine dose adjustments based on lab values, but most are not recommended for use in renal failure and many require dose adjustment based on renal function. Dabigatran has an antidote called Praxbind® (idarucizumab), while Andexxa® (andexanet alfa) is an emergency reversal agent for rivaroxaban and apixaban.

A multitude of guidelines has been published related to oral anticoagulation. Guidelines authored by four different societies are included herein.

UTILIZATION FINDINGS

There were 100 claims for 39 members, for a total of $54,980, and an average cost per claim of $549. The most highly utilized medication was Eliquis tablets with 63 claims, followed by Xarelto tablets, with 34 claims. There were no prior authorization requests.

RECOMMENDATIONS

- Pradaxa (brand) 75 mg & 150 mg capsules: Change brand to non-formulary. The generic is once again more cost effective and remain on formulary. There is no current utilization of the brand.

CLINICAL SUMMARY

The DOACs block major procoagulant activities involved in the generation of a fibrin clot, either through the inhibition of thrombin (which cleaves fibrinogen to fibrin, activates other procoagulant factors and activates platelets) or factor Xa (which works directly upstream to thrombin in the clotting cascade and cleaves prothrombin to thrombin). These products inactivate both circulating and clot-bound activated coagulation factors, and do not carry monitoring requirements or dietary restrictions like warfarin, which can make them a more convenient option for both prescribers and patients. However, they are not always the preferred option over more traditional agents such as warfarin or heparins (i.e., patients with prosthetic heart valves, pregnancy, and renal impairment) and still carry risks for major bleeding events like warfarin. The risk of bleeding episodes overall with warfarin and DOACs are low, and these agents may carry a slightly lesser risk of fatal bleeding events when compared to warfarin. In terms of efficacy, DOACs appear to be comparably effective (non-inferior) to warfarin and heparin products. The efficacy and safety of DOACs have never been compared directly with each other in a prospective, randomized clinical trial. Systematic reviews and retrospective observational data suggest similar efficacy between the DOACs, but apixaban may hold a safety advantage due to fewer observed bleeding episodes.

The American College of Chest Physicians (CHEST) has published various guidelines. In the treatment of VTE (DVT of the leg or PE) DOACs are preferred over warfarin. The same recommendation applies for the prevention of VTE in patients with atrial fibrillation (AF). In the treatment of ischemic stroke, patients with ischemic stroke or transient ischemic attack (TIA) and AF, oral anticoagulation with dabigatran is preferred over warfarin. The American Society of Clinical Oncology (ASCO) recommends DOACs as an option for anticoagulation in cancer care. The American Heart Association (AHA)/ American College of Cardiology (ACC)/Heart Rhythm Society (HRS) guidelines for the management of AF recommend NOACs over warfarin in eligible patients. American Society of Hematology (ASH) has also published several guidelines related to the management of VTE disease with oral anticoagulation. ASH guidelines suggest using DOACs over warfarin for the treatment of DVT/PE. In the prevention of VTE in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA), DOACs are preferred over low-molecular-weight heparin (LMWH). ASH has also published VTE prophylaxis guidelines, however, they do not recommend the use of DOACs over LMWH.

There is one agent, tecarfarin, in the pipeline in Phase III trials, although it's unclear when a new drug application (NDA) will be submitted. While it is similar to warfarin, tecarfarin is metabolized through the esterase pathway thereby avoiding the CYP-450 drug interactions which complicate warfarin management and is touted to potentially have a flatter dose-response curve than warfarin. Bevyxxa® (betrixaban) was another DOAC that was previously available for VTE prophylaxis in adults hospitalized for an acute medical illness at risk for thromboembolic complications due to moderate or severe restricted mobility. For independent business reasons, betrixaban was withdrawn from the market in April 2020. Dabigatran is the only DOAC to be available generically, with the first generics being launched in 2022.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
Factor Xa inhibitors		
Eliquis® (apixaban)	To reduce the risk of stroke and systemic embolism (SE) in patients with NVAF	5 mg orally twice daily; reduce dose to 2.5 mg orally twice daily if patient has at least 2 of the following characteristics: - age ≥ 80 years - body weight ≤ 60 kg - serum creatinine ≥ 1.5 mg/dL
	DVT and/or PE treatment	10 mg orally twice daily for 7 days, followed by 5 mg orally twice daily
	Reduction in the risk of recurrent DVT and/or PE following initial therapy	2.5 mg orally twice daily after at least 6 months of treatment for DVT and/or PE
	Prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery	Knee replacement: 2.5 mg orally twice daily for 12 days Hip replacement: 2.5 mg orally twice daily for 35 days
Xarelto® (rivaroxaban)	To reduce the risk of stroke and SE in patients with NVAF	20 mg orally once daily with evening meal; if CrCl ≤ 50 mL/min reduce dose to 15 mg orally once daily with evening meal
	DVT and/or PE treatment	15 mg orally twice daily with food for 21 days, followed by 20 mg orally once daily with food For patients <18 years of age dosing varies based on weight and ranges from 2.4 mg to 20 mg per day; use is not recommended in children less than 6 months of age with any of the following: - less than 37 weeks of gestation at birth - less than 10 days of oral feeding - body weight of less than 2.6 kg
	Reduction in the risk of recurrence of DVT and/or PE in adults at continued risk after completion of initial 6-month treatment	10 mg orally once daily after at least 6 months of standard anticoagulant treatment
	Prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery	Knee replacement: 10 mg orally once daily for 12 days Hip replacement: 10 mg orally once daily for 35 days
	Prophylaxis of VTE and VTE-related death during hospitalization and post hospital discharge in adults admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding	10 mg orally once daily in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days
	To reduce the risk of major cardiovascular (CV) events (CV death, myocardial infarction [MI] and stroke) in patients with CAD	2.5 mg orally twice daily in combination with aspirin (ASA) 75-100 mg once daily
	To reduce the risk of major thrombotic vascular events (myocardial infarction, ischemic stroke, acute limb ischemia, and major	2.5 mg orally twice daily in combination with ASA 75-100 mg once daily; when starting therapy after a successful lower extremity revascularization

Medication	Indications	Dosing/Administration
	amputation of a vascular etiology) in patients with PAD, including patients who have recently undergone a lower extremity revascularization procedure due to symptomatic PAD	procedure, initiate once hemostasis has been established
	Reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment	Dosing varies by weight and ranges from 2.4 mg to 20 mg per day; use is not recommended in children less than 6 months of age with any of the following: - less than 37 weeks of gestation at birth - less than 10 days of oral feeding - body weight of less than 2.6 kg
	Thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease who have undergone the Fontan procedure	Dosing varies by weight and ranges from 2.2 mg to 20 mg per day
Savaysa® (edoxaban)	To reduce the risk of stroke and SE in patients with NVAF	60 mg orally once daily in patients with CrCl >50 to ≤ 95 mL/min; reduce dose to 30 mg orally once daily in patients with CrCl 15 to 50 mL/min; do not use in patients with CrCl > 95 mL/min
	DVT and/or PE treatment following 5 to 10 days of initial therapy with a parenteral anticoagulant	60 mg orally once daily in patients with CrCl >50 to ≤ 95 mL/min; reduce dose to 30 mg orally once daily for patients with CrCl 15 to 50 mL/min, patients who weigh ≤ 60 kg, or patients who use certain P-gp inhibitors
Direct Thrombin Inhibitors		
Dabigatran (Pradaxa®)	To reduce the risk of stroke and SE in patients with NVAF	150 mg orally twice daily for patients with CrCl > 30 mL/min; 75 mg orally twice daily for patients with CrCl 15 to 30 mL/min
	DVT and/or PE treatment in patients who have been treated with a parenteral anticoagulant for 5-10 days	150 mg orally twice daily after 5-10 days of parenteral anticoagulation for patients with CrCl >30 mL/min For patients ≥3 months to <18 years of age dosing varies based on weight
	To reduce the risk of recurrence of DVT and PE in previously treated patients	150 mg orally twice daily after previous treatment for patients with CrCl >30 mL/min For patients ≥3 months to <18 years of age dosing varies based on weight
	Prophylaxis of DVT and PE in patients who have undergone hip replacement surgery	110 mg orally on first day, then 220 mg orally once daily for patients with CrCl >30 mL/min

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
Factor Xa inhibitors		
Eliquis® (apixaban)	**Premature Discontinuation:** Increased risk of thrombotic events with premature discontinuation **Spinal/Epidural Hematomas:** Spinal or epidural hematomas may occur with neuraxial anesthesia or spinal puncture in patients who are anticoagulated resulting in long-term or permanent paralysis	- Active pathological bleeding - Severe hypersensitivity to product
Xarelto® (rivaroxaban)		
Savaysa® (edoxaban)	**Reduced Efficacy in NVAF Patients with CrCl >95 mL/minute:** Edoxaban should not be used in patients with CrCl >95 mL/minute; an increased rate of ischemic stroke with edoxaban 60 mg compared to warfarin was observed **Premature Discontinuation:** Increased risk of ischemic events with premature discontinuation **Spinal/Epidural Hematomas:** Spinal or epidural hematomas may occur with neuraxial anesthesia or spinal puncture in patients who are anticoagulated resulting in long-term or permanent paralysis	
Direct Thrombin Inhibitors		
Dabigatran (Pradaxa®)	**Premature Discontinuation:** Increased risk of thrombotic events with premature discontinuation **Spinal/Epidural Hematomas:** Spinal or epidural hematomas may occur with neuraxial anesthesia or spinal puncture in patients who are anticoagulated resulting in long-term or permanent paralysis	- Active pathological bleeding - History of serious hypersensitivity reaction to product - Mechanical prosthetic heart valve

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
Factor Xa inhibitors	
Eliquis® (apixaban)	- Bleeding: Apixaban can cause serious, potentially fatal, bleeding; promptly evaluate signs and symptoms of blood loss; an agent to reverse the anti-factor Xa activity of apixaban is available - Prosthetic heart valves: Apixaban use not recommended. - Increased risk of thrombosis in patients with triple-positive antiphospholipid syndrome: Apixaban use not recommended
Xarelto® (rivaroxaban)	- Risk of bleeding: Rivaroxaban can cause serious and fatal bleeding; an agent to reverse the activity of rivaroxaban is available - Pregnancy-related hemorrhage: Use rivaroxaban with caution in pregnant women due to the potential for obstetric hemorrhage and/or emergent delivery - Prosthetic heart valves: Rivaroxaban use not recommended - Increased risk of thrombosis in patients with triple-positive antiphospholipid syndrome: Rivaroxaban use not recommended
Savaysa® (edoxaban)	- Bleeding: Serious and potentially fatal bleeding; promptly evaluate signs and symptoms of blood loss - Mechanical heart valves or moderate to severe mitral stenosis (MS): Edoxaban use not recommended - Increased risk of thrombosis in patients with triple-positive antiphospholipid syndrome: Edoxaban use not recommended
Direct Thrombin Inhibitors	
Dabigatran (Pradaxa®)	- Bleeding: Dabigatran can cause serious and fatal bleeding - Bioprosthetic heart valves: Dabigatran use not recommended - Increased risk of thrombosis in patients with triple-positive antiphospholipid syndrome: Dabigatran use not recommended

PRACTICE GUIDELINES

American College of CHEST Physicians

Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the chest guideline and expert panel report. Chest. 2021;160(6):e545-e608.

- In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over VKA as treatment-phase (first 3 months) anticoagulant therapy (Strong recommendation, moderate quality evidence).
- In patients with acute VTE in the setting of cancer (cancer-associated thrombosis) we recommend an oral Xa inhibitor (apixaban, edoxaban, rivaroxaban) over LMWH for the initiation and treatment phases of therapy (Strong recommendation, moderate quality evidence).
- In patients with confirmed antiphospholipid syndrome being treated with anticoagulant therapy, we suggest adjusted dose VKA (target INR 2.5) over DOAC therapy during the treatment phase (Weak recommendation, low quality evidence).
- In patients with superficial venous thrombosis (SVT) who refuse or are unable to use parenteral anticoagulation, we suggest rivaroxaban 10 mg daily as a reasonable alternative for fondaparinux 2.5 mg daily (Weak recommendation, low quality evidence).
- In patients with VTE diagnosed in the absence of transient risk factor (unprovoked VTE or provoked by a persistent risk factor) who cannot receive a DOAC, we suggest offering extended-phase anticoagulation with a VKA (Weak recommendation, moderate quality evidence).
- In patients offered extended-phase anticoagulation, we suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (Weak recommendation, very low quality evidence).
- In patients offered extended-phase anticoagulation, we recommend reduced-dose DOAC over aspirin or no therapy (Strong recommendation, low quality evidence) and suggest rivaroxaban over aspirin (Weak recommendation, moderate quality evidence).

Recommendation Definitions

Table 1

Grade of Recommendation	Benefit vs. Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are very confident that the true effect lies close to that of the estimate of the effect	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect
Strong recommendation, moderate quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Recommendation can apply to most patients in most circumstances. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Strong recommendation, low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Strong recommendation, very low quality evidence	Benefits clearly outweigh risk and burdens, or vice versa	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Recommendation can apply to most patients in many circumstances. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, high quality evidence	Benefits closely balanced with risks and burden	We are very confident that the true effect lies close to that of the estimate of the effect	The best action may differ depending on circumstances or patients' or societal values. Further research is very unlikely to

			change our confidence in the estimate of effect
Weak (conditional) recommendation, moderate quality evidence	Benefits closely balanced with risks and burden	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Best action may differ depending on circumstances or patients' or societal values. Higher quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate
Weak (conditional) recommendation, low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Weak (conditional) recommendation, very low quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk and burden may be closely balanced	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Other alternatives may be equally reasonable. Higher quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate
Ungraded Consensus Based Statement	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on our confidence in the estimate of effect and may change the estimate

Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201. doi: 10.1016/j.chest.2018.07.040.

- For patients with AF, we recommend against antiplatelet therapy alone (monotherapy or ASA in combination with clopidogrel) for stroke prevention alone, regardless of stroke risk (Strong recommendation, moderate quality evidence).
- In patients with AF who are eligible for oral anticoagulation (OAC), we recommend NOACs over vitamin K antagonist (VKA) (Strong recommendation, moderate quality evidence).
- In patients with prior unprovoked bleeding, warfarin-associated bleeding, or at high risk of bleeding, we suggest using apixaban, edoxaban, or dabigatran 110 mg (where available) as all demonstrate significantly less major bleeding compared with warfarin (Weak recommendation, very low quality evidence).
- For patients with AF of > 48 h or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation with well-managed VKA (INR 2-3) or an NOAC using dabigatran, rivaroxaban, edoxaban, or apixaban for at least 3 weeks before cardioversion or a transesophageal echocardiography (TEE)-guided approach with abbreviated anticoagulation before cardioversion rather than no anticoagulation (Strong recommendation, moderate quality evidence).
- For patients with AF of > 48 hours or unknown duration undergoing elective electrical or pharmacologic cardioversion, we recommend therapeutic anticoagulation (with VKA or NOAC) for at least 4 weeks after successful cardioversion to sinus rhythm rather than no anticoagulation, regardless of the baseline risk of stroke (Strong recommendation, moderate quality evidence).
- For patients with AF and hemodynamic instability undergoing urgent cardioversion (electrical or pharmacologic), after successful cardioversion to sinus rhythm, we suggest therapeutic anticoagulation (with VKA or full adherence to NOAC therapy) for at least 4 weeks rather than no anticoagulation, regardless of baseline stroke risk (Weak recommendation, low quality evidence).
- In AF patients requiring OAC undergoing elective percutaneous coronary intervention (PCI)/stenting,
    - where bleeding risk is low (HAS-BLED 0-2) relative to risk for recurrent acute coronary syndrome (ACS) and/or stent thrombosis, we suggest triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).

    - where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1 month, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).
    - where bleeding risk is unusually high and thrombotic risk relatively low, we suggest use of OAC plus single antiplatelet (preferably clopidogrel) for 6 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).
- In AF patients requiring OAC presenting with an ACS, undergoing PCI/stenting,
    - where bleeding risk is low (HAS-BLED 0-2) relative to risk for ACS or stent thrombosis, we suggest triple therapy for 6 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) until 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).
    - where bleeding risk is high (HAS-BLED ≥ 3), we suggest triple therapy for 1-3 months, followed by dual therapy with OAC plus single antiplatelet (preferably clopidogrel) up to 12 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).
    - where bleeding risk is unusually high and thrombotic risk low, we suggest OAC plus single antiplatelet (preferably clopidogrel) for 6-9 months, following which OAC monotherapy can be used (Weak recommendation, low quality evidence).
- In AF patients with ACS or undergoing PCI in whom OAC is recommended, we suggest using VKA with time in therapeutic range (TTR) > 65-70% (INR range 2.0-3.0), or to use an NOAC at a dose licensed for stroke prevention in AF (Weak recommendation, low quality evidence)
- In AF patients in which ASA is concomitantly used with OAC, we suggest a dose of 75-100 mg QD with concomitant use of proton pump inhibitor (PPI) to minimize gastrointestinal (GI) bleeding (Weak recommendation, low quality evidence).
- In AF patients in which a P2Y12 inhibitor is concomitantly used with OAC, we suggest the use of clopidogrel (Weak recommendation, low quality evidence).
- For patients with AF and stable coronary artery disease (e.g., no ACS within the previous year) and who choose oral anticoagulation, we suggest OAC with either an NOAC or adjusted dose VKA therapy alone (target INR range, 2.0-3.0) rather than the combination of OAC and ASA (Weak recommendation, low quality evidence).
- In AF patients with acute stroke without contraindications, we recommend that long-term oral anticoagulation is indicated as secondary prevention (Strong recommendation, high quality evidence).
- In patients with AF and high ischemic stroke risk, we suggest anticoagulation with an NOAC after acute spontaneous intracranial hemorrhage (ICH) (which includes subdural, subarachnoid, and intracerebral hemorrhages) after careful consideration of the risks and benefits (Ungraded consensus-based statement).
- In patients with AF and symptomatic carotid stenosis (> 50%), we suggest carotid revascularization with endarterectomy or stenting in addition to OAC as indicated (Weak recommendation, moderate quality evidence).
- In patients with AF and carotid stenosis treated with revascularization, we suggest OAC therapy, without long-term antiplatelet therapy (Ungraded consensus-based statement).
- In patients with AF, we suggest prescription of oral anticoagulants could be considered as a result of an individualized clinical assessment taking into account overall atrial high-rate episode (AHRE) burden (in the range of hours rather than minutes) and specifically, the presence of AHRE > 24 h, individual stroke risk (using CHA_2DS_2-VASc), predicted risk benefit of oral anticoagulation and informed patient preferences (Ungraded consensus-based statement).
- For patients with atrial flutter, we suggest that antithrombotic therapy decisions follow the same risk-based recommendations as for AF (Ungraded consensus-based statement).
- For women receiving OAC for prevention of stroke/thromboembolism (TE) in AF who become pregnant, we suggest discontinuation of OAC with a VKA between weeks 6 and 12 and replacement by LMWH BID (with dose adjustment according to weight and target antiXa level 4-6 h post-dose 0.8-1.2 U/mL), especially in patients with a warfarin dose required of > 5 mg/day. OAC should then be discontinued and replaced by adjusted-dose LMWH

(target anti-Xa level 4-6 h post-dose 0.8-1.2 U/mL) in the 36th week of gestation (Ungraded consensus-based statement).

- For women on treatment with long-term VKAs who are attempting pregnancy and are candidates for LMWH substitution, we suggest performing frequent pregnancy tests and use LMWH instead of VKA when pregnancy is achieved rather than switching to LMWH while attempting pregnancy (Ungraded consensus-based statement).
- For pregnant women, we suggest avoiding the use of NOACs (Ungraded consensus-based statement).
- For lactating women using warfarin or unfractionated heparin (UFH) who wish to breast-feed, we suggest continuing the use of warfarin, LMWH, or UFH (Ungraded consensus-based statement).
- For breast-feeding women, we suggest alternative anticoagulants rather than NOACs (Ungraded consensus-based statement).
- For moderate CKD (Stage III, CrCl 30-59 mL/min), we suggest oral anticoagulation in patients with a CHA_2DS_2-VASc ≥ 2 with label-adjusted NOACs or dose-adjusted VKAs (Weak recommendation, very low quality evidence).
- In severe non-dialysis CKD (Stage IV CrCl 15-30 mL/min), we suggest using VKAs and selected NOACs (rivaroxaban 15 mg QD, apixaban 2.5 mg BID, edoxaban 30 mg QD, and dabigatran 75 mg BID) with caution, based on pharmacokinetic data (Ungraded consensus-based statement).
- In end-stage renal disease (CrCl < 15 mL/min or dialysis-dependent, we suggest using well-managed VKA with TTR > 65-70% (Ungraded consensus-based statement).
  Remark: NOACs should generally not be used, although in USA, apixaban 5 mg BID is approved for use in AF patients receiving hemodialysis.
  Remark: In patients with CKD who initiate OAC, concomitant antiplatelet therapy including low-dose ASA is likely to substantially elevate bleeding risk and should be used very judiciously.
- In AF patients at risk of ischemic stroke undergoing cardiac surgery, we suggest surgical exclusion of the left atrial appendage for stroke prevention, but the need for long-term OAC is unchanged (Weak recommendation, low quality evidence).

Recommendation Definitions – see Table 1

Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e278S-e325S. doi: 10.1378/chest.11-2404.

- In patients undergoing THA or TKA, we recommend use of one of the following for at least 10-14 days rather than no antithrombotic prophylaxis: LMWH, fondaparinux, apixaban, dabigatran, rivaroxaban, low-dose UFH, adjusted-dose VKA, ASA (all Grade 1B), or an intermittent pneumatic compression device (IPCD) (Grade 1C).
- In patients undergoing THA or TKA, irrespective of the concomitant use of an IPCD or length of treatment, we suggest the use of LMWH in preference to the other agents we have recommended as alternatives: fondaparinux, apixaban, dabigatran, rivaroxaban, LDUH (all Grade 2B), adjusted-dose VKA, or ASA (all Grade 2C).
- In patients undergoing major orthopedic surgery and who decline or are uncooperative with injections or an IPCD, we recommend using apixaban or dabigatran (alternatively rivaroxaban or adjusted-dose VKA if apixaban or dabigatran are unavailable) rather than alternative forms of prophylaxis (all Grade 1B).

Recommendation Definitions

Table 2

Grade of Recommendation	Benefit vs Risk and Burdens	Methodologic Strength of Supporting Evidence	Implications
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change our confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Strong recommendation, low-or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balanced with risks and burden.	Consistent evidence from randomized controlled trials without important limitations or exceptionally strong evidence from observational studies.	The best action may differ depending on circumstances or patient or societal values. Further research is very unlikely to change our confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balanced with risks and burden.	Evidence from randomized controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise) or very strong evidence from observational studies.	Best action may differ depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on our confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced.	Evidence for at least one critical outcome from observational studies, case series, or randomized controlled trials, with serious flaws or indirect evidence.	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on our confidence in the estimate of effect and may well change the estimate.

Maarten GL, O'Donnell MJ, Khatri P, et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e601S-e636S. doi: 10.1378/chest.11-2302.

- In patients with a history of noncardioembolic ischemic stroke or transient ischemic attack (TIA), we recommend long-term treatment with ASA (75-100 mg QD), clopidogrel (75 mg QD), ASA/extended-release dipyridamole (25 mg/200 mg BID), or cilostazol (100 mg BID) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B), the combination of clopidogrel plus ASA (Grade 1B), or triflusal (Grade 2B).

- In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we recommend oral anticoagulation over no antithrombotic therapy (Grade 1A), ASA (Grade 1B), or combination therapy with ASA and clopidogrel (Grade 1B).
- In patients with a history of ischemic stroke or TIA and AF, including paroxysmal AF, we suggest oral anticoagulation with dabigatran 150 mg BID over adjusted-dose VKA therapy (target INR range, 2.0-3.0) (Grade 2B).

Recommendation Definitions – see Table 2

American Society of Clinical Oncology (ASCO)

Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology. 2019 Aug 5. doi: 10.1200/JCO.19.01461

- High-risk outpatients with cancer (Khorana score ≥ 2 prior to starting a new systemic chemotherapy regimen) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH provided there are no significant risk factors for bleeding and no drug interactions. Consideration of such therapy should be accompanied by a discussion with the patient about the relative benefits and harms, drug cost, and duration of prophylaxis in this setting (Type: evidence based; Evidence quality: intermediate to high for apixaban and rivaroxaban, intermediate for LMWH; Strength of recommendation: moderate).
- Initial anticoagulation may involve LMWH, UFH, fondaparinux, or rivaroxaban. For patients initiating treatment with parenteral anticoagulation, LMWH is preferred over UFH for the initial 5 to 10 days of anticoagulation for the patient with cancer with newly diagnosed VTE who does not have severe renal impairment (defined as CrCl < 30 mL/min) (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- For long-term anticoagulation, LMWH, edoxaban, or rivaroxaban for at least 6 months are preferred because of improved efficacy over VKAs. VKAs are inferior but may be used if LMWH or DOACs are not accessible. There is an increase in major bleeding risk with DOACs, particularly observed in GI and potentially genitourinary malignancies. Caution with DOACs is also warranted in other settings with high risk for mucosal bleeding. Drug-drug interaction should be checked prior to using a DOAC (Type: evidence based; Evidence quality: high; Strength of recommendation: strong).
- Anticoagulation with LMWH, DOACs, or VKAs beyond the initial 6 months should be offered to select patients with active cancer, such as those with metastatic disease or those receiving chemotherapy. Anticoagulation beyond 6 months needs to be assessed on an intermittent basis to ensure a continued favorable risk-benefit profile (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak to moderate).
- For patients with primary or metastatic central nervous system (CNS) malignancies and established VTE, anticoagulation as described for other patients with cancer should be offered, although uncertainties remain about choice of agents and selection of patients most likely to benefit (Type: informal consensus; Quality of evidence: low; Strength of recommendation: moderate).

Recommendation Definitions

Table 3a

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”).

No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Table 3b

Level of Evidence	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Table 3c

Strength of Recommendation	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect, however it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS)

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665.

Risk-Based Anticoagulant Therapy Recommendations

- Patients with AF and an elevated CHA_2DS_2-VASc score ≥ 2 in men and ≥ 3 in women, oral anticoagulants are recommended. Options include: warfarin (Class 1 Level A), dabigatran, rivaroxaban, apixaban (Class I, Level B), or edoxaban (Class I, Level B-R)
- NOACs (dabigatran, rivaroxaban, apixaban, and edoxaban) are recommended over warfarin in NOAC-eligible patients with AF (except with moderate-to-severe MS or a mechanical heart valve) (Class I, Level A)
- Patients with AF who have mechanical heart valves, warfarin is recommended (Class I, Level B)
- Patients with AF (except with moderate-to-severe MS or a mechanical heart valve) who are unable to maintain a therapeutic INR level, use of a DOAC is recommended. (Class I, Level C-EO)
- Patients with AF who have a CHA_2DS_2-VASc score of ≥ 2 in men or ≥ 3 in women and who have end-stage CKD or on dialysis, it might be reasonable to prescribe warfarin or apixaban (Class IIb, Level B-NR)
- Dabigatran, rivaroxaban, and edoxaban are not recommended in patients with AF and end-stage CKD or on dialysis (Class III: No benefit, Level C-EO).
- Dabigatran should not be used in patients with AF and a mechanical heart valve (Class III: Harm, Level B-R).

Specific Patient Groups and AF

- In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of ≥ 2) who have undergone PCI with stenting for acute coronary ACS, double therapy with P2Y12 inhibitors (clopidogrel) and low-dose rivaroxaban 15 mg daily is reasonable to reduce the risk of bleeding as compared with triple therapy. (Class IIa, Level B-R)
- In patients with AF at increased risk of stroke (based on CHA_2DS_2-VASc risk score of ≥ 2) who have undergone PCI with stenting for ACS, double therapy with a P2Y12 inhibitor (clopidogrel) and dabigatran 150 mg BID is reasonable to reduce the risk of bleeding as compared with triple therapy. (Class IIa, Level B-R)

Recommendation Definitions

Table 4a

Applying Class of Recommendations and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care*

Class (Strength) of Recommendation (COR)		Recommendation Phrases
Class I (Strong)	Benefit >>> Risk	• Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-effectiveness phrases† ○ Treatment/strategy A is recommended/indicated in preference to treatment B ○ Treatment A should be chosen over treatment B
Class IIa (Moderate)	Benefit >> Risk	• Is reasonable • Can be useful/effective/beneficial • Comparative-effectiveness phrases† ○ Treatment/strategy A is probably recommended/indicated in preference to treatment B ○ It is reasonable to choose treatment A over treatment B
Class IIb (Weak)	Benefit ≥ Risk	• May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain
Class III: No benefit (Moderate) (*Generally, LOE A or B use only*)	Benefit = Risk	• Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
Class III: Harm (Moderate)	Risk > Benefit	• Potentially harmful • Causes harm • Associated with excess morbidity/mortality

		• Should not be performed/administered/other

Table 4b

Level (Quality) of Evidence‡ (LOE)	Definition
Level A	• High-quality evidence‡ from more than 1 randomized controlled trial (RCT) • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Level B-R (Randomized)	• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
Level B-NR (Non-randomized)	• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
Level C-LD (Limited data)	• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Level C-EO (Expert opinion)	• Consensus of expert opinion based on clinical experience

COR and LOE are determined independently

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinic consensus that a particular test or therapy is useful or effective.

**The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).*

†For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews the incorporation of an Evidence Review Committee.

Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5):e35-e71. doi: 10.1161/CIR.0000000000000960.

- Anticoagulation with a VKA is indicated for patients with rheumatic MS and AF. (Class I, Level C-EO)
- For patients with new-onset AF ≤3 months after surgical or transcatheter biprosthetic valve replacement, anticoagulation with VKA is reasonable. (Class IIa, Level B-NR)
- It is reasonable to use a DOAC as an alternative to a VKA in patients with AF and native valve disease and should be administered on the basis of the patient's CHA_2DS_2-VASc score. (Class I, Level A)

Recommendation Definitions – see Table 4a and Table 4b

American Society of Hematology (ASH)

Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4(19):4693-4738. doi: 10.1182/bloodadvances.2020001830.

- For patients with DVT and/or PE, the ASH guideline panel suggests using DOACs over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).
- For patients with DVT and/or PE, the ASH guideline panel does not suggest 1 DOAC over another (conditional recommendation, very low certainty in the evidence of comparative effects ⊕◯ ◯ ◯).
- For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel suggests using a standard-dose DOAC or a lower-dose DOAC (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).
- For patients with breakthrough DVT and/or PE during therapeutic VKA treatment, the ASH guideline panel suggests using LMWH over DOAC therapy (conditional recommendation, very low certainty in the evidence of effects ⊕◯ ◯ ◯).

Recommendation Definitions

Table 5a

Strength of Recommendation	Interpretation
Strong	• For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not. • For clinicians: Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences. • For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. • For researchers: The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.
Conditional	• For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences. • For clinicians: Different choices will be appropriate for individual patients, and clinicians must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences. • For policy makers: Policy-making will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is duly documented. • For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Table 5b

Quality of Evidence	Symbol	Definition^
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 estimate of effect and may change the estimate
Low	⨁⨁◯◯	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	⨁◯◯◯	Any estimate of effect is very uncertain

^From the GRADE series of papers.

Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv (2018) 2 (22): 3257-3291. doi: 10.1182/bloodadvances.2018024893.

- For patients requiring administration of inhibitors or inducers of P-glycoprotein (P-gp) or strong inhibitors or inducers of CYP-450 enzymes, the ASH guideline panel suggests using an alternative anticoagulant (such as VKA or LMWH) rather than a DOAC for the treatment of VTE (conditional recommendation, low certainty in the evidence about effects ⨁◯ ◯ ◯).
- For patients receiving DOAC therapy for the treatment of VTE, the ASH guideline panel suggests against measuring the DOAC anticoagulant effect during management of bleeding (conditional recommendation, very low certainty in the evidence about effects ⨁◯ ◯ ◯).
- For patients transitioning from DOAC to VKA, the ASH guideline panel suggests overlapping DOAC and VKA therapy until the INR is within the therapeutic range over using LMWH or UFH "bridging therapy" (conditional recommendation, very low certainty in the evidence about effects ⨁◯ ◯ ◯).

Recommendation Definitions – See Table 5a and Table 5b

Anderson DR, Morgano GP, Bettett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv (2019) 3 (23): 3898–3944. https://doi.org/10.1182/bloodadvances.2019000975.

- For patients undergoing total hip arthroplasty or total knee arthroplasty in which anticoagulants are used, the ASH guideline panel suggests using DOACs over LMWH (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).
- For patients undergoing surgery, the ASH guideline panel suggests using any of the DOACs approved for use (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).
- For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel suggests using LMWH rather than warfarin (conditional recommendation based on very low certainty in the evidence of effects ⊕◯◯◯).
- For patients undergoing total hip arthroplasty or total knee arthroplasty, if a DOAC is not used, the ASH guideline panel suggests using LMWH rather than UFH (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯) .

Recommendation Definitions – See Table 5a and Table 5b

Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv (2018) 2 (22): 3198-3225. doi: 10.1182/bloodadvances.2018022954.

- In acutely ill hospitalized medical patients, the ASH guideline panel recommends using LMWH over DOACs for VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).
- In acutely ill hospitalized medical patients, the ASH guideline panel recommends inpatient VTE prophylaxis with LMWH only, rather than inpatient and extended-duration outpatient VTE prophylaxis with DOACs (strong recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯). Remark: If patients are on a DOAC for other reasons, this recommendation may not apply.

Recommendation Definitions – See Table 5a and Table 5b

CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
Ingason AB, Hreinsson JP, Ágústsson AS, et al. Rivaroxaban is associated with higher rates of gastrointestinal bleeding than other direct oral anticoagulants: a nationwide propensity score-weighted study. Ann Intern Med. 2021;174(11):1493-1502.	Nationwide population-based cohort study to compare rates of gastrointestinal bleeding (GIB) among apixaban, dabigatran, and rivaroxaban. Study population consisted of patients in the Icelandic Medicine Registry who filled a prescription for apixaban, dabigatran, or rivaroxaban from 1 March 2014 to 28 February 2019. Patients were excluded from the study if they had filled an oral anticoagulant prescription in the preceding 12 months, had end-stage renal disease, a mechanical heart valve, or mitral valve stenosis, had permanent residence outside Iceland, or were receiving 2.5 mg of rivaroxaban. Overall, 2157 patients receiving apixaban, 494 patients receiving dabigatran, and 3217 patients receiving rivaroxaban were compared.	• Clinically relevant GIB, defined as bleeding leading to medical intervention, unscheduled physician contact, or temporary treatment cessation • Clinically relevant upper or lower GIB • Major GIB
Results: For all patients, rivaroxaban had higher overall rates of GIB (3.2 vs. 2.5 events per 100 person-years; hazard ratio [HR], 1.42 [95% CI, 1.04 to 1.93]) and major GIB (1.9 vs. 1.4 events per 100 person-years; HR, 1.50 [95% CI, 1.00 to 2.24]) compared with apixaban. Rivaroxaban also had higher GIB rates than dabigatran, with similar point estimates, although the CIs were wider and included the possibility of a null effect. When only patients with atrial fibrillation were included, rivaroxaban was associated with higher rates of overall GIB than apixaban (HR, 1.40 [95% CI, 1.01 to 1.94]) or dabigatran (HR, 2.04 [95% CI, 1.17 to 3.55]). Dabigatran was associated with lower rates of upper GIB than rivaroxaban in both analyses. **Conclusion:** Rivaroxaban was associated with higher GIB rates than apixaban and dabigatran regardless of treatment indication.		
Citation	**Design**	**Endpoints**
Van Ganse E, Danchin N, Mahé I, et al. Comparative safety and effectiveness of oral anticoagulants in nonvalvular atrial fibrillation: the NAXOS study. Stroke. 2020;51(7):2066-2075.	Observational study using French National Health System claims data to compare the safety, effectiveness, and mortality of apixaban with VKAs, rivaroxaban, and dabigatran, in oral anticoagulant-naive patients with NVAF. Study population consisted of all patients aged ≥18 years with ≥1 reimbursement for oral anticoagulant treatments (VKAs, apixaban, rivaroxaban, or dabigatran) between January 2014 and December 2016. Patients with several oral anticoagulant treatments, multiple doses or multiple prescribers at the initiation date, and patients possibly treated for indications other than stroke prevention in NVAF were excluded. Overall, 321,501 patients were analyzed, of whom 35.0%, 27.2%, 31.1%, and 6.6% initiated VKAs, apixaban, rivaroxaban, and dabigatran, respectively.	• Major bleeding events leading to hospitalization (safety) • Stroke and systemic thromboembolic events (efficacy) • All-cause mortality
Results: Apixaban was associated with a lower risk of major bleeding compared with VKAs (HR, 0.43 [95% CI, 0.40–0.46]) and rivaroxaban (HR, 0.67 [95% CI, 0.63–0.72]), but not dabigatran (HR, 0.93 [95% CI, 0.81–1.08]). Apixaban was associated with a lower risk of stroke and systemic thromboembolic event compared with VKAs (HR, 0.60 [95% CI, 0.56–0.65]), but not rivaroxaban (HR, 1.05 [95% CI, 0.97–1.15]) or dabigatran (HR, 0.93 [95% CI, 0.78–1.11]). All-cause mortality was lower with apixaban than with VKAs, but not lower than with rivaroxaban or dabigatran. **Conclusion:** Apixaban was associated with superior safety, effectiveness, and lower mortality than VKAs. It was also associated with superior safety than rivaroxaban and similar safety to dabigatran along with similar effectiveness when compared with rivaroxaban or dabigatran. These observational data suggest potentially important differences in outcomes between direct oral anticoagulants, which should be explored in randomized trials.		
Citation	**Design**	**Endpoints**
Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of	Retrospective cohort analysis of data from the Truven Health MarketScan commercial and Medicare Supplement claims databases in the US to compare the effectiveness and	• Incidence of recurrent VTE (efficacy)

apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. Lancet Haematol. 2019;6(1):e20-e28.	safety of apixaban and rivaroxaban in prevention of recurrent VTE and major bleeding events in patients with VTE. Adult patients with newly diagnosed VTE (DVT or PE) who were new users of apixaban or rivaroxaban between January 2014 and December 2016. Patients who did not initiate the study drugs within 30 days of their diagnosis, those without 12 months of continuous enrolment in medical and pharmacy benefits, and those who used other anticoagulants during the baseline period were excluded. A total of 15, 254 patients were included in the cohort analysis (3,091 apixaban users and 12,163 rivaroxaban users).	• Incidence of major bleeding events (safety)
Results: The crude incidence of recurrent VTE was three per 100 person-years in the apixaban group and seven per 100 person-years in the rivaroxaban group. The incidence of major bleeding was three per 100 person-years in the apixaban group and six per 100 person-years in the rivaroxaban group. In multivariable Cox regression models, the use of apixaban compared with rivaroxaban was associated with decreased risk of recurrent VTE (HR, 0.37 [95% CI, 0.24-0.55]; p<0.0001) and major bleeding events (HR, 0.54 [95% CI, 0.37-0.82]; p=0.0031). **Conclusion:** Based on our findings, apixaban seems to be more effective than rivaroxaban in preventing the development of recurrent VTE and major bleeding events.		
Citation	**Design**	**Endpoints**
Lewis S, Glen J, Dawoud D, et al. Venous thromboembolism prophylaxis strategies for people undergoing elective total knee replacement: a systematic review and network meta-analysis. Lancet Haematol. 2019;6(10):e530-e539.	A systemic review and meta-analyses of RCTs to assess relative efficacy and safety of VTE prophylaxis strategies for people undergoing elective total knee replacement 25 RCTs (DVT, N=23; major bleeding, N=19; PE, N=12) were included.	Relative risk (RR) for the following outcomes of interest: • DVT (symptomatic and asymptomatic) • PE • Major bleeding
Results: For DVT, rivaroxaban (RR 0.12 [95% credible interval (CrI) 0.06-0.22]), followed by apixaban (RR 0.15[95% CrI 0.07-0.26]), then LMWH high prophylactic dose for standard duration (10-14 days; RR 0.18 [95% CrI 0.10-0.30]) were the top three interventions. For PE, LMWH at standard prophylactic dose for an extended duration (28-35 days; RR 0.02 [95% CrI 0.00-3.86]), followed by rivaroxaban (RR 0.08 [95% CrI 0.00-6.65]), then IPCDs (RR 0.20 [95% CrI 0.00-8.53]) were the top three interventions. For major bleeding, LMWH low prophylactic dose for standard duration (10-14 days; RR 0.08 [95% CrI 0.00-1.76], followed by LMWH at standard dose for an extended duration (28-35 days; RR 0.21 [95% CrI 0.00 10.41]), then VKA (RR 0.52 [95% CrI 0.08-2.89]) were the top three interventions for prevention. The major bleeding and PE results were determined to be highly uncertain. **Conclusion:** Single prophylaxis strategies are more effective in prevention of DVT in the elective total knee replacement population than combination strategies. Rivaroxaban ranked first for DVT prophylaxis in elective total knee replacement. There is no conclusive evidence on what treatment option is preferred for PE and major bleeding prophylaxis due to limited data.		
Citation	**Design**	**Endpoints**
Cohen AT, Hill NR, Luo X, et al. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: A comparison of efficacy and safety following treatment with direct oral anticoagulants. Int J Cardiol. 2018;269:174-181.	Systematic literature review that summarizes the evidence on stroke/SE bleeding events, mortality, and other adverse events from network meta-analyses (NMAs) that reported indirect comparisons of DOACs. Searches were conducted in PubMed, Embase, and the Cochrane Database of Systematic Reviews to identify NMAs published between January 2010 and March 2017. NMAs were eligible for inclusion if they included RCTs that evaluated stroke/SE and/or major bleeding and evaluated DOACs and VKAs. Patient populations in eligible NMAs were required to include ≥90% of patients with NVAF or	• Major bleeding • Stroke/SE • Mortality

	report results for NVAF populations separately. A total of 22 NMAs were included in the final summary.	
Results: No statistically significant differences were observed for apixaban compared with any DOAC in the NMAs that assessed stroke/SE. Apixaban was associated with a lower risk for major bleeding compared with rivaroxaban in 16 of 20 NMAs and dabigatran 150 mg in 13 of 16 NMAs. Four of 6 NMAs showed lower risk for GI bleeding for apixaban compared with rivaroxaban and dabigatran 150 mg; however, this outcome was not assessed by most NMAs. **Conclusion:** This systematic literature review of network meta analyses showed varying levels of bleeding risk among DOACs, with apixaban generally having a lower risk than rivaroxaban and dabigatran 150 mg.		
Citation	**Design**	**Endpoints**
Almutairi AR, Zhow L, Gellad WF, et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017 Jul;39(7):1456-1478.e36.	A systematic review and meta-analysis which examined efficacy and safety comparing DOACs and VKAs for AF and VTE. Both phase III randomized controlled trials and observational studies were simultaneously examined and analyzed comparative safety/efficacy by disease, study design, and individual DOAC agent. 13 RCTs and 27 observational studies (AF, N=32; VTE, N=8) were included.	• The primary outcomes were stroke/ SE for AF; recurrent VTE/fatal PE for VTE; and major bleeding for both conditions.
Results: A total of 13 RCTs and 27 observational studies (AF, n = 32; VTE, n = 8) were included. For AF, dabigatran and VKAs were comparable for stroke/SE risk in 1 RCT (HR, 0.77 [95% CI, 0.57-1.03]) and 6 observational studies (HR, 1.03 [95% CI, 0.83-1.27]). Rivaroxaban had a 20% decreased risk of stroke/SE in 3 RCTs (HR, 0.80 [95% CI, 0.67-0.95]) compared with VKA, but the effect was nonsignificant in 3 observational studies (HR, 0.78 [95% CI, 0.59-1.04]). Apixaban decreased stroke/SE risk (HR, 0.79 [95% CI, 0.66-0.95]) compared with VKA in 1 RCT, but edoxaban was comparable to VKA (HR, 0.99 [95% CI, 0.77-1.28]) in 1 RCT (no observational studies available for apixaban/edoxaban). Dabigatran, apixaban, and edoxaban decreased the risk of hemorrhagic stroke, mortality, major bleeding, and ICH by 10% to 71% compared with VKAs but not rivaroxaban. For VTE, NOACs and VKAs were comparable for recurrent VTE/fatal PE/DVT/PE risk in 7 RCTs and 1 observational study. The 7 RCTs demonstrated a 32% to 69% decreased risk of major bleeding for dabigatran, rivaroxaban, and apixaban compared with VKAs. No difference was shown in 1 rivaroxaban observational study (HR, 0.77 [95% CI, 0.40-1.49]) and 1 edoxaban RCT (HR, 0.84 [95% CI, 0.59-1.20]). Except for dabigatran, the NOACs had a 61% to 86% decreased risk of ICH and GI bleeding. **Conclusion**: DOACs and warfarin have similar efficacy and safety profiles. Data may slightly favor the DOAC agents, especially in regards to safety endpoints.		
Citation	**Design**	**Endpoints**
Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017 Nov 28;359:j5058.	A systematic review, network meta-analysis, and cost effectiveness analysis for DOACs for patients with AF. Phase II or III RCTs comparing either a DOAC, VKA, or antiplatelet regimen for prevention of stroke in NVAF were included. Trials including warfarin comparators were only included if study targets were within therapeutic ranges (INR 2.0-3.0). 23 randomized trials involving 94,656 patients were analyzed.	• Outcomes extracted included all stroke, stroke or SE, ischemic stroke, hemorrhagic stroke, myocardial infarction, all-cause mortality, all bleeding, minor bleeding, major bleeding, intracranial bleeding, GI bleeding, and clinically relevant bleeding.
Results: Apixaban 5 mg BID (odds ratio 0.79, 95% confidence interval 0.66 to 0.94), dabigatran 150 mg BID (0.65, 0.52 to 0.81), edoxaban 60 mg QD (0.86, 0.74 to 1.01), and rivaroxaban 20 mg QD (0.88, 0.74 to 1.03) reduced the risk of stroke or SE compared with warfarin. The risk of stroke or SE was higher with edoxaban 60 mg QD (1.33, 1.02 to 1.75) and rivaroxaban 20 mg QD (1.35, 1.03 to 1.78) than with dabigatran 150 mg BID. The risk of all-cause mortality was lower with all DOACs than with warfarin. Apixaban 5 mg BID (0.71, 0.61 to 0.81), dabigatran 110 mg BID (0.80, 0.69 to 0.93), edoxaban 30 mg QD (0.46, 0.40 to 0.54), and edoxaban 60 mg QD (0.78, 0.69 to 0.90) reduced the risk		

of major bleeding compared with warfarin. The risk of major bleeding was higher with dabigatran 150 mg BID than apixaban 5 mg BID (1.33, 1.09 to 1.62), rivaroxaban 20 mg BID than apixaban 5 mg BID (1.45, 1.19 to 1.78), and rivaroxaban 20 mg BID than edoxaban 60 mg QD (1.31, 1.07 to 1.59). The risk of intracranial bleeding was substantially lower for most DOACs compared with warfarin, whereas the risk of GI bleeding was higher with some DOACs than warfarin. Apixaban 5 mg BID was ranked the highest for most outcomes, and was cost effective compared with warfarin.
Conclusion: This SR/NMA suggests superior efficacy and safety profiles of most DOAC agents when compared directly to warfarin. Head-to-head trials comparing DOAC agents are needed.

Citation	Design	Endpoints
Eikelboom JW, Connolly SJ, Bosch J, et al. for the COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377:1319-1330.	A phase III, randomized, double-blind, controlled trial including 27,395 participants with stable atherosclerotic vascular disease which compared treatment with rivaroxaban 2.5 mg BID plus ASA 100 mg QD, rivaroxaban 5 mg BID, or 100 mg QD. In another randomized comparison (still ongoing), pantoprazole is being compared with placebo in patients participating in the trial who are not receiving a proton-pump inhibitor. Inclusion criteria: CAD or PAD, age ≥ 65 years, or age < 65 years and documented atherosclerosis or revascularization involving at least 2 vascular bets, or at least 2 additional risk factors. Exclusion criteria: need for dual antiplatelet therapy, other non-ASA antiplatelet therapy or oral anticoagulant therapy, stroke within 1 month or any history of hemorrhagic or lacunar stroke, severe heart failure with known ejection fraction <30% or New York Heart Association (NYHA) class III or IV symptoms, estimated glomerular filtration rate (eGFR)<15 mL/min.	• The primary efficacy outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The primary safety outcome was major bleeding occurrence.

Results: The study was stopped early due to superiority of the rivaroxaban + ASA arm. Rivaroxaban 2.5 mg BID + daily ASA 100 mg showed a significant 24% reduction of the risk of major CV events in patients with chronic CAD and/or PAD, compared to ASA alone. This finding was driven by a 42% reduction in stroke (significant), 22% reduction in CV death (significant) and 14% reduction in heart attack (not significant). The risk of major bleeding was significantly higher in patients taking the rivaroxaban/ASA regimen compared to ASA alone, with no significant increase in fatal or intracranial bleeds. Most of the major bleeding was into the GI tract. A reduction in composite MACE was shown with the rivaroxaban 5 mg dose, but was not statistically significant.
Conclusion: Rivaroxaban 2.5 mg BID plus daily ASA therapy showed significant benefits toward reducing patient risk of MACE including CV death in those with chronic, stable CAD/PAD.

Citation	Design	Endpoints
Weitz JI, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism for the EINSTEIN CHOICE Investigators. N Engl J Med 2017; 376(13):1211-1222.	Randomized, double-blind, phase III study enrolled 3,396 participants were randomized to receive either once-daily rivaroxaban (at 10 or 20 mg) or ASA 100 mg. Inclusion criteria: Adult patients with symptomatic proximal DVT or PE; had been treated for 6 to 12 months with an anticoagulant agent, including a vitamin K antagonist or a direct oral anticoagulant agent such as dabigatran, rivaroxaban, apixaban, or edoxaban; and had not interrupted therapy for more than 7 days before randomization. Exclusion criteria: contraindication to continued anticoagulant therapy or if they required extended anticoagulant therapy at therapeutic doses or antiplatelet therapy, CrCl < 30 ml/min, hepatic disease with coagulopathy.	• Primary efficacy outcome was symptomatic recurrent fatal or nonfatal VTE. The principal safety outcome was major bleeding.

Results: The primary efficacy outcome occurred in 17 of 1107 patients (1.5%) receiving 20 mg of rivaroxaban and in 13 of 1127 patients (1.2%) receiving 10 mg of rivaroxaban, as compared with 50 of 1131 patients (4.4%) receiving ASA (hazard ratio for 20 mg of rivaroxaban vs. ASA, 0.34; 95% CI, 0.20 to 0.59; hazard ratio for 10 mg of rivaroxaban vs. ASA, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Rates of major bleeding were 0.5% in the group receiving 20 mg of rivaroxaban, 0.4% in the group receiving 10 mg of rivaroxaban, and 0.3% in the ASA group; the rates of clinically relevant non-major bleeding were 2.7%, 2.0%, and 1.8%, respectively. The incidence of adverse events was similar in all three groups. **Conclusion:** Among patients with VTE needing continued anticoagulation, the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with ASA, without a significant increase in bleeding rates.		
Citation	**Design**	**Endpoints**
Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764.	Randomized, double-blind, double-dummy trial included 2589 patients with acute VTE treated with LMWH or unfractionated heparin for 5-11 days. Dabigatran 150 mg BID was compared with warfarin in these patients. Inclusion Criteria: Adults with acute, symptomatic, objectively verified proximal DVT of the legs or PE and for whom 6 months of anticoagulant therapy was considered to be an appropriate treatment. Exclusion Criteria: duration of symptoms longer than 14 days, PE with hemodynamic instability or requiring thrombolytic therapy, another indication for warfarin therapy, recent unstable cardiovascular disease, a high risk of bleeding, liver disease, CrCl < 30 ml/min, a life expectancy of less than 6 months, a contraindication to heparin, pregnancy or risk of becoming pregnant, or a requirement for long-term antiplatelet therapy.	• The primary outcome was recurrent symptomatic VTE and related deaths during 6 months of treatment. The safety endpoint was major bleeding.
Results: The primary efficacy outcome occurred in 30 patients (2.3%) treated with dabigatran compared with 28 patients (2.2%) treated with warfarin. Major bleeding occurred in 15 patients (1.2%) treated with dabigatran and 22 patients (1.7%) treated with warfarin. **Conclusion:** Dabigatran has similar effects on VTE recurrence and lower risk of bleeding in comparison to warfarin.		
Citation	**Design**	**Endpoints**
Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799.	Randomized, double-blind study included 5,395 patients with acute VTE and compared apixaban (10 mg BID for 7 days, followed by 5 mg BID for 6 months) to conventional therapy with enoxaparin followed by warfarin. Inclusion Criteria: Adults with confirmed, symptomatic proximal DVT or PE (with or without DVT). Exclusion Criteria: Active bleeding or a high risk of bleeding; if they had cancer and long-term treatment with low-molecular-weight heparin was planned; if less than 6 months of anticoagulant treatment was planned; or if they had another indication for long-term anticoagulation therapy, dual antiplatelet therapy, treatment with ASA at a dose of more than 165 mg daily, or treatment with potent inhibitors of cytochrome P-450 3A4.	• The primary efficacy outcome was recurrent symptomatic VTE or death related to VTE. Primary safety outcomes were major bleeding alone and major bleeding plus clinically relevant non-major bleeding.
Results: Primary efficacy outcome occurred in 59 of 2,609 patients (2.3%) in the apixaban group compared with 71 of 2,635 (2.7%) in the conventional therapy group. Apixaban was non-inferior to conventional therapy. Major bleeding occurred in 0.6% of patients using apixaban compared to 1.8% of patients using conventional therapy.		

The composite outcome of major bleeding and clinically relevant non-major bleeding occurred in 4.3% of the patients treated with apixaban compared with 9.7% of those in the conventional-therapy group. **Conclusion**: Apixaban alone was non-inferior to conventional therapy for the treatment of acute VTE. Apixaban was associated with significantly less major bleeding than conventional therapy.		
Citation	**Design**	**Endpoints**
Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406.	Randomized, double-blind, non-inferiority study of 4,921 patients with DVT and 3,319 patients with PE, who were initially treated with heparin, were randomly assigned to receive edoxaban (60 mg daily or 30 mg daily) or to receive warfarin. Inclusion Criteria: Adult patients with objectively diagnosed, acute, symptomatic DVT involving the popliteal, femoral, or iliac veins or acute, symptomatic PE (with or without DVT). Exclusion Criteria: contraindications to heparin or warfarin, cancer for which long-term treatment with low-molecular-weight heparin was anticipated, had another indication for warfarin therapy, continued to receive treatment with ASA at a dose of more than 100 mg daily or dual antiplatelet therapy, or had CrCl < 30 mL/min.	• The primary efficacy outcome was recurrent symptomatic VTE. The primary safety outcome was major or clinically relevant non-major bleeding.
Results: Edoxaban was non-inferior to warfarin regarding the primary efficacy outcome. The primary efficacy outcome occurred in 130 patients (3.2%) receiving edoxaban and in 146 patients (3.5%) receiving warfarin. The safety outcome occurred in 349 patients (8.5%) in the edoxaban group and 423 patients (10.3%) in the warfarin group. **Conclusion:** Edoxaban administered after heparin was non-inferior to standard therapy with warfarin. Edoxaban was associated with significantly less bleeding.		
Citation	**Design**	**Endpoints**
EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287. Epub 2012 Mar 26.	Randomized, open-label, event-driven, non-inferiority trial included 4,832 with acute symptomatic PE with or without DVT. The study compared rivaroxaban (15 mg BID for 3 weeks followed by 20 mg daily) with standard therapy of enoxaparin followed by VKA for 3, 6, or 12 months. Inclusion criteria: cute, symptomatic, objectively confirmed proximal DVT, without symptomatic PE. Exclusion criteria: another indication for a vitamin K antagonist; a CrCl < 30 mL/min; clinically significant liver disease; bacterial endocarditis; active bleeding or a high risk of bleeding, contraindicating anticoagulant treatment; systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breast-feeding; concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers.	• The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was major or clinically relevant non-major bleeding.
Results: Rivaroxaban was non-inferior to standard therapy for the primary efficacy outcome with 50 events vs. 44 events. The primary safety outcome occurred in 10.3% of patients in the rivaroxaban group compared with 11.4% of those in the standard-therapy group. Major bleeding was observed in 26 patients (1.1%) treated with rivaroxaban and 52 patients (2.2%) treated with standard-therapy. **Conclusion**: Rivaroxaban alone was non-inferior to standard therapy for both initial and long-term treatment of PE and demonstrated potentially improved benefit-risk profile.		
Citation	**Design**	**Endpoints**

ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883. Epub 2011 Aug 10.	Double-blind randomized trial of 14,264 patients with NVAF and at increased risk of stroke were randomized to receive rivaroxaban 20 mg daily or dose-adjusted warfarin. Per-protocol, as-treated primary analysis was designed to determine if rivaroxaban was non-inferior to warfarin for the primary endpoint of stroke or SE. Inclusion Criteria: Adults with NVAF, as documented on electrocardiography, who were at moderate-to-high risk for stroke. Exclusion Criteria: Prosthetic heart valve, planned cardioversion, active endocarditis, active bleeding, planned invasive procedure, sustain uncontrolled hypertension, treatment with ASA > 100 mg daily, indication for anticoagulant therapy for other condition.	• Primary endpoint was occurrence of stroke or SE.
Results: The primary endpoint occurred in 188 patients (1.7% per year) in the rivaroxaban-treated group and 241 patients (2.2% per year) in the warfarin-treated group. Major and non-major clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year). There were significant reductions in intracranial hemorrhage (0.5% vs 0.7%) and fatal bleeding (0.2% vs 0.5%) in the rivaroxaban treated group. **Conclusion:** Rivaroxaban was non-inferior to warfarin for prevention of stroke and SE in patients with AF. There were no significant differences between groups in the risk of major bleeding. Intracranial and fatal bleeding occurred less frequently in rivaroxaban group.		
Citation	**Design**	**Endpoints**
ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981.	Randomized, double-blind trial, compared apixaban (5 mg BID) with warfarin in 18,201 patients with AF and at least one additional risk factor for stroke. The trial was designed to test non-inferiority. It tested superiority of the primary outcome and rates of major bleeding and deaths. Inclusion Criteria: Adults with AF or flutter plus at least one additional risk factor for stroke. Exclusion criteria: AF due to a reversible cause, moderate or severe MS, conditions other than AF that required anticoagulation, stroke within the previous 7 days, a need for ASA at a dose of >165 mg a day or for both ASA and clopidogrel, and severe renal insufficiency.	• Primary outcome was ischemic or hemorrhagic stroke or SE.
Results: The rate of primary outcome was 1.27% per year in the apixaban group compared with 1.60% per year in the warfarin group. The rate of major bleeding was 2.13% per year in the apixaban group compared with 3.09% per year in the warfarin group. The rate of hemorrhagic stroke was 0.24% per year in the apixaban group compared with 0.47% per year in the warfarin group. Rate of ischemic or uncertain type of stroke was 0.97% per year in apixaban group and 1.05% per year in the warfarin group. **Conclusion:** In patients with AF, apixaban was superior to warfarin in preventing stroke or SE.		
Citation	**Design**	**Endpoints**
EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499.	Open-label, randomized, event-driven, non-inferiority study included 3,449 patients and compared oral rivaroxaban alone (15 mg BID for 3 weeks followed by 20 mg daily) with subcutaneous enoxaparin followed by a vitamin k antagonist for 2, 5 or 12 months in patients with acute symptomatic DVT. In parallel, a double-blind, randomized, event-driven superiority trail compared rivaroxaban alone (20 mg QD) with placebo for an additional 6 or 12 months in patients who completed 6 or 12 months of treatment.	• Primary efficacy outcome was recurrent VTE. Primary safety outcomes were major bleeding or clinically relevant non-major bleeding in the initial-treatment study and major bleeding in the continued-treatment study.

	Inclusion criteria: acute, symptomatic, objectively confirmed proximal DVT, without symptomatic PE. Exclusion criteria: another indication for a vitamin K antagonist; a CrCl < 30 mL/min; clinically significant liver disease; bacterial endocarditis; active bleeding or a high risk of bleeding, contraindicating anticoagulant treatment; systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg; childbearing potential without proper contraceptive measures, pregnancy, or breast-feeding; concomitant use of strong cytochrome P-450 3A4 inhibitors or inducers.	
Results: Rivaroxaban had non-inferior efficacy with respect to the primary outcome (36 events vs. 51 events with enoxaparin-VKA). The primary safety outcome occurred in 8.1% of the patients in each group. In the continued-treatment study, rivaroxaban showed superior efficacy compared to placebo with 8 events vs. 42 events with placebo. **Conclusion**: Rivaroxaban is a single-drug approach to both short term and continued treatment of VTE.		

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (10/1/2023 - 12/31/2023)

Medication	Rx	Mbrs	Total	Avg/Rx	Total	Approved (%)	Current	Recommend
Factor Xa Inhibitors								
Eliquis® (apixaban) 2.5 mg, 5 mg tablets	63	23	$34,506.84	$547.73	0	0 (0%)	F-QL (60/30)	No change
Eliquis® (apixaban) 5 mg tablet dose pack	0	0	$0.00	$0.00	0	0 (0%)	F-QL (74/30)	No change
Xarelto® (rivaroxaban) 2.5 mg, 10 mg, 15 mg, 20 mg tablets	34	15	$19,976.35	$587.54	0	0 (0%)	2.5mg & 15mg: F-QL (60/30) 10mg & 20mg: (30/30)	No change
Xarelto® (rivaroxaban) 15 mg-20 mg tablet dose pack	0	0	$0.00	$0.00	0	0 (0%)	F-QL (51/30)	No change
Xarelto® (rivaroxaban) 1 mg/ml oral suspension	0	0	$0.00	$0.00	0	0 (0%)	F-QL (600/30)	No change
Savaysa® (edoxaban) 15 mg, 30 mg, 60 mg tablets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Direct Thrombin Inhibitors								
Dabigatran (Pradaxa®) 75 mg, 150 mg capsules	3	1	$497.36	$165.79	0	0 (0%)	(Brand & Generic) F-QL (60/30)	**Change brand to NF**
Pradaxa® (dabigatran) 110 mg capsules	0	0	$0.00	$0.00	0	0 (0%)	F-QL (60/30)	No change
Pradaxa® (dabigatran) 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg pellet packets	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
TOTAL	**100**	**39**	**$54,980.55**	**$549.81**	**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. Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc.; November, 2023.
2. Xarelto (rivaroxaban) [prescribing information]. Titusville, NJ: Janssen Pharmaceuticals Inc.; February, 2023.
3. Eliquis (apixaban) [prescribing information]. Princeton, NJ: Bristol-Myers Squibb; October, 2021.
4. Savaysa (edoxaban) [prescribing information]. Parsippany, NJ: Daiichi Sankyo; October, 2023.
5. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the chest guideline and expert panel report. Chest. 2021;160(6):e545-e608.
6. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201. doi: 10.1016/j.chest.2018.07.040.
7. Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in Orthopedic Surgery Patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e278S-e325S. doi: 10.1378/chest.11-2404.
8. Maarten GL, O'Donnell MJ, Khatri P, et al. Antithrombotic and Thrombolytic Therapy for Ischemic Stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2):e601S-e636S. doi: 10.1378/chest.11-2302.
9. Key NS, Khorana AA, Kuderer NM, et al. Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: ASCO Clinical Practice Guideline Update. Journal of Clinical Oncology. 2019 Aug 5. doi: 10.1200/JCO.19.01461
10. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019 Jul 9;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665.
11. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143(5):e35-e71. doi: 10.1161/CIR.0000000000000960.
12. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4(19):4693-4738. doi: 10.1182/bloodadvances.2020001830.
13. Witt DM, Nieuwlaat R, Clark NP, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv (2018) 2 (22): 3257-3291. doi: 10.1182/bloodadvances.2018024893.
14. Anderson DR, Morgano GP, Bettett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv (2019) 3 (23): 3898–3944. https://doi.org/10.1182/bloodadvances.2019000975.
15. Schünemann HJ, Cushman M, Burnett AE, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv (2018) 2 (22): 3198-3225. doi: 10.1182/bloodadvances.2018022954.
16. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26; 336(7650): 924–926. doi: 10.1136/bmj.39489.470347.AD.
17. Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008 May 3; 336(7651): 995–998. doi: 10.1136/bmj.39490.551019.BE.
18. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ. 2008 May 10; 336(7652): 1049–1051. doi: 10.1136/bmj.39493.646875.AE.
19. Ingason AB, Hreinsson JP, Ágústsson AS, et al. Rivaroxaban is associated with higher rates of gastrointestinal bleeding than other direct oral anticoagulants : a nationwide propensity score-weighted study. Ann Intern Med. 2021;174(11):1493-1502.
20. Van Ganse E, Danchin N, Mahé I, et al. Comparative safety and effectiveness of oral anticoagulants in nonvalvular atrial fibrillation: the NAXOS study. Stroke. 2020;51(7):2066-2075.
21. Dawwas GK, Brown J, Dietrich E, Park H. Effectiveness and safety of apixaban versus rivaroxaban for prevention of recurrent venous thromboembolism and adverse bleeding events in patients with venous thromboembolism: a retrospective population-based cohort analysis. Lancet Haematol. 2019;6(1):e20-e28.
22. Lewis S, Glen J, Dawoud D, et al. Venous thromboembolism prophylaxis strategies for people undergoing elective total knee replacement: a systematic review and network meta-analysis. Lancet Haematol. 2019;6(10):e530-e539.
23. Cohen AT, Hill NR, Luo X, et al. A systematic review of network meta-analyses among patients with nonvalvular atrial fibrillation: A comparison of efficacy and safety following treatment with direct oral anticoagulants. Int J Cardiol. 2018;269:174-181.
24. Eikelboom JW, Connolly SJ, Bosch J, et al. for the COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017; 377:1319-1330. DOI: 10.1056/NEJMoa1709118.
25. Weitz JI, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism for the EINSTEIN CHOICE Investigators. N Engl J Med 2017; 376(13):1211-1222.
26. Almutairi AR, Zhow L, Gellad WF, et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017 Jul;39(7):1456-1478.e36. doi: 10.1016/j.clinthera.2017.05.358.

27. Lopez-Lopez JA, Sterne JAC, Thom HHZ, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017 Nov 28;359:j5058. doi: 10.1136/bmj.j5058.
28. EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med. 2012;366(14):1287. Epub 2012 Mar 26.
29. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799.
30. Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(15):1406.
31. Schulman S, Kakkar AK, Goldhaber SZ et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. Circulation. 2014;129(7):764.
32. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883. Epub 2011 Aug 10.
33. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981.
34. Biomedtracker. Cambridge, MA: Informa Business Intelligence, Inc. https://www.biomedtracker.com/. Accessed on December 11, 2023.
35. IPD Analytics. Bay Harbor Islands, Florida: IPD Analytics, LLC. http://www.ipdanalytics.com. Accessed on December 11, 2023.
36. Leung LK. Direct oral anticoagulants and parenteral direct thrombin inhibitors: Dosing and adverse effects. Up to Date. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on December 11, 2023.
37. Garcia DA, Crowther M. Management of bleeding in patients receiving direct oral anticoagulants. Up to Date. Waltham, MA: UpToDate Inc. http://www.uptodate.com. Accessed on December 11, 2023.

PERFORMRx℠

Sodium-glucose Transporter-2 (SGLT2) Inhibitors

Therapeutic Class Review

CLASS OVERVIEW

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by hyperglycemia due to insulin resistance and impairment in insulin secretion. Treatment of T2DM should always consider diet, exercise, weight loss, education, glycemic control, avoidance of drugs that aggravate insulin abnormalities, minimization of long term cardiovascular risk factors, and evaluation of micro- and macrovascular complications. Diet and lifestyle changes can help improve these metabolic parameters, but pharmacologic intervention is usually necessary for adequate control. The 2023 American Diabetes Association (ADA) guidelines recommend a patient-centered approach to pharmacologic therapy that considers cardiovascular comorbidities, hypoglycemia risk, patient weight, cost, risk for adverse effects, and patient preference. The guidelines also recommend a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated cardiovascular disease benefit for individuals with T2DM who have established atherosclerotic cardiovascular disease (ASCVD) or indicators of high cardiovascular risk, established kidney disease, or heart failure (HF), as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of patient-specific factors.

HF results from structural or functional cardiac abnormalities that impair ventricular ability to fill with or eject blood. HF may be caused by disease of the heart valves, vessels, myocardium, pericardium, endocardium, or metabolic disorders. Approximately 6 million individuals in the US are living with HF. The prevalence has increased owing to an aging population and medical interventions prolonging the life span of cardiac patients. The mainstays of treatment for HF with reduced ejection fraction (HFrEF) have long included a diuretic, a beta-blocker (BB), and a renin-angiotensin system (RAS) inhibitor (i.e., angiotensin converting enzyme inhibitor [ACEi], angiotensin II receptor blocker [ARB], or angiotensin receptor-neprilysin inhibitor [ARNI]). Due to recently published evidence, the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) guidelines now recommend SGLT2 inhibitors in patients with symptomatic chronic HfrEF to reduce hospitalization for HF (HHF) and cardiovascular mortality, irrespective of the presence of T2DM. They also state that SGLT2 inhibitors may be beneficial in decreasing HHF and cardiovascular mortality in patients with HF with preserved ejection fraction (HfpEF).

SGLT2 inhibitors have a glucosuric effect that reduces HbA1C, weight, systolic blood pressure and are increasingly being favored over other therapies for treating diabetes and HF. Empagliflozin (Jardiance®) and canagliflozin (Invokana®) have been shown to reduce major adverse cardiac events (MACE; cardiovascular morbidity and mortality, myocardial infarction, stroke), improve renal outcomes (end stage renal disease, doubling of serum creatinine, or death from renal or cardiovascular causes), and reduce HHF in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD). Dapagliflozin (Farxiga®) improves HHF and renal outcomes but was not shown to improve MACE. When added to the standard of care, Farxiga® was shown to reduce the risk of CV death and hospitalization for adults with NYHA functional class II-IV HfrEF, regardless of diabetes status. However, in May of 2023, the FDA expanded Farxiga's indication to reduce the risk of CV death and hospitalization for adults with all classifications of HF, including heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). Given the new approved indication, Farxiga® and Jardiance® have demonstrated efficacy in both HFrEF and HFpEF. Invokana® did not provide adequate evidence of benefit in HF to receive this indication. Ertugliflozin (Steglatro®) was not shown to improve MACE or renal outcomes but had a significant reduction in HHF.

As of 2023, two new SGLT2 inhibitors were approved by the FDA. Bexagliflozin (Brenzavvy®) was approved in the beginning of 2023 as clinical trials have provided adequate results in its significant reduction of HbA1c for adults with T2DM. Later in the year, sotagliflozin (Inpefa®) was approved for reduction of CV death and hospitalization for adults with T2DM, chronic kidney disease (CKD), and other cardiovascular risk factors. The authorized generics for Farxiga and selected strengths of Xigduo XR were released in January 2024. Clinical trials have also demonstrated efficacy in its reduction of CV death and hospitalization for patients with HF. Due to the recent approvals, Brenzavvy® and Inpefa® have not been recommended in current guidelines. This review covers SGLT2 inhibitors used for the treatment of diabetes, kidney disease, and HF.

UTILIZATION FINDINGS

There were 168 claims for 80 members, for a total cost of $70,814 and an average cost per claim of $432. The most highly utilized medication was Steglatro, with 106 claims, followed by Farxiga with 28 claims, and Jardiance with 27 claims. There were 22 prior authorizations with 12 approvals (55%).

RECOMMENDATIONS

- Change to F-ST (trial and failure of one of the following: metformin, branded/generic drugs containing metformin, branded ARNi, generic ACEi, generic ARB, generic mineralocorticoid receptor antagonists (MRAs) or generic beta blockers)
    - Steglatro and Segluromet currently at F-ST (trial and failure of metformin containing products) status, will have additional drugs added as step therapy options: branded ARNi, generic ACEi, generic ARB, generic mineralocorticoid receptor antagonists (MRAs) or generic beta blockers
        - Steglatro® (ertugliflozin) 5, 15 mg oral tablet
        - Segluromet® (ertugliflozin-metformin) 2.5 mg-500 mg, 2.5 mg-1,000 mg, 7.5 mg-500 mg, 7.5 mg-1,000 mg oral tablet
    - The medications below will change from F-PA to F-ST (trial and failure of one of the following: metformin, branded/generic drugs containing metformin, branded ARNi, generic ACEi, generic ARB, generic mineralocorticoid receptor antagonists (MRAs) or generic beta blockers):
        - Farxiga® (dapagliflozin) 5, 10 mg oral tablet (brand)
        - Xigduo® XR (dapagliflozin and metformin extended release) 2.5 mg-1,000 mg, 5 mg-500 mg, 5 mg-1,000 mg, 10 mg-500 mg, 10 mg-1,000 mg oral tablet (brand)
            - A point-of-sale message will be added notifying pharmacies that the brands are preferred.
- Change from F-ST (trial and failure of metformin) to F-PA
    - Steglujan® (ertugliflozin-sitagliptin) 5 mg-100 mg, 15 mg-100 mg oral tablet
        - There is no current utilizations of this product

CLINICAL SUMMARY

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by hyperglycemia due to insulin resistance and impairment in insulin secretion. This is due to damage and destruction of pancreatic beta islet cells caused by both genetic and environmental factors and is often accompanied by multiple comorbidities including hypertension, elevated cholesterol, and increased cardiovascular risk. The most common symptoms of T2DM are increased thirst, frequent urination, and increased hunger, however, long-term metabolic effects can lead to both macrovascular and microvascular complications. This may include blurred vision/vision loss, nerve damage, kidney damage, hearing impairment, and cardiovascular disease.

Treatment of T2DM should always consider diet, exercise, weight loss, education, glycemic control, avoidance of drugs that aggravate insulin abnormalities, minimization of long term cardiovascular risk factors, and evaluation of micro- and macrovascular complications. Treatment goals are set for glycemic, blood pressure, and lipid control. Diet and lifestyle changes can help improve these metabolic parameters, but pharmacologic intervention is usually necessary for adequate control. The 2023 American Diabetes Association (ADA) guidelines recommend a patient-centered approach to pharmacologic therapy that considers cardiovascular comorbidities, hypoglycemia risk, patient weight, cost, risk for adverse effects, and patient preference. The guidelines also recommend a sodium–glucose cotransporter 2 (SGLT2) inhibitor or glucagon-like peptide 1 (GLP-1) receptor agonist with demonstrated cardiovascular disease benefit for individuals with T2DM who have established atherosclerotic cardiovascular disease (ASCVD) or indicators of high cardiovascular risk, established kidney disease, or heart failure (HF), as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of patient-specific factors. The ADA goals for glycemic control are an A1C <7%, with preprandial and postprandial plasma glucose of 70 to 130 mg/dL and <180 mg/dL, respectively. The ACE and AACE have set lower target values, with an A1C of ≤6.5%, and preprandial and postprandial plasma glucose of <110 mg/dL and <140 mg/dL, respectively. Hemoglobin (A1C) should be monitored twice a year in patients that have met glycemic goals and quarterly in patients who have either not met goals or have had changes in therapy. Target A1C levels should be individualized and must consider hypoglycemic risk with complications.

Metformin is first-line for most patients. For patients with established cardiovascular disease, a glucagon like peptide-1 (GLP-1) receptor agonist with proven cardiovascular disease (CVD) benefit is preferred but can be substituted for a sodium-glucose transporter-2 (SGLT2) inhibitor if kidney function is adequate. GLP-1 receptor agonists including liraglutide (Victoza®), semaglutide (Ozempic®, Rybelsus®), and dulaglutide (Trulicity®) were shown in clinical trials to reduce the composite of major cardiovascular events including death from cardiovascular causes, nonfatal myocardial infarction, or non-fatal stroke. For patients with HF or chronic kidney disease (CKD), an SGLT2 inhibitor with evidence of reducing HF and/or CKD progression is preferred but can be substituted with a GLP-1 receptor agonist with proven CVD benefit if an SGLT2 inhibitor is not tolerated or kidney function is inadequate. If weight gain is of concern or weight loss is required, a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor should be added to metformin. If cost is of the highest concern, a sulfonylurea or thiazolidinedione is preferred after trial of metformin. If the patient does not have these specified comorbidities, any antihyperglycemic is preferred after trial of metformin. SGLT2 inhibitors are available in single-drug formulations or in combination with a dipeptidyl peptidase-4 inhibitor and/or metformin.

HF results from structural or functional cardiac abnormalities that impair ventricular ability to fill with or eject blood. HF may be caused by disease of the heart valves, vessels, myocardium, pericardium, endocardium, or metabolic disorders. Approximately 6 million individuals in the US are living with HF. The prevalence has increased owing to an aging population and medical interventions prolonging the life span of cardiac patients. HF due to left ventricular (LV) dysfunction is categorized according to LV ejection fraction (LVEF). HF with reduced ejection fraction (HFrEF) is defined as LVEF ≤40%; HF with preserved ejection fraction (HFpEF) is defined as LVEF ≥50%. Approximately 10-24% of patients will have HF with mid-range ejection fraction (HFmrEF), or LVEF 41-49%; the remaining patients are approximately

evenly distributed between HFrEF and HFpEF. The primary goals of HF therapy are to reduce morbidity by improving quality of life and functional status and reducing symptoms, decrease hospitalization, and reduce mortality.

The American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) classify HF as stage A, B, C, or D considering both structural disease and symptoms in an effort to guide therapy decisions.

- Stage A are those patients at risk for HF but without structural heart disease or symptoms of HF.
- Stage B are those patients with structural heart disease but without signs or symptoms of HF.
- Stage C are those patients with structural heart disease with prior or current symptoms of HF.
- Stage D are those patients with symptoms of HF that interfere with daily life.

New York Heart Association (NYHA) has published a functional classification of heart disease. Because it focuses on symptoms, it is essentially limited to categorizing patients in ACC/AHA/HFSA stages C and D HF. A patient may move between classes as symptoms wax and wane.

- Class I: No limitations of physical activity. Ordinary physical activity does not cause fatigue, dyspnea, or palpitations.
- Class II: Slight limitation of physical activity and comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (mild CHF).
- Class III: Marked limitation of physical activity and comfortable at rest. Less than ordinary physical activity leads to symptoms (moderate CHF).
- Class IV: Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).

The mainstays of treatment for HFrEF have long included a diuretic, a beta-blocker (BB), and a renin-angiotensin system (RAS) inhibitor (i.e., angiotensin converting enzyme inhibitor [ACEi], angiotensin II receptor blocker [ARB], or angiotensin receptor-neprilysin inhibitor [ARNI]). Due to recently published evidence, the 2022 AHA/ACC/HFSA guidelines now recommend SGLT2 inhibitors in patients with symptomatic chronic HFrEF to reduce hospitalization for HF (HHF) and cardiovascular mortality, irrespective of the presence of T2DM. They also state that SGLT2 inhibitors may be beneficial in decreasing HHF and cardiovascular mortality in patients with HFpEF. Diuretics are used to treat volume overload and improve symptoms but have not demonstrated a survival benefit. Secondary therapy, used on the basis of patient-specific indications, includes mineralocorticoid receptor agonists (MRA), Corlanor (ivabradine), Verquvo (vericiguat), Entresto (sacubitril/valsartan), hydralazine plus nitrate, and digoxin.

SGLT2 inhibitors have a glucosuric effect that reduces HbA1C, weight, systolic blood pressure and are increasingly being favored over other therapies for treating diabetes and HF. Empagliflozin (Jardiance®) and canagliflozin (Invokana®) have been shown to reduce major adverse cardiac events (MACE; cardiovascular morbidity and mortality, myocardial infarction, stroke), improve renal outcomes (end stage renal disease, doubling of serum creatinine, or death from renal or cardiovascular causes), and reduce HHF in patients with T2DM and established atherosclerotic cardiovascular disease (ASCVD). Dapagliflozin (Farxiga®) improves HHF and renal outcomes but was not shown to improve MACE. When added to the standard of care, Farxiga® was shown to reduce the risk of CV death and hospitalization for adults with NYHA functional class II-IV HFrEF, regardless of diabetes status. However, in May of 2023, the FDA expanded Farixga's indication to reduce the risk of CV death and hospitalization for adults with all classifications of HF, including heart failure with mildly reduced ejection fraction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF). Given the new approved indication, Farxiga® and Jardiance® have demonstrated efficacy in both HFrEF and HFpEF.. Invokana® did not provide adequate evidence of benefit in HF to receive this indication. Ertugliflozin (Steglatro®) was not shown to improve MACE or renal outcomes but had a significant reduction in HHF and is also under investigation (phase II) for HFrEF and HFpEF.

As of 2023, two new SGLT2 inhibitors were approved by the FDA. Bexagliflozin (Brenzavvy®) was approved in the beginning of 2023 as clinical trials have provided adequate results in its significant reduction of HbA1c for patients with T2DM. Later in the year, sotagliflozin (Inpefa®) was approved for reduction of CV death and hospitalization for adults with T2DM, chronic kidney disease (CKD), and other cardiovascular risk factors. Clinical trials have also demonstrated efficacy in its reduction of CV death and hospitalization for patients with HF. Due to the recent approvals, Brenzavvy® and Inpefa® have not been recommended in current guidelines.

INDICATIONS, DOSING and ADMINISTRATION

Medication	Indications	Dosing/Administration
SGLT-2 Inhibitor Monotherapy		
Farxiga® (dapagliflozin) 5, 10 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. • To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors. • To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure. • To reduce the risk of sustained eGFR decline, end stage kidney disease cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.	• Diabetes mellitus, type 2, treatment: ○ Hyperglycemia: Initial: 5 mg once daily; may increase to 10 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals ○ Heart failure and/or patients with or at risk for ASCVD: 10 mg once daily ○ Diabetic kidney disease (off-label): 5 mg once daily in patients with urinary albumin excretion >300 mg/day • Heart failure with reduced ejection fraction (HFrEF): 10 mg once daily • Chronic Kidney disease: 10 mg once daily
Invokana® (canagliflozin) 100, 300 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease • To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria	• Diabetes mellitus, type 2, treatment: ○ Hyperglycemia: Initial: 100 mg once daily prior to first meal of the day; may increase to 300 mg once daily after 4 to 12 weeks if needed to achieve glycemic goals ○ Atherosclerotic cardiovascular disease (ASCVD): 100 or 300 mg once daily ○ Diabetic kidney disease: 100 mg once daily prior to the first meal of the day in patients with urinary albumin excretion >300 mg/day; no further dose titration is necessary for renal benefit.
Jardiance® (empagliflozin) 10, 25 mg oral tablet	• To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. • To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. • To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression • As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients ≥ 10 years of age with type 2 diabetes mellitus.	• Diabetes mellitus, type 2, treatment: ○ Hyperglycemia: Initial: 10 mg once daily; may increase to 25 mg once daily if needed to achieve glycemic goals ○ ASCVD: 10 or 25 mg once daily ○ HF: 10 mg once daily • HF: 10 mg once daily
Steglatro® (ertugliflozin) 5, 15 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults	• Diabetes mellitus, type 2, treatment: Initial: 5 mg once daily; may increase to

Medication	Indications	Dosing/Administration
	with type 2 diabetes mellitus.	15 mg once daily (maximum: 15 mg/day).
Brenzavvy® (bexagliflozin) 20 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	• Diabetes mellitus, type 2, treatment: 20 mg once daily in the morning.
Inpefa® (Sotagliflozin) 200 mg oral tablet	• To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with type 2 diabetes, chronic kidney disease, and other cardiovascular risk factors. • To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visits in adults with heart failure.	• Cardiovascular risk reduction: Initial: 200 mg once daily not more than 1 hour before first meal of the day; may increase to 400 mg daily after ≥ 2 weeks; may decrease to 200 mg daily as necessary based on tolerability. • Cardiovascular risk reduction: Initial: 200 mg once daily not more than 1 hour before first meal of the day; may increase to 400 mg daily after ≥ 2 weeks; may decrease to 200 mg daily as necessary based on tolerability.
Combination SGLT-2 Inhibitors/metformin		
Xigduo® XR (dapagliflozin and metformin extended release) 2.5 mg-1,000 mg, 5 mg-500 mg, 10 mg-500 mg, 5 mg-1,000 mg, 10 mg-1,000 mg oral tablet	• To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. • To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction. • To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.	• Diabetes mellitus, type 2, treatment: ○ Initial: Dosing range: dapagliflozin 5 mg/metformin 500 mg once daily to dapagliflozin 10 mg/metformin 2 g once daily. Maximum: dapagliflozin 10 mg/metformin 2 g once daily. ○ Risk reduction of hospitalization for heart failure: Dapagliflozin 10 mg once daily plus appropriate dose of metformin. Maximum: Dapagliflozin 10 mg/metformin 2 g once daily.
Invokamet® (canagliflozin-metformin) 50 mg-500 mg, 50 mg-1,000 mg, 150 mg-500 mg, 150 mg-1,000 mg oral tablet Invokamet® XR (canagliflozin-metformin extended release) 50 mg-500 mg, 50 mg-1,000 mg, 150 mg-500 mg, 150 mg-1,000 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease • To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria	• Diabetes mellitus, type 2, treatment: ○ Patients naive to canagliflozin or metformin: Initial: Canagliflozin 100 mg/metformin 1 g per day in 2 divided doses (immediate release) or once daily (extended release). ○ Patients on metformin: Initial: Canagliflozin 100 mg/day plus similar total daily dose of metformin in 2 divided doses (immediate release) or once daily (extended release). Patients taking an evening dose of metformin extended release should skip their last dose before starting canagliflozin/metformin extended release the following morning. ○ Patients on canagliflozin: Initial: Metformin 1 g/day plus same total

Medication	Indications	Dosing/Administration
		daily dose of canagliflozin in 2 divided doses (immediate release) or once daily (extended release). ○ Patients switching from combination therapy of canagliflozin and metformin as separate tablets: Administer same total daily dose of canagliflozin plus similar total daily dose of metformin in 2 divided doses (immediate release) or once daily (extended release). ○ Patients switching from immediate release to extended release: Use current total daily dose. ○ Maximum: Canagliflozin 300 mg/metformin 2 g per day.
Synjardy® (empagliflozin-metformin) 5 mg-500 mg, 5 mg-1,000 mg, 12.5 mg-500 mg, 12.5 mg-1,000 mg oral tablet Synjardy® XR (empagliflozin-metformin extended release) 5 mg-1,000 mg, 10 mg-1,000 mg, 12.5 mg-1,000 mg, 25 mg-1,000 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease	• Diabetes mellitus, type 2, treatment: ○ Initial: Individualize initial dose based on patient's current antidiabetic regimen. May gradually increase dose based on effectiveness and tolerability. ○ Patients on metformin: Empagliflozin 10 mg/day plus similar total daily dose of metformin, administered in 2 divided doses (immediate release) or once daily (extended release). ○ Patients on empagliflozin: Metformin 1 g/day plus similar total daily dose of empagliflozin, administered in 2 divided doses (immediate release) or once daily (extended release). ○ Maximum: Empagliflozin 25 mg/metformin 2 g/day, administered in 2 divided doses (immediate release) or once daily (extended release).
Segluromet® (ertugliflozin-metformin) 2.5 mg-500 mg, 2.5 mg-1,000 mg, 7.5 mg-500 mg, 7.5 mg-1,000 mg oral tablet	• as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	• Diabetes mellitus, type 2, treatment: ○ Initial: Individualize initial dose based on patient's current antidiabetic regimen. May gradually increase dose based on effectiveness and tolerability. ○ Patients initiating ertugliflozin and already taking metformin: Ertugliflozin 5 mg/day plus a similar total daily dose of metformin, administered in 2 divided doses. ○ Patients initiating metformin and already taking ertugliflozin: Metformin 1 g/day plus a similar

Medication	Indications	Dosing/Administration
		total daily dose of ertugliflozin, administered in 2 divided doses. ○ Patients already taking ertugliflozin and metformin: Administer the same total daily dose of ertugliflozin and a similar total daily dose of metformin in 2 divided doses. ○ Maximum: Ertugliflozin 15 mg/metformin 2 g per day.
Combination SGLT-2/DPP-4 Inhibitors		
Qtern® (dapagliflozin-saxagliptin) 5 mg-5 mg, 10 mg-5 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	• Diabetes mellitus, type 2, treatment: ○ Initial: Dapagliflozin 5 mg/saxagliptin 5 mg once daily in patients not already taking dapagliflozin; may increase to dapagliflozin 10 mg/saxagliptin 5 mg once daily in patients currently tolerating dapagliflozin 5 mg/saxagliptin 5 mg who require additional glycemic control.
Glyxambi® (empagliflozin-linagliptin) 10-5, 25-5 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease	• Diabetes mellitus, type 2, treatment: Initial: Empagliflozin 10 mg/linagliptin 5 mg once daily; may increase to empagliflozin 25 mg/linagliptin 5 mg once daily
Steglujan® (ertugliflozin-sitagliptin) 5-100 mg, 15-100 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus	• Diabetes mellitus, type 2, treatment: Initial: Ertugliflozin 5 mg/sitagliptin 100 mg once daily; if further glycemic control is needed dose may be increased to ertugliflozin 15 mg/sitagliptin 100 mg once daily (maximum: ertugliflozin 15 mg/sitagliptin 100 mg/day).
Triple-Drug-Therapy (SGLT-2/DPP-4 inhibitors/metformin)		
Trijardy® XR (empagliflozin-linagliptin-metformin extended release) 5 mg-2.5 mg-1,000 mg, 10 mg-5 mg-1,000 mg, 12.5 mg-2.5 mg-1,000 mg, 25 mg-5 mg-1,000 mg oral tablet	• As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus • To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease	• Diabetes mellitus, type 2, treatment: ○ Initial: Individualize based on patient's current antidiabetic regimen. ○ Patients not taking empagliflozin: Switch to combination product containing a similar total daily dose of metformin, empagliflozin 10 mg/day, and linagliptin 5 mg/day given once daily. ○ Patients taking empagliflozin: Switch to combination product containing a similar total daily dose of metformin, same total daily dose of empagliflozin, and linagliptin 5 mg/day given once daily. ○ Dosage adjustment: May gradually titrate dose based on effectiveness

Medication	Indications	Dosing/Administration
		and tolerability; maximum: empagliflozin 25 mg/linagliptin 5 mg/metformin 2 g once daily.

BOXED WARNINGS and CONTRAINDICATIONS

Medication	Boxed Warnings	Contraindications
SGLT-2 Inhibitor Monotherapy		
Farxiga® (dapagliflozin) oral tablet	None.	History of serious hypersensitivity to dapagliflozin or any component of the formulation; patients on dialysis.
Invokana® (canagliflozin) oral tablet	None.	Serious hypersensitivity (eg, anaphylaxis, angioedema) to canagliflozin or any component of the formulation; patients on dialysis.
Jardiance® (empagliflozin) oral tablet	None.	History of serious hypersensitivity to empagliflozin or any component of the formulation; patients on dialysis.
Steglatro® (ertugliflozin) oral tablet	None.	History of serious hypersensitivity reaction to ertugliflozin or any component of the formulation; patients on dialysis.
Brenzavvy® (bexagliflozin) oral tablet	None.	History of serious hypersensitivity to bexagliflozin or any component of the formulation; patients on dialysis.
Inpefa® (sotagliflozin) oral tablet	None.	History of serious hypersensitivity to sotagliflozin or any component of the formulation.
Combination SGLT-2 Inhibitors/metformin		
Xigduo XR® (dapagliflozin/metformin extended release) oral tablet	Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.	History of serious hypersensitivity to dapagliflozin, metformin, or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2), ESRD or patients on dialysis; acute or chronic metabolic acidosis (including diabetic ketoacidosis, with or without coma)
Invokamet® (canagliflozin/metformin) oral tablet Invokamet® XR (canagliflozin/metformin extended release) oral tablet	Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.	History of serious hypersensitivity (eg, anaphylaxis, angioedema) to canagliflozin, metformin, or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2) or patients on dialysis; acute or chronic metabolic acidosis (including diabetic ketoacidosis)
Synjardy® (empagliflozin/metformin) oral tablet Synjardy® XR (empagliflozin/metformin extended release) oral tablet	Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.	History of serious hypersensitivity to empagliflozin, metformin, or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2), end-stage renal disease (ESRD), or patients on dialysis; acute or chronic metabolic acidosis (including diabetic ketoacidosis)
Segluromet® (ertugliflozin-metformin) oral tablet	Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.	History of serious hypersensitivity to ertugliflozin, metformin, or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2), end-stage renal disease, or patients on dialysis; acute or chronic metabolic acidosis (including diabetic ketoacidosis, with or without coma)
Combination SGLT-2/DPP-4 Inhibitors		
Qtern®	None.	Serious hypersensitivity (eg, anaphylactic

Medication	Boxed Warnings	Contraindications
(dapagliflozin/saxagliptin) oral tablet		reactions, angioedema, exfoliative skin conditions) to dapagliflozin, saxagliptin, or any component of the formulation; moderate to severe renal impairment (eGFR <45 mL/minute/1.73 m2), end-stage renal disease, or patients on dialysis.
Glyxambi® (empagliflozin/linagliptin) oral tablet	None.	Serious hypersensitivity (eg, anaphylactic reactions, angioedema, exfoliative skin conditions) to dapagliflozin, saxagliptin, or any component of the formulation; moderate to severe renal impairment (eGFR <45 mL/minute/1.73 m2), end-stage renal disease, or patients on dialysis.
Steglujan® (ertugliflozin-sitagliptin) oral tablet	None.	History of serious hypersensitivity (eg, anaphylaxis, angioedema) reaction to ertugliflozin, sitagliptin, or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2), end stage renal disease, or patients on dialysis.
Triple-Drug-Therapy (SGLT-2/DPP-4 inhibitors/metformin)		
Trijardy® XR (empagliflozin-linagliptin-metformin extended release) oral tablet	Lactic acidosis: Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.	Hypersensitivity (eg, anaphylaxis, angioedema, exfoliative skin conditions, urticaria, bronchial hyperreactivity) to empagliflozin, linagliptin, metformin or any component of the formulation; severe renal impairment (eGFR <30 mL/minute/1.73 m2), end-stage renal disease, or dialysis; acute or chronic metabolic acidosis, including diabetic ketoacidosis.

WARNINGS/PRECAUTIONS

Medication	Warnings/Precautions
	SGLT-2 Inhibitor Monotherapy
Farxiga® (dapagliflozin) oral tablet	**Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), acute infection, renal impairment **Special populations:** older adults may be predisposed to renal impairment or failure. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Surgical procedures: Consider temporary discontinuation of therapy at least 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy
Invokana® (canagliflozin) oral tablet	**Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), acute infection, renal impairment **Special populations:** Elderly patients (≥65 years of age) may have an increased risk of symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, dizziness, syncope, and dehydration) during therapy, especially with the 300 mg dose; elderly patients ≥75 years of age may experience a more pronounced risk. HbA1c reductions may be less in patients >65 years of age compared to younger patients. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients (ADA 2020). • Surgical procedures: Consider temporary discontinuation of therapy at least 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Jardiance® (empagliflozin) oral tablet	**Concerns related to adverse effects:** bone fractures, lower limb amputation **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis) **Special populations:** Older adults: Risk of intravascular volume depletion may be increased in patients ≥75 years of age. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Surgical procedures: Consider temporary discontinuation of therapy at least 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Steglatro® (ertugliflozin) oral tablet	**Concerns related to adverse effects:** bone fractures, genital mycotic infections, hypotension, ketoacidosis, lower limb amputation, necrotizing fasciitis, renal effects, urinary tract infection **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), hepatic impairment, renal impairment **Special populations:** Elderly patients may be predisposed to symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, dizziness, syncope, dehydration) and renal impairment or failure. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for

Medication	Warnings/Precautions
	hospitalized patients. • Surgical procedures: Consider temporary discontinuation ≥4 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Brenzavvy® (bexagliflozin) oral tablet	**Disease-related concerns:** Bariatric surgery: (altered absorption, dehydration, euglycemia diabetic ketoacidosis) **Special populations:** Elderly patients may be predisposed to symptoms related to intravascular volume depletion (e.g., hypotension, orthostatic hypotension, dizziness, syncope, dehydration) and renal impairment of failure. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or for glycemic control in patients with type 1 diabetes. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for glycemic control in hospitalized patients. Surgical procedures: Consider temporary discontinuation ≥ 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Inpefa® (sotagliflozin) oral tablet	**Concerns related to adverse effects:** hypoglycemia, renal effects. **Disease-related concerns:** Bariatric surgery: (altered absorption, dehydration, euglycemia diabetic ketoacidosis) **Special populations:** Older adults be may predisposed to symptoms related to intravascular volume depletion (e.g., hypotension, orthostatic hypotension, dizziness, syncope, dehydration) **Other warnings/precautions:** Surgical procedures: Consider temporary discontinuation ≥ 3 days prior to surgery; ensure patient is clinically stable and has resumed oral intake prior to reinitiating therapy
Combination SGLT-2 Inhibitors/metformin	
Xigduo XR® (dapagliflozin/metformin extended release) oral tablet	**Concerns related to adverse effects:** bone fractures, genital mycotic infections, hypersensitivity reactions, hypotension, ketoacidosis, lactic acidosis: [US Boxed Warning], lower limb amputation, necrotizing fasciitis, renal effects, urinary tract infection, long-term metformin use is associated with vitamin B12 deficiency **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), heart failure, hepatic impairment, renal impairment, stress-related states **Special populations:** • Elderly: Use with caution; risk of metformin-associated lactic acidosis increases with age. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis (DKA) or patients with type 1 diabetes mellitus. • Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism. • Iodinated contrast: According to the manufacturer, it is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with a history of hepatic disease, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. • Surgical procedures: Consider temporary discontinuation of dapagliflozin-containing products at least 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Invokamet® (canagliflozin/metformin) oral tablet Invokamet® XR	**Concerns related to adverse effects:** bone fracture, genital mycotic infections, hyperkalemia, hypersensitivity reactions, ketoacidosis, lactic acidosis: [US Boxed Warning], lower limb amputation: [US Boxed Warning], necrotizing fasciitis, renal effects, urinary tract infection, long-term metformin use is associated with vitamin B12 deficiency, volume

Medication	Warnings/Precautions
(canagliflozin/metformin extended release) oral tablet	depletion **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), heart failure, hepatic impairment, renal impairment, stress-related states **Special populations:** Elderly: Use with caution; risk of metformin associated lactic acidosis increases with age. Elderly patients (≥65 years of age) may have an increased risk of symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, postural dizziness, syncope, and dehydration) during canagliflozin therapy. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism. • Hospitalized patients: Use of SGLT2 inhibitors (eg, canagliflozin) is not routinely recommended for hospitalized patients. • Iodinated contrast: According to the manufacturer, it is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR 45 to 60 mL/minute/1.73 m2; or with a history of hepatic disease, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. • Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (fever, trauma, infection, surgery). • Surgical procedures: Consider temporary discontinuation of canagliflozin-containing products 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Synjardy® (empagliflozin/metformin) oral tablet Synjardy® XR (empagliflozin/metformin extended release) oral tablet	**Concerns related to adverse effects:** bone fractures, genital mycotic infections, hypersensitivity, hypotension, ketoacidosis, lactic acidosis: [US Boxed Warning], lower limb amputation, necrotizing fasciitis, renal effects, urinary tract infection, long-term metformin use is associated with vitamin B12 deficiency **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), heart failure, hepatic impairment, renal impairment, stress-related states **Special populations:** Elderly: Use with caution; risk of metformin associated lactic acidosis increases with age. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Iodinated contrast: According to the manufacturer, it is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR 45 to 60 mL/minute/1.73 m2; or with a history of hepatic disease, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. • Surgical procedures: Consider temporary discontinuation of empagliflozin-containing products ≥3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Segluromet® (ertugliflozin-metformin) oral tablet	**Concerns related to adverse effects:** bone fractures, genital mycotic infections, hypersensitivity, hypotension, ketoacidosis, lactic acidosis: [US Boxed Warning], lower limb amputation, necrotizing fasciitis, renal effects, urinary tract infection, long-term metformin use is associated with vitamin B12 deficiency

Medication	Warnings/Precautions
	Disease-related concerns: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), heart failure, hepatic impairment, renal impairment, stress-related states **Special populations:** Elderly: Use with caution; risk of metformin associated lactic acidosis increases with age. Risk of intravascular volume depletion, renal impairment, and UTI may be increased in elderly patients. **Other warnings/precautions:** • Appropriate use: Not indicated for use in patients with type 1 diabetes mellitus or with diabetic ketoacidosis (DKA). • Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Iodinated contrast: According to the manufacturer, it is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with an eGFR 30 to 60 mL/minute/1.73 m2; or with a history of hepatic disease, alcoholism, or heart failure; or in patients who will receive intra-arterial iodinated contrast. • Surgical procedures: Consider temporary discontinuation of ertugliflozin-containing products at least 4 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Combination SGLT-2/DPP-4 Inhibitors	
Qtern® (dapagliflozin/saxagliptin) oral tablet	**Concerns related to adverse effects:** arthralgia, bone fractures, bullous pemphigoid, genital mycotic infections, hematologic effects, hypersensitivity, hypotension, ketoacidosis, lower limb amputation, necrotizing fasciitis, pancreatitis, renal effects, urinary tract infection **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis), heart failure, hepatic impairment, renal impairment **Special populations:** • Elderly: Elderly patients may be predisposed to symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, dizziness, syncope, dehydration) and/or renal impairment/failure. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. **Dosage form specific issues:** ER tablet: Inactive ingredients may appear in the stool as a soft mass resembling the tablet. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy. • Surgical procedures: Consider temporary discontinuation of dapagliflozin-containing products ≥3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Glyxambi® (empagliflozin/linagliptin) oral tablet	**Concerns related to adverse effects:** arthralgia, bone fractures, bullous pemphigoid, genital mycotic infections, hematologic effects, hypersensitivity, hypotension, ketoacidosis, lower limb amputation, necrotizing fasciitis, pancreatitis, renal effects, urinary tract infection **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis,), cardiovascular disease **Special populations:** Elderly: Use with caution; risk of intravascular volume depletion, renal impairment, and UTI may be increased in elderly patients. **Other warnings/precautions:**

Medication	Warnings/Precautions
	• Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Surgical procedures: Consider temporary discontinuation of empagliflozin-containing products at least 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
Steglujan® (ertugliflozin-sitagliptin) oral tablet	**Concerns related to adverse effects:** arthralgia, bone fractures, bullous pemphigoid, genital mycotic infections, hematologic effects, hypersensitivity, hypotension, ketoacidosis, lower limb amputation, necrotizing fasciitis, pancreatitis, renal effects, urinary tract infection **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis,), cardiovascular disease, hepatic impairment, renal impairment **Special populations:** Elderly patients may be predisposed to symptoms related to intravascular volume depletion (eg, hypotension, orthostatic hypotension, dizziness, syncope, and dehydration) and renal impairment or failure. **Other warnings/precautions:** • Appropriate use: Not indicated for use in patients with type 1 diabetes mellitus (or in patients with diabetic ketoacidosis). • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. • Patient education: Diabetes self-management education is essential to maximize the effectiveness of therapy. • Surgical procedures: Consider temporary discontinuation of ertugliflozin-containing products ≥4 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.
	Triple-Drug-Therapy (SGLT-2/DPP-4 inhibitors/metformin)
Trijardy® XR (empagliflozin-linagliptin-metformin extended release) oral tablet	**Concerns related to adverse effects:** arthralgia, bone fractures, bullous pemphigoid, genital mycotic infections, hypersensitivity, hypotension, ketoacidosis, lactic acidosis: [US Boxed Warning], lower limb amputation, necrotizing fasciitis, pancreatitis, renal effects, urinary tract infection, long-term metformin use is associated with vitamin B12 deficiency; monitor vitamin B12 serum concentrations periodically with long-term therapy. **Disease-related concerns**: Bariatric surgery: (altered absorption, dehydration, euglycemic diabetic ketoacidosis,), heart failure, hepatic impairment, renal impairment **Special populations:** • Elderly: Use with caution; risk of metformin-associated lactic acidosis increases with age. • Hospitalized patients: Use of SGLT2 inhibitors is not routinely recommended for hospitalized patients. **Dosage form specific issues:** • ER tablet: Incompletely dissolved tablets may appear in the stool. Assess glycemic control if patient observes tablets in the stool. **Other warnings/precautions:** • Appropriate use: Not for use in patients with diabetic ketoacidosis or patients with type 1 diabetes mellitus. • Ethanol use: Instruct patients to avoid excessive acute or chronic ethanol use; ethanol may potentiate metformin's effect on lactate metabolism. • Iodinated contrast: According to the manufacturer, it is recommended to temporarily discontinue metformin at the time of or before iodinated contrast imaging procedures in patients with a history of hepatic disease, alcoholism, HF, or in patients who will receive intraarterial iodinated contrast. • Stress-related states: It may be necessary to discontinue metformin and administer insulin if the patient is exposed to stress (eg, fever, trauma, infection, surgery).

Medication	Warnings/Precautions
	• Surgical procedures: Consider temporary discontinuation of empagliflozin-containing products 3 days prior to surgery; ensure risk factors for ketoacidosis are resolved prior to reinitiating therapy.

PRACTICE GUIDELINES

AHA/ACC/HFSA Heart Failure Guidelines (2022)

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2022; 79(19):e263-e421.

General Recommendations

- Guideline-directed medical therapy (GDMT) for heart failure (HF) with reduced ejection fraction (HFrEF) now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i).
- SGLT2i have a Class of Recommendation 2a in HF with mildly reduced ejection fraction (HFmrEF). Weaker recommendations (Class of Recommendation 2b) are made for ARNi, ACEi, ARB, MRA, and beta blockers in this population.
- New recommendations for HFpEF are made for SGLT2i (Class of Recommendation 2a), MRAs (Class of Recommendation 2b), and ARNi (Class of Recommendation 2b). Several prior recommendations have been renewed including treatment of hypertension (Class of Recommendation 1), treatment of atrial fibrillation (Class of Recommendation 2a), use of ARBs (Class of Recommendation 2b), and avoidance of routine use of nitrates or phosphodiesterase-5 inhibitors (Class of Recommendation 3: No Benefit).
- Improved LVEF is used to refer to those patients with previous HFrEF who now have an LVEF >40%. These patients should continue their HFrEF treatment.
- Value statements were created for select recommendations where high-quality, cost-effectiveness studies of the intervention have been published.
- Amyloid heart disease has new recommendations for treatment including screening for serum and urine monoclonal light chains, bone scintigraphy, genetic sequencing, tetramer stabilizer therapy, and anticoagulation.
- Evidence supporting increased filling pressures is important for the diagnosis of HF if the LVEF is >40%. Evidence for increased filling pressures can be obtained from noninvasive (e.g., natriuretic peptide, diastolic function on imaging) or invasive testing (e.g., hemodynamic measurement).
- Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care.
- Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of HF were revised to emphasize the new terminologies of "at risk" for HF for stage A and pre-HF for stage B.
- Recommendations are provided for select patients with HF and iron deficiency, anemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease, and malignancy.

Pharmacological Treatment for HFrEF

- Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi
  - In patients with HFrEF and NYHA class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality (1, A).
  - In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible (1, A).
  - In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality (1, A).
  - In patients with previous or current symptoms of chronic HFrEF, in whom ARNi is not feasible, treatment with an ACEi or ARB provides high economic value (Value statement, A).
  - In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality (1, BR).
  - In patients with chronic symptomatic HFrEF, treatment with an ARNi instead of an ACEi provides high economic value (Value statement, A).

- ARNi should not be administered concomitantly with ACEi or within 36 hours of the last dose of an ACEi (3: Harm, C-BR).
- ARNi should not be administered to patients with any history of angioedema (3: Harm, C-LD).
- ACEi should not be administered to patients with any history of angioedema (3: Harm, C-LD).

- Beta Blockers
  - In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations (1, A)
  - In patients with HFrEF, with current or previous symptoms, beta-blocker therapy provides high economic value (Value statement, A)
- Mineralocorticoid Receptor Antagonists (MRAs)
  - In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if eGFR is >30 mL/min/1.73 m2and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency (1, A)
  - In patients with HFrEF and NYHA class II to IV symptoms, MRA therapy provides high economic value (Value statement, A).
  - In patients taking MRA whose serum potassium cannot be maintained at <5.5 mEq/L, MRA should be discontinued to avoid life-threatening hyperkalemia (3: Harm, B-NR)
- Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)
  - In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes (1, A).
  - In patients with symptomatic chronic HFrEF, SGLT2i therapy provides intermediate economic value (Value statement, A)
- Hydralazine and Isosorbide Dinitrate
  - For patients self-identified as African American with NYHA class III-IV HFrEF who are receiving optimal medical therapy, the combination of hydralazine and isosorbide dinitrate is recommended to improve symptoms and reduce morbidity and mortality (1, A)
  - For patients self-identified as African American with NYHA class III to IV HFrEF who are receiving optimal medical therapy with ACEi or ARB, beta blockers, and MRA, the combination of hydralazine and isosorbide dinitrate provides high economic value (Value statement, B-NR)
  - In patients with current or previous symptomatic HFrEF who cannot be given first-line agents, such as ARNi, ACEi, or ARB, because of drug intolerance or renal insufficiency, a combination of hydralazine and isosorbide dinitrate might be considered to reduce morbidity and mortality (2b, C-LD)

Pharmacological Treatment for HFpEF

- Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity (1, C-LD).
- In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (2a, B-R).
- In patients with HFpEF, management of AF can be useful to improve symptoms (2a, C-EO).
- In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (2b, B-R).
- In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (2b, B-R)
- In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (2b, B-R)

- In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or QOL is ineffective (3: No-benefit, B-R)

Level of Evidence	Description
Class 1	• Strong recommendation; Benefit >>> Risk
Class 2a	• Moderate recommendation; Benefit >> Risk
Class 2b	• Weak recommendation; Benefit ≥ Risk
Class 3	• No benefit (moderate recommendation); Benefit = Risk
Class 3	• Harm (strong recommendation); Risk > Benefit
Level A	• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
Level B-Randomized (BR)	• Moderate-quality evidence from 1 or more RCTs • Meta-analyses of moderate-quality RCTs
Level B-Non-randomized (B-NR)	• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
Level C-Limited Data (LD)	• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
Level C-Expert Opinion (EO)	• Consensus of expert opinion based on clinical experience

<u>American Diabetes Association Guidelines (2023)</u>

ElSayed NA, Aleppo G, Aroda VR, et al., American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Care in Diabetes—2023*. Diabetes Care 2023;46(Suppl. 1):S140–S157

- Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or continuous subcutaneous insulin infusion (A).
- Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk (A).
- Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity (B).
- Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals (A).
- In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk (A).
- Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy (A).
- Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals (A).
- Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits (A).
- Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (A).
- The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high (E).
- A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include cardiovascular comorbidities, hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (E).

- Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of patient-specific factors (A).
- In patients with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible (A).
- If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit (A).
- Recommendation for treatment intensification for patients not meeting treatment goals should not be delayed (A)
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment (E).
- Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 IU/kg/day, high bedtime-morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy (E).

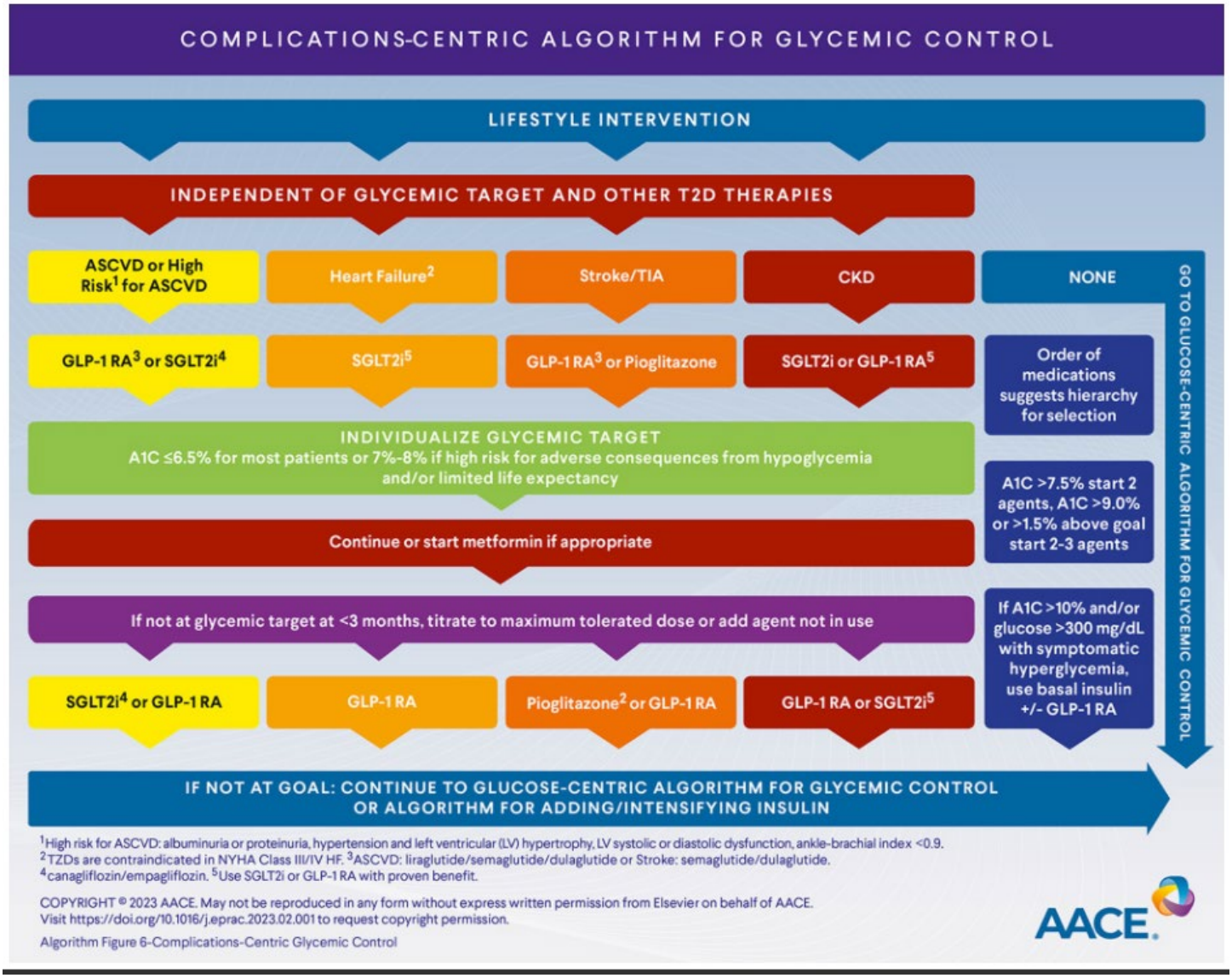
American Diabetes Association standards of medical care in diabetes – 2020 grading/recommendation level definitions

Level of Evidence	Description
A	Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered, including • Evidence from a well-conducted multicenter trial • Evidence from a meta-analysis that incorporated quality ratings in the analysis Compelling nonexperimental evidence, i.e., “all or none” rule developed by the Centre for Evidence-Based Medicine at the University of Oxford Supportive evidence from well-conducted randomized controlled trials 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

American Association of Clinical Endocrinology Guidelines (2023)

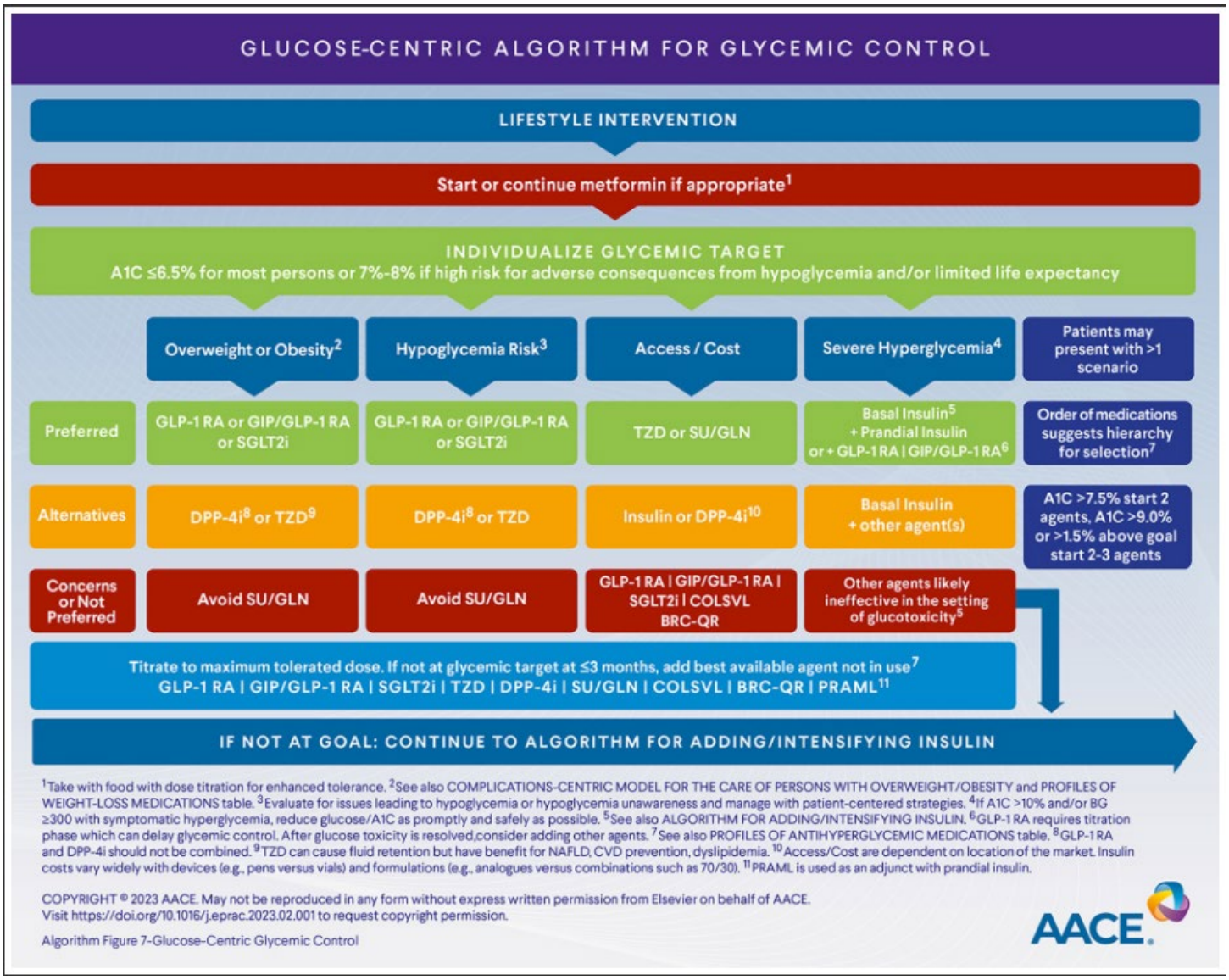
Samson SL, Vellanki P, Blonde L, et a. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm – 2023 update. Endocrine Practice. 2023;29(5):p305-p340.

Complications-Centric Algorithm for Glycemia Control:



Algorithm Figure 6-Complications-Centric Glycemic Control

Glucose-Centric Algorithm for Glycemic Control:



CLINICAL TRIALS/SYSTEMATIC REVIEWS/META-ANALYSES

Citation	Design	Endpoints
EMPA-REG OUTCOME Zinman, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015;373:2117-2128	N=7020 Randomized, placebo controlled, multi-centered trial enrolled 7,020 patients with type 2 diabetes and high cardiovascular risk Inclusion criteria: Adult patients with type 2 diabetes and high cardiovascular risk Exclusion criteria: Uncontrolled hyperglycemia, indication of liver disease, planned cardiac surgery within 3 months, eGFR < 30 ml/min/1.73 m^2, bariatric surgery in past two years, history of cancer, treatment with anti-obesity drugs, systemic steroids, pre-menopausal women who are not practicing acceptable birth control, alcohol or drug abuse Randomized 1:1:1: • Empagliflozin 10 mg once daily vs. empagliflozin 25 mg once daily vs. Placebo	**Primary endpoint:** • Composite outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke

Results:
Primary: Composite outcome of death from cardiovascular causes, nonfatal MI, or nonfatal stroke occurred in 10.5% of the pooled empagliflozin group and 12.1% of the placebo group (HR 0.86; 95% CI, 0.74 to 0.99; p<0.001 for NI, p=0.04 for superiority). Other: NI criteria were met for a composite outcome of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina, but empagliflozin was not superior to placebo (p=0.08). Empagliflozin significantly reduced the risk of death from cardiovascular causes (p<0.001), death from any cause (p<0.001), and hospitalization for heart failure (p=0.002) vs. placebo. Rates of MI and stroke were similar with empagliflozin and placebo (p=NS). Mean A1C at 206 weeks was 7.81% empagliflozin and 8.16% placebo (p-value not reported). In subgroup analyses, there was no difference between empagliflozin and placebo for the primary outcome in patients aged <65 years or with A1C ≥8.5%.
Safety**:** Empagliflozin resulted in fewer serious and non-serious adverse events vs. placebo (p<0.001), and fewer severe adverse events vs. placebo (p<0.05). Genital infections were more common with empagliflozin (p<0.001). Acute renal failure (p<0.01) and acute kidney injury (p<0.05) were more common with placebo.
Conclusion: Limitations existed including mean baseline A1C was 8.06% to 8.08% in all groups. Background glucose-lowering and cardiovascular risk therapies were managed according to local practices. NI margin of 1.3 vs. placebo has questionable clinical significance. At baseline, mean BP was 135/76 mmHg, total cholesterol was 163 mg/dL, and LDL was 85 mg/dL. At baseline, 95% were on antihypertensives, almost 90% were on an anticoagulant, and about 80% were on lipid-lowering drugs. Lifestyle related risk factors (e.g., smoking) were not reported. Individual empagliflozin doses were not significantly different from placebo for the primary outcome, making the results difficult to translate into clinical practice. Despite limitations, the EMPA-REG OUTCOME study is the first study that has demonstrated a macrovascular/ cardiovascular outcome benefit with any individual antihyperglycemic therapy. Empagliflozin is the only SGLT2 inhibitor to demonstrate significant reduction in both cardiovascular risk and death in a dedicated outcomes trial. This trial has led to approval for the indication of risk reduction of cardiovascular mortality in adults with type 2 diabetes mellitus and established CVD.

Citation	Design	Endpoints
VERTIS-SITA Dagogo-Jack S, Liu J, Eldor R, et al. Safety and Efficacy of Ertugliflozin in the Treatment of Participants With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin. *Diabetes Obes Metab*. 2017 Sep 17	N=464 Phase III, randomized controlled, double-blind, placebo controlled, parallel assignment trial Inclusion criteria Adults 18 years of age or older with type 2 diabetes on stable therapy of metformin with either sitagliptin or another DPP-4 inhibitor or sulfonylurea and is willing to switch to sitagliptin, BMI ≥ 18 mg/m^2, male, or postmenopausal/surgically sterile female, if female is of reproductive potential, participant agrees to abstinence or to use 2 acceptable combination of birth control. Exclusion criteria	**Primary Endpoints:** • Change from baseline in A1C at week 26 • Percentage of participants experiencing an adverse event up to week 54 • Percentage of participants discontinuing study treatment due to an adverse event up to week 52

	Known hypersensitivity, on weight-loss program or weight-loss medication, undergone bariatric surgery in past 12 months or > 12 months and is not weight stable, treatment with any non-protocol approved drug within 12 weeks of study participation, history of cardiovascular disease/event, history of malignancy, history of HIV, history of active liver disease, excessive consumption of alcohol Participants were randomized to the following arms: • Ertugliflozin 5 mg orally once daily for 52 weeks and participants remained on stable doses of metformin and sitagliptin; ertugliflozin 5 mg and 10 mg tablet once daily for 52 weeks and participants remained on stable doses of metformin and sitagliptin; vs. placebo for ertugliflozin 5 mg once daily for 52 weeks and participants remained on stable doses of metformin and sitagliptin.	**Key secondary outcome measures:** • Change from baseline in fasting plasma glucose at week 26 • Change from baseline in body weight at week 52 • Percentage of participants with an A1C < 7% at week 26 • Change from baseline in A1C at week 52
Results: <u>Primary:</u> • Change in baseline A1C at week 26: Ertugliflozin 5 mg: -0.78 %; ertugliflozin 15 mg: -0.86%, placebo: -0.09% (p < 0.001) • Percentage of participants experiencing an AE up to week 54: Ertugliflozin 5 mg: 57.7%; ertugliflozin 15 mg: 60.1%, placebo: 63.4% • Percentage of participants discontinuing treatment due to an AE up to week 52: Ertugliflozin 5 mg: 4.5%; ertugliflozin 15 mg: 3.9%, placebo: 3.9% <u>Secondary</u>: • Change from baseline in fasting plasma glucose at week 26: Ertugliflozin 5 mg: -26.91 mg/dL; ertugliflozin 15 mg: --33.04 mg/dL; placebo: -1.76 mg/dL (p < 0.001) • Change from baseline in body weight at week 52: Ertugliflozin 5 mg: -3.46 kg; ertugliflozin 15 mg: -2.83 kg; placebo: -0.95 kg • Percentage of participants with an A1C < 7% at week 26: Ertugliflozin 5 mg: 32.1%; ertugliflozin 15 mg: 39.9%, placebo: 17% (p < 0.001) • Change from baseline in A1C at week 52: Ertugliflozin 5 mg: -0.75%; ertugliflozin 15 mg: -0.81%, placebo: -0.02% **Conclusion:** Ertugliflozin added to metformin and sitagliptin was well-tolerated, and provided clinically meaningful glycemic control similar to A1C lowering of other FDA approved SGLT2 inhibitors.		
Citation	**Design**	**Endpoints**
VERTIS MONO Terra SG, Focht K, Davies M, et al. A Study of the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Participants With Type 2 Diabetes Mellitus and Inadequate Glycemic Control Despite Diet and Exercise*. Diabetes Obes Metab*. 2017 May 19(5):721-728	N=461 Phase III randomized double-blind placebo controlled trial <u>Inclusion criteria</u> Adults 18 years of age or older with type 2 diabetes, no prior allowable oral antidiabetic agents for at least 8 weeks prior to study or on a single allowable oral agent at start of study, must be willing to discontinue this medication at screening visit and remain off medication during trial <u>Exclusion criteria</u> History of cardiovascular disease/events, history of malignancy, blood pressure or lipid lowering medication not on a stable dose, pregnant, breast feeding, or expected to conceive during trial including 14 days following the last dose of study drug Participants were randomized to the following arms: Experimental: Ertugliflozin 5 mg/Ertugliflozin 5 mg (n = 156) • Phase A: Ertugliflozin 5 mg administered once daily for 26 weeks.	**Primary endpoints:** • Change from baseline in A1C at week 26 • Percentage of participants experiencing and adverse event • Percentage of participants discontinuing study treatment due to an AE **Key secondary outcome measures:** • Percentage of participants with A1C <7% at week 26 • Change from baseline in FPG at week 26 • Change from baseline in body weight

	• Phase B: Ertugliflozin 5 mg administered once daily for 26 weeks. Experimental: Ertugliflozin 15 mg/Ertugliflozin 15 mg (n = 151) • Phase A: Ertugliflozin 15 mg administered once daily for 26 weeks. • Phase B: Ertugliflozin 15 mg administered once daily for 26 weeks. Placebo/Metformin (n = 153) • Phase A: Placebo to ertugliflozin administered once daily for 26 weeks.	at week 26

Results:

Primary:

- Change from baseline in A1C at week 26: Ertugliflozin 5 mg: -0.79%; ertugliflozin 15 mg: -0.96%; placebo: 0.20% ($p < 0.001$)
- Percentage of participants experiencing and adverse event: Ertugliflozin 5 mg: 64.1%; ertugliflozin 15 mg: 62.5%; placebo: 66.7%
- Percentage of participants discontinuing study treatment due to an AE: Ertugliflozin 5 mg: 4.5%; ertugliflozin 15 mg: 3.9%; placebo: 6.5%

Secondary:

- Percentage of participants with A1C <7% at week 26: Ertugliflozin 5 mg: 28.2%; ertugliflozin 15 mg: 35.8%; placebo: 13.1% ($p < 0.001$)
- Change from baseline in FPG at week 26: Ertugliflozin 5 mg: -33.96 mg/dL; ertugliflozin 15 mg: -43.44 mg/dL; placebo: 0.57 mg/dL ($p <0.001$)
- Change from baseline in body weight at week 26: Ertugliflozin 5 mg: -3.18 kg; ertugliflozin 15 mg: -3.58 kg; placebo: -1.42 kg ($p< 0.001$)

Conclusion: Ertugliflozin 5 and 15 mg treatment for 26 weeks provides effective glycemic control when used as monotherapy similar to that observed in other FDA approved SGLT2 inhibitors.

Citation	Design	Endpoints
VERTIS MET Rosenstock J, Frias J, Pall D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes Obes Metab*. 2017;1-10.	N=621 Randomized, double-blind, controlled phase III trial Inclusion criteria: 18 years of age and older with type 2 diabetes and A1C 7.5-10.5% on stable metformin monotherapy (≥ 1500 mg/day for at least 8 weeks) Exclusion criteria: Patients not stabilized on metformin prior to study initiation Participants were randomized to receive: • Ertugliflozin 5 mg once daily + metformin (n = 207); ertugliflozin 15 mg once daily + metformin (n = 205); placebo + metformin (n = 209)	**Primary endpoint:** • Change from baseline in A1C at week 26 **Key secondary endpoints:** • Change from baseline body weight • Proportion of subjects with A1C < 7% at week 26

Results:

Primary: Change from baseline in A1C at week 26: ertugliflozin 5 mg: -0.7%; ertugliflozin 15 mg: -0.9%; placebo: < -0.1% ($p < 0.001$)

Secondary: Change from baseline body weight: ertugliflozin 5 mg: -3.0 kg*; ertugliflozin 15 mg: -1.3 kg; placebo: -2.9*($p < 0.001$*)

Proportion of subjects with A1C < 7% at week 26: ertugliflozin 5 mg: 35.3%*; ertugliflozin 15 mg: 40%*; placebo: 15.8% ($p < 0.001$*)

Conclusion: Ertugliflozin 5 and 15 mg treatment for 26 weeks provides effective glycemic control when used in addition to metformin similar to that observed in other FDA approved SGLT2 inhibitors.

Citation	Design	Endpoints
VERTIS SITA2 Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin. *Diabetes Obes Metab*.	N=464 Phase III randomized, double-blind, placebo controlled trial Inclusion criteria: Adults aged 18 years of age or older with type 2 diabetes and inadequate glycemic control on stable metformin ≥ 1500 mg/day and sitagliptin 100 mg/day Exclusion criteria: Patients not receiving stable metformin or sitagliptin prior to	**Primary endpoint:** • Change from baseline in A1c at week 26 **Key secondary efficacy endpoints:** • Change from baseline in FPG at week 26

2017.	initiation Participants were randomized to receive ertugliflozin 5 mg, ertugliflozin 15 mg, or placebo	• Change from baseline body weight at week 26 • Proportion of subjects with A1c < 7% at week 26
Results: Primary: Change from baseline in A1c at week 26: ertugliflozin 5 mg: -0.8%; ertugliflozin 15 mg: -0.9%; placebo: -0.1% ($p < 0.001$) Secondary: Change from baseline in FPG: ertugliflozin 5 mg: -26.9 mg/dL; ertugliflozin 15 mg: -33.0mg/dL; placebo: -1.8 mg/dL ($p < 0.001$) Change from baseline body weight: ertugliflozin 5 mg: -3.4 kg; ertugliflozin 15 mg: -3.0 kg; placebo: -1.3 ($p < 0.001$) Proportion of subjects with A1c < 7% at week 26: ertugliflozin 5 mg: 50%; ertugliflozin 15 mg: 61%; placebo: 26% ($p < 0.001$) **Conclusion:** Ertugliflozin added to metformin and sitagliptin was well-tolerated, and provided clinically meaningful glycemic control similar to A1c-lowering of other FDA-approved SGLT2 inhibitors.		
Citation	**Design**	**Endpoints**
VERTIS SU Hollander P, et al. Safety and efficacy of ertugliflozin compared to glimepiride in patients with T2DM inadequately controlled on metformin. European Association for the Study of Diabetes; Lisbon, Portugal, Sept 11-15 2017.	N=1326 Phase III randomized controlled, double blind trial Inclusion criteria: Adults with type 2 diabetes inadequately controlled on metformin with an A1C of 7-9% on stable metformin ≥ 1500 mg/day Exclusion criteria: Patients not receiving stable metformin prior to initiation. Randomized 1:1:1 to one of the following treatments: Ertugliflozin 5 mg; ertugliflozin 15 mg; glimepiride (initiated at 1 mg daily and titrated to a maximum of 6 or 8 mg/day)	**Primary endpoint:** • Non-inferiority of ertugliflozin 15 mg to glimepiride in change from baseline A1c at week 52 (defined as the upper bound of the two-sided 95% CI of the mean treatment difference < -0.3%) **Key secondary endpoints:** • Change from baseline in A1c for ertugliflozin 5 mg versus glimepiride • Change from baseline in body weight
Results: Primary: Non-inferiority of ertugliflozin 15 mg to glimepiride in change from baseline A1c at week 52: • Ertugliflozin 15 mg (n = 440): -0.6%; glimepiride (n = 437): -0.7%; ertugliflozin 15 mg vs glimepiride difference (95% CI): 0.1 (-0.0, 0.2) Secondary: Change from baseline in A1c for ertugliflozin 5 mg versus glimepiride • Ertugliflozin 5 mg (n = 448): -0.6%; glimepiride (n = 437): -0.7%; ertugliflozin 5 mg vs glimepiride difference (95% CI): 0.2 (0.1, 0.3) Change from baseline in body weight • Ertugliflozin 5 mg (n = 448): -3.0 kg; ertugliflozin 15 mg (n = 440): -3.4 kg; glimepiride (n = 437): 0.9 kg; ertugliflozin 5 mg vs glimepiride difference (95% CI): -3.9 kg (-4.4, -3.4) [nominal $p < 0.001$, non-inferiority was not demonstrated]; ertugliflozin 15 mg vs glimepiride difference (95% CI): -4.3 (-4.8, -3.8) [$p< 0.001$] **Conclusion:** Ertugliflozin 15 mg was demonstrated to be non-inferior to glimepiride at A1C lowering.		
Citation	**Design**	**Endpoints**
CANVAS CV Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the	N=10,142 Integrated data from a phase III (CANVAS) and phase IV (CANVAS-R) randomized, PBO-controlled trials Arms: canagliflozin 100 mg, 300 mg or PBO	**Primary:** • Composite of CV death or HHF **Secondary:** • Safety

CANVAS Program. Circulation. 2018 Jul 31; 138(5): 458–468. doi: 10.1161/CIRCULATIONAHA.118034222.	Inclusion criteria: inadequately controlled T2DM (HbA1c ≥7% and ≤10.5%) and either ≥30 years old with history of CV event or ≥50 years old with high risk of CV events Exclusion criteria: history of diabetic ketoacidosis, T1DM, pancreas or beta-cell transplantation; DM secondary to pancreatitis or pancreatectomy; ≥ 1 severe hypoglycemic episodes within 6 months before screening	

Results:
Primary: CV death or HHF was reduced in those treated with canagliflozin compared with PBO (16.3 versus 20.8 per 1000 patient-years; HR, 0.78; 95% CI, 0.67–0.91), as was fatal or HHF (HR, 0.70; 95% CI, 0.55–0.89) and HHF alone (HR, 0.67; 95% CI, 0.52–0.87). The benefit on CV death or HHF may be greater in patients with a prior history of HF (HR, 0.61; 95% CI, 0.46–0.80) compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72–1.06; P interaction =0.021).
Secondary: The effects of canagliflozin compared with PBO on key safety outcomes were similar in participants with and without HF at baseline (all interaction P values >0.130), except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of HF (P=0.03).
Conclusion: In patients with T2DM and an elevated risk of CVD, canagliflozin reduced the risk of CV death or HHF across a broad range of different patient subgroups. Benefits may be greater in those with a history of HF at baseline.

Citation	Design	Endpoints
DAPA-HF McMurray JJ, Solomon S, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019; 381:1995-2008 DOI: 10.1056/NEJMoa1911303	N=4744; All patients being treated with standard of care (ACEi, ARB, ARNI) plus beta-blocker (+/- mineralocorticoid receptor antagonist, diuretic, or implantable device) International, multicenter, randomized, double-blind, placebo-controlled trial Inclusion criteria: Patients with NYHA functional class II-IV heart failure with reduced ejection fraction (HFrEF), elevated NT-proBNP levels Exclusion criteria: type 1 DM, symptomatic hypotension, acute decompensated heart failure Randomized to dapagliflizon 10 mg daily or placebo for a median time-frame of 18 months to determine whether dapagliflozin reduces the risk of cardiovascular (CV) death and hospitalization due to heart failure.	**Primary endpoint:** • Time to first occurrence of composite of CV death, hospitalization for heart failure or urgent heart failure visit

Results: Dapagliflozin reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85]; p<0.0001).
Conclusion: Farxiga reduced the risk of the composite outcome of CV death or worsening of heart failure by 26% compared to placebo in patients with NYHA class II-IV HFrEF with or without T2DM.

Citation	Design	Endpoints
DECLARE-TIMI58 Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-357. doi: 10.1056/NEJMoa1812389.	N=17190 Phase III, randomized (1:1), double-blind, PBO-controlled Arms: dapagliflozin 10 mg QD or PBO Inclusion criteria: ≥40 years of age, T2DM, an HbA1C ≥6.5% but <12.0%, and a creatinine clearance of ≥60 mL/min; multiple risk factors for ASCVD or established ASCVD; participants with multiple risk factors were men ≥55 years of age or women ≥60 years of age who had ≥one traditional risk factors, including HTN, dyslipidemia (defined as a LDL >130 mg/dL or the use of lipid-lowering therapies), or use of tobacco Exclusion criteria: T1DM, history of bladder cancer or history of radiation therapy to the lower abdomen or pelvis at any time, chronic cystitis and/or recurrent UTI, pregnancy or	**Primary:** • MACE • CV death or HHF **Secondary:** • Renal composite outcome, defined as a sustained decrease of ≥40% in estimated eGFR • to <60 mL/min/1.73 m^2, new ESKD, or death from renal or CV causes • Death from any cause

	breast-feeding	

Results:
Primary: Dapagliflozin did not result in a lower rate of MACE than PBO (8.8% and 9.4% in the two groups, respectively; HR, 0.93; 95% CI, 0.84 to 1.03; P=0.17). With respect to efficacy, dapagliflozin resulted in a lower rate of CV death or HHF than PBO (4.9% vs. 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; P=0.005).
Secondary: The incidence of the renal composite outcome was 4.3% in the dapagliflozin group and 5.6% in the PBO group (HR, 0.76; 95% CI, 0.67 to 0.87). The rate of death from any cause did not differ significantly between the groups (6.2% in the dapagliflozin group and 6.6% in the PBO group; HR, 0.93; 95% CI, 0.82 to 1.04).
Conclusion: The authors concluded "In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure."

Citation	Design	Endpoints
VERTIS-CV Cannon CP, Kumbhani, Bhatt DL. (June 2020). Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial. Paper presented at the meeting of the American College of Cardiology. Virtual Conference.	N=8246 Multicenter, randomized, double-blind, placebo-controlled trial Inclusion criteria: Age ≥40 years, T2DM diagnosis according to American Diabetes Association (ADA) guidelines: glycated hemoglobin (HbA1c) 7.0-10.5% (53-91 mmol/mol), established ASCVD involving the coronary, cerebrovascular, and/or peripheral artery systems, stable on allowable antihyperglycemic agents (AHAs) or on no background AHA for ≥8 weeks prior to study participation Exclusion criteria: History of type 1 DM or ketoacidosis, experiencing a CV event (e.g., myocardial infarction [MI] or stroke) or undergoing coronary or peripheral intervention procedure between the screening visit and randomization Undergoing any CV surgery (e.g., valvular surgery) within 3 months of the screening visit, planned revascularization or peripheral intervention procedure or other CV surgery, estimated glomerular filtration rate <30 ml/min/1.73 m2 at the screening visit, New York Heart Association class IV heart failure (HF) at screening visit (class III-IV prior to protocol amendment) Randomized in a 1:1:1 fashion to either ertugliflozin 5 mg, 15 mg, or placebo for 3.5 years.	**Primary endpoint:** • CV death, nonfatal MI, stroke **Secondary endpoints:** • HF hospitalization • HbA1c at 18 weeks • Mean decrease in body weight • Symptomatic hypoglycemia event • Urinary tract infection • Amputation • Renal outcomes (renal death, dialysis, double of serum creatinine)

Results: The primary outcome, CV death, nonfatal MI, or stroke for ertugliflozin vs. placebo: 11.9% vs. 11.9% (hazard ratio 0.97, 95% confidence interval 0.85-1.11, $p < 0.001$ for noninferiority); CV death: 1.8% vs. 1.9% ($p = 0.39$); MI: 1.7% vs. 1.6% ($p = 0.66$); stroke: 0.8% vs. 0.8% ($p = 0.99$). Secondary outcomes, HF hospitalization: 2.5% vs. 3.6% ($p = 0.006$); HbA1c at 18 weeks for 5 mg ertugliflozin vs. placebo: -0.5% ($p < 0.0001$); HbA1c at 18 weeks for 15 mg ertugliflozin vs. placebo: -0.5% ($p < 0.0001$); mean decrease in body weight for ertugliflozin 5 mg vs. placebo: 2.4 kg; for ertugliflozin 15 mg vs. placebo: 2.8 kg; symptomatic hypoglycemic event: 27.2% vs. 28.8%; urinary tract infection: 12.1% vs. 10.2% ($p < 0.05$); amputation: 2.0% vs. 1.6% ($p > 0.05$); renal composite (renal death, dialysis/transplant, doubling of serum creatinine): 3.2% vs. 3.9% ($p = 0.08$) Doubling of serum creatinine: 3.1% vs. 3.8%
Conclusion: Ertugliflozin did not produce a statistically significant drop in combined incidence of CV death or rate of renal adverse events. It did, however, reduce the risk of heart failure hospitalization.

Citation	Design	Endpoints
EMPEROR-Reduced Packer M, Anker S, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin	N=3730 Phase III, randomized (1:1), double-blind, PBO-controlled trial Arms: empagliflozin 10 mg QD or PBO Inclusion criteria: Adults ≥ 18 years at screening with HFrEF and elevated NT-proBNP;	**Primary:** • Composite of CV death or hospitalization for worsening HF **Secondary:**

in Heart Failure. N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.	appropriate dose of medical therapy for HF consistent with prevailing local and international CV guidelines Exclusion criteria: MI, coronary artery bypass graft surgery, or other major CV surgery, stroke or transient ischemic attack in past 90 days; heart transplant recipient or listed for heart transplant; acute decompensated HF; systolic BP ≥180 mmHg, symptomatic HoTN and/or a systolic BP <100 mmHg; liver disease; impaired renal function (eGFR < 20 mL/min/1.73 m^2 or requiring dialysis); history of ketoacidosis; women who are pregnant, nursing, or who plan to become pregnant during the trial	• Safety
Results: Primary: During a median of 16 months, a primary outcome event occurred in 19.4% of patients in the empagliflozin group and in 24.7% of patients in the PBO group (p<0.001). A subgroup analysis showed that the effect of empagliflozin on the primary outcome was consistent regardless of diabetes status. Secondary: Uncomplicated genital tract infection was reported more frequently in the empagliflozin group (1.3% vs. 0.4%), but the frequency of HoTN, volume depletion and hypoglycemia were similar in the two groups. **Conclusion**: The authors concluded that "Among patients receiving recommended therapy for HF, those in the empagliflozin group had a lower risk of cardiovascular death or HHF than those in the PBO group, regardless of the presence or absence of diabetes."		
Citation	**Design**	**Endpoints**
BEST John J.V. McMurray, Mason W. Freeman, Joe Massaro, et al. 32-or: the bexagliflozin Efficacy and Safety Trial (BEST): A Randomized, Double-Blind, Placebo-Controlled, Phase IIII, Clinical Trial. *Diabetes* 1 June 2020; 69 (Supplement_1): 32–OR.	N= 1,701 Phase III, multicenter, randomized, double-blind, placebo controlled Arms: After a single-blind, 2-week, placebo run-in period, subjects were randomized 2:1 to Brenzavvy 20 mg QD or placebo. Patients could be on other established background therapy for type 2 diabetes. Inclusion criteria: diagnosis of T2DM, stable treatment regimen of T2DM for the past 3 months, subjects present with at least one of the following 3 histories: Group 1: A history of atherosclerotic vascular disease Group 2: A history of heart failure Group 3: Age ≥ 55 years with diabetes for ≥ 10 years, uncontrolled hypertension, currently smoking, reduced kidney function, or cholesterol problems Exclusion criteria: Diagnosis of T1DM, history of genitourinary tract infections, abnormal liver function, history of MI, stroke, or hospitalization for HF within the past 3 months, prior kidney transplant, pregnant or nursing	**Primary:** • Change in HbA1c from baseline to week 24 **Secondary:** • Change in systolic blood pressure from baseline to week 24 in patients with SBP ≥140 mmHg • Change in body weight from baseline to week 48 in patients with BMI ≥25 kg/m2 Exploratory: • MACE+ (CV death, myocardial infarction, stroke, or unstable angina) was tested in a non-inferiority analysis to demonstrate upper 95% CI <1.8
Results: Primary: • Treatment with Brenzavvy provided a statistically significant reduction in HbA1c at week 24 compared to treatment with placebo. The change from baseline HbA1c was -0.4 in the placebo group, and -0.8 in the Brenzavvy arm. In the placebo group, 17% of subjects achieved HbA1c <7%, compared to 29% in the Brenzavvy group. Secondary: • The mean changes from baseline to Week 24 were -0.3 kg and -2.7 kg in the placebo and Brenzavvy groups, respectively. The difference from placebo (95% CI) for Brenzavvy was -2.3 kg (-2.8, -1.9). • The mean changes in SBP from baseline to Week 24 were -6.6 mmHg and -9.2 mmHg in the placebo and Brenzavvy groups, respectively. The difference from placebo (95%		

CI) for Brenzavvy was -2.7 mmHg (-5.2, -0.1).

Exploratory: The proportion of patients who experienced at least one MACE event was 10.1% (57/567) in the placebo group and 7.9% (89/1132) in the Brenzavvy group (4.2 MACE events per 100 person-years for placebo and 3.3 MACE events per 100 person-years for Brenzavvy). No increased risk for MACE was observed in the Brenzavvy group compared to the control group [estimated hazard ratio of 0.77 (95% CI: 0.56, 1.08)]. The Brenzavvy group was not superior to the placebo group in reducing MACE.

Conclusion: In high-risk T2D patients, bexagliflozin was well tolerated and improved HbA1c, SBP, and weight.

Citation	Design	Endpoints
SOLOIST-WHF Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117-128.	N=1222 Phase III, double-blind, randomized (1:1), placebo-controlled trial Arms: sotagliflozin 200 mg once daily (with dose increase to 400 mg depending on side effects) or placebo Inclusion criteria: Adults 18-85 years of age and have been hospitalized due to presence of signs and symptoms of HF and received treatment with IV diuretic therapy, previous diagnosis of type 2 diabetes or lab evidence to support diagnosis of T2DM Exclusion criteria: End-stage HF or recent acute coronary syndrome, stroke, percutaneous coronary intervention or coronary-artery bypass surgery, estimated eGFR of <30 ml/min/1.73m2, not clinically stable	**Primary:** • Total number of deaths from cardiovascular causes and hospitalizations and urgent visits for HF (first and subsequent) **Secondary:** • Total number of hospitalizations and urgent visits for HF

Results:

Primary:

- 600 events occurred among 1222 patients (n=245 in sotagliflozin group, n=355 in placebo group). The rate of event was 51.0 per 100 patient years in sotagliflozin group and 76.3 per 100 patient years in placebo group (HR 0.67; 95% CI, 0.52 to 0.85; p<0.001) resulting in an absolute difference of 25.3 events per 100 patient years (95% CI, 5.1 to 45.6).

Secondary:

- Hospitalization and urgent visits for HF: 194 events in sotagliflozin group and 297 in placebo group (HR 0.64; 95% CI, 0.49 to 0.83; p<0.001)

Conclusion: In patients with diabetes and recent worsening heart failure, sotagliflozin therapy, initiated before or shortly after discharge, resulted in a significantly lower total number of deaths from cardiovascular causes and hospitalization and urgent visits for heart failure than placebo.

FORMULARY PLACEMENT, UTILIZATION AND COST EXPERIENCE (10/1/2023 - 12/31/2023)

UTILIZATION HISTORY			COST		PRIOR AUTH HISTORY		FORMULARY PLACEMENT	
Medication	**Rx**	**Mbrs**	**Total**	**Avg/Rx**	**Total**	**Approved (%)**	**Current**	**Recommend**
SGLT-2 Inhibitor Monotherapy								
Dapagliflozin (Farxiga®) 5, 10 mg oral tablet	28	13	$15,424.96	$550.89	2	2 (100%)	F-PA	**(Brand) → F-ST***
Invokana® (canagliflozin) 100, 300 mg oral tablet	4	1	$2,312.84	$578.21	0	0 (0%)	NF	No change
Jardiance® (empagliflozin) 10, 25 mg oral tablet	27	16	$15,091.29	$558.94	20	10 (50%)	F-PA	No change
Steglatro® (ertugliflozin) 5, 15 mg oral tablet	106	49	$36,994.82	$349.01	0	0 (0%)	F-ST (t/f metformin)	**F-ST: Add ST* medications**
Brenzavvy™ (bexagliflozin) 20 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Inpefa™ (sotagliflozin) 200 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Combination SGLT-2 Inhibitors/metformin								
Xigduo® XR (dapagliflozin and metformin extended release) 2.5 mg-1,000 mg, 5 mg-500 mg, 5 mg-1,000 mg, 10 mg-500 mg, 10 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	**(Brand) → F-ST***
Invokamet® (canagliflozin-metformin) 50 mg-500 mg, 50 mg-1,000 mg, 150 mg-500 mg, 150 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Invokamet® XR (canagliflozin-metformin extended release) 50 mg-500 mg, 50 mg-1,000 mg, 150 mg-500 mg, 150 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Synjardy® (empagliflozin-metformin) 5 mg-500 mg, 5 mg-1,000 mg, 12.5 mg-500 mg, 12.5 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Synjardy® XR (empagliflozin-metformin extended release) 5 mg-1,000 mg, 10 mg-1,000 mg, 12.5 mg-1,000 mg, 25 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	NF	No change
Segluromet® (ertugliflozin-metformin) 2.5 mg-500 mg, 2.5 mg-1,000 mg, 7.5 mg-500 mg, 7.5 mg-1,000 mg oral tablet	3	1	$990.72	$330.24	0	0 (0%)	F-ST (t/f metformin)	**F-ST: Add ST* medications**
Combination SGLT-2/DPP-4 Inhibitors								
Qtern® (dapagliflozin-saxagliptin) 5 mg-5 mg, 10 mg-5 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Glyxambi® (empagliflozin-linagliptin) 10 mg-5 mg, 25 mg-5 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Steglujan® (ertugliflozin-sitagliptin) 5 mg-100 mg, 15 mg-100 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-ST (t/f metformin)	**→ F-PA**

Triple-Drug-Therapy (SGLT-2/DPP-4 Inhibitors/metformin)								
Trijardy® XR (empagliflozin-linagliptin-metformin extended release) 5 mg-2.5 mg-1,000 mg, 10 mg-5 mg-1,000 mg, 12.5 mg-2.5 mg-1,000 mg, 25 mg-5 mg-1,000 mg oral tablet	0	0	$0.00	$0.00	0	0 (0%)	F-PA	No change
Total	**168**	**80**	**$70,814.63**	**$421.52**	**22**	**12 (55%)**		

*F-ST (trial and failure of one of the following: metformin, branded/generic drugs containing metformin, branded ARNi, generic ACEi, generic ARB, generic mineralocorticoid receptor antagonists (MRAs) or generic beta blockers)
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:

- Separate SGLT2 inhibitors from the combined policy into its own new policy and list updated preferred medications and step therapy and prior authorization requirements

SGLT2 inhibitors and Combinations	
Therapeutic Classes (AHFS)	Glucose Cotransport 2 Inhibitors (SGLT2 inhibitors)
Medications	**Formulary, step therapy required** • Steglatro (ertigluflozin) • Segluromet (ertigluflozin/metformin) • Farxiga (dapaglifozin) • Xigduo XR (dapagliflozin/metformin) **Formulary, PA required/Non-formulary** • Jardiance (empagliflozin) • Synjardy/Synjardy XR (empagliflozin/metformin) • Dapaglifozin (Farxiga) • Dapagliflozin/metformin (Xigduo XR) • Invokana (canaglifozin) • Invokamet (canagliflozin/metformin) • Steglujan (ertugliflozin/sitagliptin) • Trijardy XR (empagliflozin-linagliptin-metformin) • Glyxambi (empagliflozin/linagliptin) • Qtern (dapagliflozin/saxagliptin) • Inpefa (sotagliflozin) Any other newly marketed sodium glucose cotransport 2 inhibitor (SGLT2 inhibitor)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Formulary, step therapy required medications** For formulary, step-therapy required medications, approve if: • 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 **Formulary, PA required/Non-formulary medications** For medications that require prior authorization or are non-formulary, approve if:

	• The above criteria are met AND documentation of trial and failure, intolerance, contraindication or inability to use one preferred formulary step therapy medication
Criteria Statement	Preferred formulary, step therapy required medications <insert medication name> are reserved for members who have used (or cannot/should not use) one of the following medications: metformin, branded/generic drugs 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 blockers. Medications that require prior authorization or are non-formulary <insert medication name> are reserved for members who have used (or cannot/should not use) one of the following medications: metformin, branded/generic drugs 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 blockers AND one preferred, formulary step therapy required medication.
Last P&T Review Date	3/2024

REFERENCES

1. BioMedTracker. Informa Business Intelligence Inc. Available at: http://www.biomedtracker.com/.
2. UpToDate. Wolters Kluwer. Available at: http://www.uptodate.com/.
3. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Journal of the American College of Cardiology. 2022; 79(19):e263-e421.
4. Garber AJ, Handelsman Y, Grunberger G, et al. Consensus statement by the American Associate of Clinical Endocrinologists and American College of Endocrinology on the comprehensive type 2 diabetes management algorithm – 2020 executive summary. Endocrine Practice. 2020; 26(1). Available at: https://www.aace.com/pdfs/diabetes/algorithm-exec-summary.pdf.
5. Riddle MC, Aroda VR, Bakris G, et al. American Diabetes Association Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022; 45(Suppl. 1): S125-S132.
6. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med.* 2015:373:2117-2128.
7. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved). US National Library of Medicine. NCT03057951. Available at https://clinicaltrials.gov/ct2/show/NCT03057951
8. EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced) US National Library of Medicine. NCT03057977. Available at https://clinicaltrials.gov/ct2/show/NCT03057977
9. Dagogo-Jack S, Liu J, Eldor R, et al. Safety and Efficacy of Ertugliflozin in the Treatment of Participants With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Metformin and Sitagliptin. *Diabetes Obes Metab*. 2017 Sep 17. doi: 10.1111/dom.13116
10. Terra SG, Focht K, Davies M, et al. A Study of the Efficacy and Safety of Ertugliflozin Monotherapy in the Treatment of Participants With Type 2 Diabetes Mellitus and Inadequate Glycemic Control Despite Diet and Exercise. *Diabetes Obes Metab*. 2017 May 19(5):721-728
11. Rosenstock J, Frias J, Pall D, et al. Effect of ertugliflozin on glucose control, body weight, blood pressure and bone density in type 2 diabetes mellitus inadequately controlled on metformin monotherapy. *Diabetes Obes Metab*. 2017;1-10
12. Dagogo-Jack S, Liu J, Eldor R, et al. Efficacy and safety of the addition of ertugliflozin in patients with type 2 diabetes mellitus inadequately controlled with metformin and sitagliptin. *Diabetes Obes Metab*. 2017 Sept 17. doi: 10.1111/dom13116
13. Pratley R, et al. Safety and efficacy of ertugliflozin plus sitagliptin versus either treatment alone in subjects with type 2 diabetes inadequately controlled with metformin. 52nd European Association for the Study of Diabetes Annual Meeting 2016; Munich, Germany September 12-16, 2016; ePoster 728
14. Hollander P, et al. Safety and efficacy of ertugliflozin compared to glimepiride in patients with T2DM inadequately controlled on metformin. European Association for the Study of Diabetes; Lisbon, Portugal, Sept 11-15 2017.
15. Rådholm K, Figtree G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus: Results From the CANVAS Program. Circulation. 2018 Jul 31; 138(5): 458–468. doi: 10.1161/CIRCULATIONAHA.118034222.
16. McMurray JJ, Solomon S, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New England Journal of Medicine. 2019; 381:1995-2008; DOI: 10.1056/NEJMoa1911303.
17. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019;380(4):347-357. doi: 10.1056/NEJMoa1812389.
18. Cannon CP, Kumbhani, Bhatt DL. (June 2020). Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial - VERTIS CV. Paper presented at the meeting of the American College of Cardiology. Virtual Conference. Available at https://www.acc.org/~/media/Clinical/PDF-Files/Approved-PDFs/2020/05/15/12/18/ADA20-Presentation-Slides-VERTIS-CV.pdf.
19. Packer M, Anker S, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.
20. Halvorsen Y-D, Conery AL, Lock JP, Zhou W, Freeman MW. Bexagliflozin as an adjunct to metformin for the treatment of type 2 diabetes in adults: A 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2023;25(10):2954-2962.
21. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med. 2021;384(2):117-128.
22. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update [published correction appears in Endocr Pract. 2023 Sep;29(9):746]. *Endocr Pract*. 2023;29(5):305-340. doi:10.1016/j.eprac.2023.02.001

Alameda MRGs for review Q1 2024 P&T

Recommendation:

- Add new medication Agamree to policy
- Update diagnosis documentation requirements to align with and be inclusive of the language in the trails for both medications
- Remove bullet point for weakness before 5 years and serum creatinine kinase, as it only applies to Emflaza
- Remove requirements for baseline eye exam, BMD screening, and calcium/vitamin D supplements to remove prescriber burden. These should be monitored but are not boxed warnings.
- Simplify reauthorization to require clinical benefit and appropriate dose

~~Corticosteroids for Duchenne Muscular Dystrophy (DMD~~Emflaza ~~(deflazacort)~~	
Therapeutic Classes (AHFS)	Glucocorticoids
Medications	Formulary, PA required Emflaza (deflazacort) Agamree (vamorolone)
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be a neurologist ~~,~~or provider who specializes in the treatment of DMD
Coverage Duration	**Initial Approval** 6 months **Later Approval** 12 months; If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**For Approval:** • Confirmed diagnosis of Duchenne Muscular Dystrophy (such as documented mutation of dystrophin gene), genetic sequencing indicating mutations attributed to Duchene Muscular Dystrophy, ~~OR~~ muscle biopsy indicating absence of dystrophin protein, etc.), and copies of testing were submitted with request • ~~Patient has onset of weakness before 5 years of age, and serum creatinine kinase activity of at least 10 times the upper limit of normal (ULN) at some stage in their illness~~ • ~~Prescriber attests to completing a baseline eye examination~~ • ~~Prescriber attests to completing a baseline spine radiograph and bone mineral density (BMD) screening~~ • ~~Patient is or will be taking adequate calcium and vitamin D supplementation~~ • ~~Patient has trial and failure with prednisone administered at a dose no lower than 0.75 mg/kg per day or 10 mg/kg per week for at least 12 months~~ • ~~Documented medical reason why prednisone is not able to be continued, and Emflaza would be medically necessary and not have the same side effect as the preferred agents~~ • Trial and failure with prednisone for at least 12 months, and documented medical reason why prednisone cannot be continued • The request is for an FDA approved dose

	Reauthorization: • Documentation or attestation of clinical benefit (such as improved muscle strength, muscle function, or overall symptom improvement) • ~~Physician attests that the patient's muscle strength has stabilized or improved since starting treatment~~ • ~~Patient's claim history shows consistent therapy (monthly fills)~~ • ~~Physician attests patient has had repeat spine radiographs, eye, and BMD screenings as appropriate~~ • The request is for an FDA approved dose
Criteria Statement	Emflaza and Agamree are~~is~~ reserved for members who have Duchenne Muscular Dystrophy who have used (or cannot/should not use) prednisone for 12 months.
Last P&T Review Date	~~6/2023~~3/2024

Recommendation:

- Differentiate adult vs pediatric criteria.
- Update diagnosis to match labeling.

Corlanor (ivabradine)	
Therapeutic Classes (AHFS)	Cardiac drugs, miscellaneous
Medications	Formulary, PA required: Corlanor (ivabradine)
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	Provider must be a cardiologist
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Initial authorization:**
	All of the following conditions must be met in adult patients:
	• Diagnosis of stable symptomatic chronic heart failure (NYHA Class II-IV~~III~~)
	• Documented left ventricular ejection fraction less than or equal to 35%
	• Documentation (claims history or chart notes) patient is on maximally tolerated doses of beta-blockers or have contraindication to beta blocker use
	• Documentation that the patient has a resting heart rate greater than or equal to 70 bpm
	• Documentation that the patient has had a previous admission to a hospital for worsening heart failure within the past 12 months while on at least two medications from two different medication classes used in the treatment of heart failure with reduced ejection fraction
	• Documentation Corlanor is being used in combination with an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB) or angiotensin II receptor blocker/ neprilysin inhibitor (ARNI) unless not tolerated or contraindicated.
	• Corlanor may **not** be approved if the request indicates **any** of the following:
	  ○ Severe hypotension (less than 90/50 mmHg)
	  ○ Severe hepatic impairment (Child-Pugh class C)
	  ○ Patient's heart rate maintained exclusively by a pacemaker
	
	All of the following conditions must be met in pediatric patients.
	• Member has stable heart failure (NYHA/Ross functional class II-IV) due to dilated cardiomyopathy and a left ventricular ejection fraction ≤ 45%
	• Member is in sinus rhythm with an elevated resting heart rate
	
	Reauthorization:
	• The medication is being prescribed at an appropriate FDA approved dose and indication
	• The member has been receiving the medication and documentation was provided that the prescriber has evaluated the member and recommends continuation of therapy (clinical benefit).

Criteria Statement	Corlanor is reserved for adult members with heart failure and who have used (or cannot/should not use) beta blockers, and an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor blocker (ARB), or an angiotensin II receptor blocker/ neprilysin inhibitor (ARNI) and who have been hospitalized due to heart failure in the previous 12 months. Corlanor is reserved for pediatric members with heart failure and are in sinus rhythm with an elevated resting heart rate.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Update to include the diagnosis of homozygous sitosterolemia as a reason ezetimibe can be approved.

Ezetimibe (Zetia)	
Therapeutic Classes (AHFS)	Cholesterol Absorption Inhibitors
Medications	Formulary, step therapy required Ezetimibe (Zetia) 10 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	**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: • Documented trial and failure, intolerance, contraindication, or inability to use, a formulary preferred statin in the previous 100 days OR~~.~~ • Diagnosis of homozygous sitosterolemia
Criteria Statement	Ezetimibe is reserved for members who have used or who cannot or should not use statin medications or for members with a diagnosis of homozygous sitosterolemia.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Retire. Age limits removed during a previous P&T meeting. All medications listed in this policy are formulary with quantity limit.

Estrogen Patches and Injectables	
Therapeutic Classes (AHFS)	Estrogens
Medications	Formulary, with age restrictions (minimum age 40 years) • Estradiol-*once*-weekly 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1mg patch: restricted to members ≥40 years old and #4 per 28 days / #12 per 84 days • Estradiol-*twice*-weekly 0.025, 0.05, 0.075, 0.1mg patch: restricted to members ≥40 years old and #8 per 28 days /#24 per 84 days Formulary, with quantity limit • Estradiol valerate 20mg/mL, 40mg/mL vial: 1 vial per 30 days
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**" below
Age Restrictions	See "**PA Review Criteria**" below
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 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	*For GID/gender dysphoria coverage, please refer to the Gender Dysphoria medication guidelines* INITIAL CRITERIA for estradiol patches if member is < 40 years of age: • Documentation member does NOT have: active liver disease, history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • For vasomotor symptoms or genitourinary syndrome of menopause (GSM), documentation of trial and failure, contraindication, intolerance and/or side effects to formulary oral estrogen or estrogen plus progestin agents • For prevention of osteoporosis in postmenopausal patient, documented T-score between T-score between -1 and -2.5 at the femoral neck or spine, and a 10 year hip fracture probability (FRAX) ≥3% or a 10 year major osteoporosis-related fracture probability ≥20% AND documentation of trial and failure, contraindication, intolerance and/or side effects to formulary oral estrogen agents or an oral bisphosphonate. RENEWAL CRITERIA for estradiol patches if member is <40 years of age: • Documentation member does NOT have: active liver disease, history of DVT/PE, thromboembolic disease, stroke and/or MI within the last 12 months; known or suspected breast cancer • For vasomotor symptoms or genitourinary syndrome of menopause (GSM), documentation of improvement in symptoms • For prevention of osteoporosis in postmenopausal patient, improvement or stabilization of bone mineral density (BMD). **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	**Estrogen patch for members less than 40 years old:** Estradiol patches are reserved for members for prevention of osteoporosis, who have previously used (or cannot/should not take) oral estradiol or Premarin tablet or an oral bisphosphonate, with no previous history of cardiovascular events, liver disease, or breast cancer. OR Estradiol patches are reserved for members with a diagnosis of menopausal symptoms who have previously used (or cannot/should not take) oral estradiol or Premarin tablet with no previous history of cardiovascular events, liver disease, or breast cancer.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Update policy name
- Add new medication Liqrev to policy
- Reword Opsumit statement for clarity

Vasodilators for Pulmonary Arterial Hypertension (PAH) ~~Criteria~~	
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) **Prostanoids**: 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 Stimulators:** Formulary, prior authorization required Adempas (riociguat) **Non-Prostanoid IP Prostacyclin Receptor Agonists**: Formulary, prior authorization required Uptravi (selexipag) **and any other newly marketed PAH treatment agents.**
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	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 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 requests will be approved for a 6 month duration.

Vasodilators for Pulmonary Arterial Hypertension (PAH) ~~Criteria~~	
	If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**PA CRITERIA FOR INITIAL APPROVAL:**
	• 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 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)
	• 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~~bosentan (Tracleer) tablet AND ambrisentan (Letairis).~~
	• 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)
	
	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 scheduled is provided (if applicable).

Vasodilators for Pulmonary Arterial Hypertension (PAH) ~~Criteria~~	
	• 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. 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 documentation as to why the member is unable to be treated with existing therapy.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Remove duration of 30 days. This is duplicative language and already listed in the coverage duration section.
- Streamline language regarding aspirin used under the diagnosis of ACS or history of MI section

Brilinta (ticagrelor) tablet	
Therapeutic Classes (AHFS)	Platelet aggregation inhibitors
Medications	Formulary, PA required Brilinta (ticagrelor) 60, 90 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	**Initial Approval**: For stable CAD, primary prevention: 12 months For ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (ABCD2 score ≥4), 30 days For ACS or history of MI: 12 months (for the 90mg twice daily dose only) during the first year after an ACS event **Later Approvals**: For stable CAD, primary prevention and ACS or history of MI: 12 months For ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (ABCD2 score ≥4), do not approve If conditions are not met, the request will be sent to a clinical reviewer.

PA Review Criteria	**Initial Approval**
	• For a diagnosis of coronary artery disease (stable) and high risk for ischemic cardiovascular events, primary prevention
	  ○ 60mg twice daily dose is used in combination with aspirin
	OR
	• For a diagnosis of minor ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (ABCD2 score ≥4)
	  ○ 90mg twice daily dose is used in combination with aspirin
	  ~~○ Duration of therapy is 30 days~~
	OR
	• For a diagnosis of acute coronary syndrome (ACS) OR a history of myocardial infarction (MI)
	  ○ 90mg twice daily dose is used in combination with aspirin
	  ○ Patient has trialed and failed clopidogrel AND prasugrel or documentation has been provided to show that there is a medical reason why ticagrelor should be preferred over clopidogrel (for example: the patient has diabetes, over 50% stenosis in more than one vessel, or is over the age of 60, etc.) AND prasugrel (for

	example: the patient is at high risk of bleeding complications, or has history of transient ischemic attack (TIA), or stroke). ~~o Concurrent maintenance doses of aspirin over 100mg should be avoided~~ **Later Approval** • For a diagnosis of coronary artery disease (stable) and high risk for ischemic cardiovascular events, primary prevention, the patient is stable and the provider recommends continuation of therapy • For a diagnosis of minor ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (ABCD2 score ≥4), continuation past 30 days is not indicated, do not approve • For a diagnosis of acute coronary syndrome (ACS) OR a history of myocardial infarction (MI), the patient is stable on the previous 90mg twice daily dose and converts to the 60mg twice daily dose after 12 months of therapy, unless the provider submits a reason why (e.g. the patient has an ongoing high ischemic risk) the 90mg twice daily dose continues to be necessary
Criteria Statement	Brilinta is reserved for members with a diagnosis of stable coronary artery disease with a high risk for cardiovascular events. Brilinta is reserved for members with a diagnosis of minor ischemic stroke (NIHSS score ≤5) or high-risk transient ischemic attack (ABCD2 score ≥4). Brilinta is reserved for patients who have either acute coronary syndrome or a past heart attack who have tried and failed or are unable to take clopidogrel AND prasugrel.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Retire policy, separate into 3 new drug class specific policies, seen below and in SGLT-2 class review document

GLP-1 Agonists, SGLT2 inhibitors, DPP-4 Inhibitors and Combinations	
Therapeutic Classes (AHFS)	Incretin Mimetics (GLP-1 Agonists), Sodium Glucose Cotransport 2 Inhibitors (SGLT2 inhibitors), Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
Medications	**Formulary, Step therapy required (prior use of metformin)** Alogliptin (Nesina) Alogliptin/metformin (Kazano) Alogliptin/pioglitazone (Oseni) Januvia (sitagliptin) Janumet, Janumet XR (sitagliptin/metformin) Steglatro (ertigluflozin) Segluromet (ertigluflozin/metformin) Steglujan (ertugliflozin/sitagliptin) Trulicity (dulaglutide) Ozempic (semaglutide) Rybelsus (semaglutide) Mounjaro (tirzepatide) **Formulary, PA required** Jardiance (empagliflozin) Trijardy XR (empagliflozin-linagliptin-metformin) Glyxambi (empagliflozin/linagliptin) Farxiga (dapaglifozin) Xigduo XR (dapagliflozin/metformin) Qtern (dapagliflozin/saxagliptin) Invokana (canaglifozin) Invokamet (canagliflozin/metformin) Tradjenta (lingagliptin) Jentadueto, Jentadueto XR (linagliptin/metformin) Onglyza (saxagliptin) Kombiglyze XR (saxagliptin/metformin) Byetta, Bydureon, Bydureon Bcise (exenatide) Victoza (liraglutide) **Non-Formulary** Synjardy/Synjardy XR (empagliflozin/metformin) Any other newly marketed incretin mimetic (GLP-1 Agonist), sodium glucose cotransport 2 inhibitor (SGLT2 inhibitor), dipeptidyl peptidase-4 (DPP-4) inhibitor
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months

	Later Approvals 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**<u>Criteria for Heart Failure</u>** • Member has a diagnosis of symptomatic heart failure (NYHA functional class II-IV) • If left ventricular ejection fraction (LVEF) is reduced (i.e. ≤ 40%) the member is currently being prescribed or will be prescribed the following treatment regimen or documentation has been provided that the member is not able to tolerate these agents: o Angiotensin-converting enzyme (ACE) inhibitor OR angiotensin receptor blocker (ARB) OR angiotensin receptor/neprilysin inhibitor (ARNI) o Evidence-based beta-blocker (must be bisoprolol, carvedilol, or metoprolol succinate) **<u>Criteria for Chronic Kidney Disease</u>** • Member has a diagnosis of chronic kidney disease • Member has an eGFR between 25 and 75 mL/min/1.73m^2 lasting for at least 3 months • Member has a urine microalbumin or albumin creatinine ratio (UACR) ≥ 200 mg/g • Member is currently being prescribed or will be prescribed the following treatment regimen or documentation has been provided that the member is not able to tolerate these agents: Angiotensin-Converting Enzyme (ACE) Inhibitor OR Angiotensin Receptor Blocker (ARB) **<u>Criteria for Type 2 Diabetes</u>** For formulary, step-therapy required medications, approve if: • Documentation of trial and failure, intolerance, contraindication, or inability to use metformin IR or ER in the previous 90 days OR dual therapy with metformin is required due to initial Hemoglobin A1C (average blood glucose level over 2 to 3 months) ≥ 7.5% • If request is for a DPP4 inhibitor: no current use of ANY GLP-1 Agonists (based on claims history) • If request is for a GLP1 agonist: no current use of ANY DPP-4 inhibitors (based on claims history) For formulary medications that require prior authorization, approve if: • The above criteria is met AND documentation of trial and failure, intolerance, contraindication or inability to use one preferred alternative in the same class [i.e., for approval of Victoza (liraglutide), the member must have tried and failed or have a reason not to use Trulicity (dulaglutide), Ozempic (semaglutide), Mounjaro (tirzepatide), or Rybelsus (semaglutide)] For those with established cardiovascular disease (CVD) or heart failure, approve if: • Above Metformin criteria is met • Request is for Invokana (canagliflozin) or Farxiga (dapagliflozin) to reduce risk of cardiovascular events AND/OR to reduce risk of CKD progression For those with established cardiovascular disease (CVD), approve if: • Above Metformin criteria is met • Request is for Jardiance (empagliflozin) to reduce risk of cardiovascular events
Criteria Statement	Formulary, step therapy required DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 agonist medications are reserved for members with type 2 diabetes who have used (or

	cannot/should not use) metformin IR or ER or have Hemoglobin A1C (average blood glucose level over 2 to 3 months) ≥ 7.5% DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 agonist medications that require prior authorizations are reserved for members with type 2 diabetes who have used (or cannot/should not use) formulary, step-therapy required DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 agonist medications. Medications indicated for heart failure are reserved for members with symptomatic heart failure. If the left ventricular ejection fraction (LVEF) is reduced (i.e. ≤ 40%), the medications are reserved for members who have used (or cannot/should not use) an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) or an angiotensin receptor/neprilysin inhibitor (ARNI) AND an evidence-based beta-blocker (bisoprolol, carvedilol, or metoprolol succinate). Medications indicated for chronic kidney disease are reserved for members with chronic kidney disease, who have used (or cannot/should not use) an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). Invokana or Farxiga are reserved for members who have a diagnosis of cardiovascular disease (CVD) or heart failure to reduce risk of cardiovascular events AND/OR to reduce risk of chronic kidney disease (CKD) progression who have used (or cannot/should not use) metformin IR or ER. Jardiance is reserved for members who have a diagnosis of cardiovascular disease (CVD) to reduce risk of cardiovascular events who have used (or cannot/should not use) metformin IR or ER.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- New policy

GLP-1 Agonists	
Therapeutic Classes (AHFS)	GLP-1 Agonists
Medications	**<u>Formulary, Step therapy required (prior use of metformin)</u>** • Trulicity (dulaglutide) • Ozempic (semaglutide) • Rybelsus (semaglutide) • Mounjaro (tirzepatide) **<u>Formulary, PA required</u>** • Byetta, Bydureon, Bydureon Bcise (exenatide) • Victoza (liraglutide) Any other newly marketed incretin GLP-1 Agonist
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**<u>Criteria for Type 2 Diabetes</u>** For formulary, step-therapy required medications, approve if: • Documentation of trial and failure, intolerance, contraindication, or inability to use metformin For formulary medications that require prior authorization, approve if: • The above criteria are met AND documentation of trial and failure, intolerance, contraindication or inability to use one preferred formulary step therapy required alternative
Criteria Statement	Preferred formulary, step therapy required medications <insert medication name> are reserved for members with type 2 diabetes who have used (or cannot/should not use) metformin. Medications that require prior authorization <insert medication name> are reserved for members with type 2 diabetes who have used (or cannot/should not use) metformin AND one preferred, formulary step therapy required medication.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- New policy
- Add new medication Zituvio

DPP-4 Inhibitors and Combinations	
Therapeutic Classes (AHFS)	Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
Medications	**Formulary, Step therapy required (prior use of metformin)** • Alogliptin (Nesina) • Alogliptin/metformin (Kazano) • Alogliptin/pioglitazone (Oseni) • Januvia (sitagliptin) • Janumet, Janumet XR (sitagliptin/metformin) **Formulary, PA required/ Non-formulary** • Tradjenta (lingagliptin) • Jentadueto, Jentadueto XR (linagliptin/metformin) • Onglyza (saxagliptin) • Kombiglyze XR (saxagliptin/metformin) • Zituvio (sitagliptin) Any other newly marketed dipeptidyl peptidase-4 (DPP-4) inhibitor
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	N/A
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	N/A
Coverage Duration	**Initial Approval** 12 months **Later Approvals** 12 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**Criteria for Type 2 Diabetes** For formulary, step-therapy required medications, approve if: • Documentation of trial and failure, intolerance, contraindication, or inability to use metformin For formulary medications that require prior authorization, approve if: • The above criteria are met AND documentation of trial and failure, intolerance, contraindication or inability to use one preferred formulary step therapy required alternative
Criteria Statement	Preferred formulary, step therapy required medications <insert medication name> are reserved for members with type 2 diabetes who have used (or cannot/should not use) metformin. Medications that require prior authorization <insert medication name> are reserved for members with type 2 diabetes who have used (or cannot/should not use) metformin AND one preferred, formulary step therapy required medication
Last P&T Review Date	3/2024

Recommendation:

- Update the coverage duration for initial approvals to one month for tolcapone to evaluate clinical response and 12 months for other agents.

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

	(such as dopamine agonists [e.g., pramipexole or ropinirole] or monoamine oxidase B inhibitors [e.g., selegiline])
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Include "baseline" for clarity and update wording and format for clarity of review.
- Add in criteria for patients not at very high risk. The guidelines cover very high risk and not very high risk patients with established ASCVD who need additional therapy, but their LDL targets are different (more aggressive in the very high risk group).

PCSK-9 Monoclonal Antibodies (mAbs)	
Therapeutic Classes (AHFS)	PCSK9 Monoclonal Antibodies (mAbs)
Medications	Formulary, prior authorization Repatha (evolocumab) Praluent (alirocumab)
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 cardiologist or a specialist in the treatment of lipid disorders.
Coverage Duration	**Initial Approval** 3 months **Later Approvals** 6 months If conditions are not met, the request will be sent to a clinical reviewer.
PA Review Criteria	**INITIAL AUTHORIZATION:** **For all requests** • Request is appropriate for member (e.g. age) as indicated in package labeling or standard of care guidelines • Patient has tried and failed simvastatin 40mg, atorvastatin 40mg-80mg, or rosuvastatin 20-40mg (consistently for 3 months via claim history or chart notes). If patient is not able to tolerate simvastatin, atorvastatin or rosuvastatin, documentation was provided that patient is taking another statin at the highest tolerated dose, or a medical reason was provided why the member is not able to use these therapies. • If prescriber indicates member is "statin intolerant", documentation was provided including description of the side effects, duration of therapy, "wash out", re-trial, and then change of agents. • Patient has tried and failed ezetimibe in combination with highest-tolerated intensity statin (if clinically appropriate) consistently for 3 months, OR, patient has an LDL-C that is >25% above goal LDL-C while adherent to treatment with highest-tolerated intensity statin (if clinically appropriate) consistently for 3 months • Documentation was provided indicating provider has counseled member on smoking cessation and following a "heart healthy diet". **Diagnosis of Familial Hypercholesterolemia (FH)** • Member has a diagnosis of familial hypercholesterolemia, as evidenced by one of the following: ○ Documentation provided, including two fasting lipid panel lab reports with abnormal baseline low density lipoprotein (LDL) levels ≥190 for FH in adults or ≥160 for FH in children. ○ Results of positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) **Diagnosis of hyperlipidemia (Primary OR Secondary Prevention):**

<table>
<tr><th colspan="2">PCSK-9 Monoclonal Antibodies (mAbs)</th></tr>
<tr><td></td><td>

If the diagnosis is primary severe hyperlipidemia (i.e. baseline LDL ≥ 190 mg/dL)

LDL remains ≥ 100 mg/dL despite maximally tolerated LDL-lowering therapy

If the diagnosis is secondary atherosclerotic cardiovascular disease (ASCVD) prevention

The patient is “very high risk” (both of the following):

(i.e. a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions, see table below)

<table>
<tr><td rowspan="4">Major ASCVD Events</td><td>Recent ACS (within past 12 months)</td></tr>
<tr><td>History of MI (other than recent ACS event above)</td></tr>
<tr><td>History of ischemic stroke</td></tr>
<tr><td>Symptomatic PAD</td></tr>
<tr><td rowspan="8">High-risk Conditions</td><td>Age ≥ 65 years</td></tr>
<tr><td>Heterozygous familial hypercholesterolemia</td></tr>
<tr><td>History of prior CABG or PCI intervention outside the major ASCVD event(s)</td></tr>
<tr><td>DM</td></tr>
<tr><td>HTN</td></tr>
<tr><td>CKD (eGFR 15-59 mL/min/1.73 m2)</td></tr>
<tr><td>Current smoker</td></tr>
<tr><td>CHF</td></tr>
</table>
ACS – acute coronary syndrome; CABG – coronary artery bypass graft; CHF – congestive heart failure; CKD – chronic kidney disease; DM – diabetes mellitus; HTN – hypertension; MI – myocardial infarction; PAD – peripheral artery disease; PCI – percutaneous coronary intervention

LDL remains ≥ 55 mg/dL or non-HDL (i.e. total cholesterol minus HDL) ≥ 85 mg/dL despite maximally tolerated LDL-lowering therapy

OR

The patient is not at very high risk:

LDL remains ≥ 70 mg/dL or non-HDL (i.e. total cholesterol minus HDL) ≥ 100 mg/dL despite maximally tolerated LDL-lowering therapy

If the above criteria are met, the request will be approved for up to a 3 month duration; if all of the above criteria are not met, the request will be sent to a clinical reviewer.
<u>REAUTHORIZATION CRITERIA FOR ALL INDICATIONS:</u>

Documentation submitted indicates that the member has obtained clinical benefit from the medication including repeat fasting lipid panel lab report, and the member has had a reduction in LDL from baseline, prior to starting PCSK9 inhibitor therapy
The patient’s claim history shows consistent therapy (i.e. monthly fills)

</td></tr>
<tr><td>Criteria Statement</td><td>For familial hypercholesterolemia, Repatha and Praluent are reserved for members who have used (or cannot/should not use) simvastatin 40 mg, atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg tablets AND ezetimibe, are following a heart healthy diet, a non-smoker or trying to quit smoking, has two cholesterol tests with low density lipoprotein (LDL) ≥190 for adults or ≥160 for children or results of positive genetic testing for an LDL-C–raising gene defect.
For hyperlipidemia (primary or secondary prevention) Repatha and Praluent are reserved for members who have used (or cannot/should not use) simvastatin 40 mg,</td></tr>
</table>

PCSK-9 Monoclonal Antibodies (mAbs)	
	atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg tablets AND ezetimibe, following a heart healthy diet, a non-smoker or trying to quit smoking. For primary severe hyperlipidemia, LDL that remains ≥ 100 mg/dL despite maximally tolerated LDL-lowering therapy. For secondary atherosclerotic cardiovascular disease (ASCVD), LDL remains ≥ 55 mg/dL or non-HDL (i.e. total cholesterol minus HDL) ≥ 85 mg/dL for those at very high risk, or LDL remains ≥ 70 mg/dL or non-HDL (i.e. total cholesterol minus HDL) ≥ 100 mg/dL for those not at very high risk, despite maximally tolerated LDL-lowering therapy.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Reword exclusion criteria statement for clarify
- Change initial approval to 6 months. The GINA guidelines suggest an initial trial with Xolair for ***at least*** 4 months. Increase duration for operational ease.

Xolair (omalizumab) for Asthma and Urticaria	
Therapeutic Classes (AHFS)	RESPIRATORY TRACT AGENTS, MISCELLANEOUS
Medications	**Xolair (omalizumab)**
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), and the Drug Package Insert.
Exclusion Criteria	Use of Xolair concomitantly with another pulmonary biologic ~~Patients actively using~~ (e.g. Cinqair, Fasenra, Dupixent, Tezspire, or Nucala)
Required Clinical Information	See "PA Review Criteria"
Age Restrictions	N/A
Prescriber Restrictions	**Asthma:** Pulmonologist or Allergist or one was consulted **Chronic Idiopathic Urticaria:** Allergist, Immunologist, Dermatologist, or one was consulted
Coverage Duration	**Initial Approval** Up to a 6 ~~4~~ month duration **Later Approvals** Up to a 6 months duration If criteria is not met, request will be sent to a Medical Director/clinical reviewer for medical necessity review.
PA Review Criteria	****For nasal polyposis, please refer to the "Biologic Agents for Nasal Polyposis" policy**** **INITIAL AUTHORIZATION FOR ASTHMA:** • The patient has at least a 6 month history of moderate-to-severe asthma. • The drug is indicated for the patient's age and is prescribed at an approved dose according to the patient's weight and IgE level • Patient is taking maximally tolerated ICS/LABA combination in addition to a LAMA (e.g. tiotropium) for at least 3 months or there is a documented medical reason why the patient is unable to take these medications • Patient's asthma is uncontrolled as defined by having one of the following: ○ Frequent severe exacerbations requiring two or more bursts of systemic glucocorticoids (more than three days each) in the previous year ○ History of serious exacerbation: at least one hospitalization, intensive care unit stay, or mechanical ventilation in the previous year ○ Airflow limitation defined as a forced expiratory volume in 1 second (FEV1) less than 80% of predicted ○ Poor symptom control including at least THREE of the following: ▪ Asthma Control Questionnaire (ACQ) consistently > 1.5 or Asthma Control Test (ACT) < 20 ▪ Daytime asthma symptoms more than twice per week ▪ Use of an inhaled short acting B-2 agonist to relieve asthma symptoms more than twice per week (not including use prior to exercise) ▪ Limited physical activity due to asthma symptoms ▪ Nighttime awakening due to asthma symptoms

	• The patient has a positive documented immediate response on RAST test and/or skin prick test to at least 1 common allergen (e.g. dermatophagoides farinae, dermatophagoides pteronyssinus, dog, cat, or cockroach) and there is documented evidence that the positive skin tested allergen(s) is an asthma trigger (copy of results required). • Pre-treatment serum IgE levels must be greater than or equal to 30IU/mL **INITIAL AUTHROIZATION FOR CHRONIC IDIOPATHIC URTICARIA:** • The drug is indicated for the patient's age and is prescribed at an approved dose • The patient has a documented history of urticaria for at least 6 weeks • The patient requires oral steroids to control symptoms. • The patient remains symptomatic despite a minimum two week trial (or has medical reason for not utilizing) of two formulary second generation H1 antihistamines at the maximum tolerated dose **REAUTHORIZATION AFTER 4 MONTHS OF THERAPY FOR ASTHMA OR CHRONIC IDIOPATHIC URTICARIA:** • Documentation submitted indicates that the member has benefited clinically from the medication (e.g. patient has marked improvement in pulmonary function tests such as FEV1 or peak expiratory flow rate, decrease in asthma exacerbations, decrease in skin manifestations or severe itching, and/or a decrease in inhaled or oral corticosteroid use since receiving Xolair therapy). • The prescribed dose is within approved FDA dosing guidelines.
Criteria Statement	N/A
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Minor changes in wording of prescriber restrictions and diagnosis requirement for ease of access

Agents for Atopic Dermatitis	
Therapeutic Classes (AHFS)	Skin and mucous membrane agents, anti-inflammatory agents, misc (skin)
Medications	**Formulary, Step therapy required:** Tacrolimus (Protopic) Pimecrolimus (Elidel) **Formulary, Prior Authorization Required:** Dupixent (dupilumab) Rinvoq (upadacitinib) **Non-formulary:** Eucrisa (crisaborole) Opzelura (ruxolitinib) Adbry (tralokinumab-ldrm) Cibinqo (abrocitinib) Any other newly marketed agent for atopic dermatitis
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	Tacrolimus (Protopic), pimecrolimus (Elidel), and Opzelura (ruxolitinib): Immunocompromised members
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	N/A
Prescriber Restrictions	Dupixent, Rinvoq, Adbry, Cibinqo and Opzelura requests: Provider must be a prescribed by, or in consultation with, a pediatrician, family practitioner (for members under 21 years of age), dermatologist, immunologist, or allergist
Coverage Duration	For Opzelura: If the criteria are met, the request will be approved with up to an 8 week duration and all reauthorization requests will be approved for up to a 6 month duration. For all others: If the criteria are met, the request will be approved with up to a 6 month duration; if the criteria are not met, the request will be referred to a clinical reviewer for medical necessity review.
PA Review Criteria	**Initial Authorization:** **Criteria for approval for pimecrolimus (Elidel)** • Diagnosis of mild to moderate atopic dermatitis • For mild atopic dermatitis: trial and failure of, intolerance, or inability to use, one formulary medium to high potency topical corticosteroid • For moderate atopic dermatitis: trial and failure of, intolerance, or inability to use, one formulary medium to high potency topical corticosteroid AND topical tacrolimus **Criteria for approval of tacrolimus (Protopic)** • Diagnosis of moderate to severe atopic dermatitis • Trial and failure of, intolerance, or inability to use, one formulary medium to high potency topical corticosteroid

	Criteria for approval for Eucrisa
	• Diagnosis of mild to moderate atopic dermatitis
	• Trial and failure of, intolerance, or inability to use, one formulary medium to high potency topical corticosteroid
	• Trial and failure of, intolerance, or inability to use tacrolimus or pimecrolimus
	
	Criteria for approval for Dupixent or Rinvoq
	• Provider attestation of ~~D~~diagnosis of moderate to severe atopic dermatitis
	• Trial and failure of ONE of the following:
	  ○ One formulary medium to high potency topical corticosteroid
	  ○ Topical tacrolimus or pimecrolimus
	  ○ Eucrisa (crisaborole)
	
	Criteria for approval for Adbry:
	○ Diagnosis of moderate to severe atopic dermatitis (AD)
	○ For moderate AD: Trial and failure, or contraindication/intolerance to ALL of the following:
	  ○ One formulary medium to high potency topical corticosteroid
	  ○ Topical tacrolimus or pimecrolimus
	  ○ Eucrisa (crisaborole)
	○ For severe AD: Trial and failure of, or contraindication/intolerance to, ALL of the following:
	  ○ One formulary topical medium to high potency topical corticosteroid
	  ○ Topical tacrolimus
	
	Criteria for approval for Cibinqo:
	• Diagnosis of refractory, moderate to severe, AD
	• For moderate AD: Trial and failure of, or contraindication to, ALL of the following:
	  ○ One formulary topical medium to high potency topical corticosteroid
	  ○ Topical tacrolimus or pimecrolimus
	  ○ Eucrisa (crisaborole)
	• For severe AD: Trial and failure of, or contraindication to ALL of the following:
	  ○ One formulary medium to high potency topical corticosteroid
	  ○ Topical tacrolimus
	• Trial and failure of, intolerance to, or contraindication to another systemic drug product
	
	Criteria for approval for Opzelura:
	• Diagnosis of mild to moderate atopic dermatitis
	• Member must have 3% to 20% of BSA atopic dermatitis involvement (excluding scalp)
	• Trial and failure of, intolerance, or inability to use to ALL of the following:
	  ○ One formulary medium to high potency topical corticosteroid
	  ○ Topical tacrolimus or pimecrolimus
	  ○ Eucrisa (crisaborole)
	
	****A MAXIMUM OF ONE 60gm TUBE OF OPZELURA MAY BE APPROVED PER WEEK****
	
	Reauthorization:
	• Prescriber attests that the member has experienced improvement in symptoms (e.g. significant clearing of the skin, reduction in itching)

Criteria Statement	For mild to moderate atopic dermatitis pimecrolimus is reserved for members who have used (or cannot/should not use) one topical steroid.

	For moderate atopic dermatitis pimecrolimus is reserved for members who have used (or cannot/should not use) one topical steroid and tacrolimus. For moderate to severe atopic dermatitis tacrolimus is reserved for members who have used (or cannot/should not use) one topical steroid. For mild to moderate atopic dermatitis Eucrisa is reserved for members who have used (or cannot/should not use) one topical steroid and tacrolimus or pimecrolimus. For moderate to severe atopic dermatitis Dupixent or Rinvoq are reserved for members who have used (or cannot should not use) ONE of the following: one topical steroid, tacrolimus or pimecrolimus, or Eucrisa. For moderate atopic dermatitis Adbry is reserved for members who have used (or cannot should not use) ALL of the following: one topical steroid, tacrolimus or pimecrolimus, and Eucrisa. For severe atopic dermatitis Adbry is reserved for members who have used (or cannot/should not use) ALL of the following: one topical steroid and tacrolimus. For moderate atopic dermatitis Cibinqo is reserved for members who have used (or cannot/should not use) ALL of the following: one topical steroid, tacrolimus or pimecrolimus, and Eucrisa AND another systemic drug product. For severe atopic dermatitis Cibinqo is reserved for members who have used (or cannot/should not use) ALL of the following: one topical steroid and tacrolimus AND another systemic drug product. For mild to moderate atopic dermatitis Opzelura is reserved for members who have used (or cannot/should not use) ALL of the following: one topical steroid, tacrolimus or pimecrolimus, and Eucrisa.
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Minor changes in wording of prescriber restrictions requirement for ease of access

Pulmonary Biologics for Asthma and Eosinophilic Conditions	
Therapeutic Classes (AHFS)	Interleukin antagonists
Medications	Nucala (mepolizumab) Fasenra (benralizumab) Cinqair (reslizumab) Dupixent (dupilumab) Tezspire (tezepelumab) Any other newly marketed 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), and the Drug Package Insert.
Exclusion Criteria	• When being used for relief of acute bronchospasm or status asthmaticus • In combination with another monoclonal antibody for the treatment of asthma or eosinophilic conditions
Required Clinical Information	See "PA Review Criteria" below
Age Restrictions	Per Package Insert Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	Prescriber must be prescribed by or in consultation with an allergist, pulmonologist, immunologist, rheumatologist, gastroenterologist, dermatologist, or other provider who specializes in the treatment of asthma or eosinophilic conditions
Coverage Duration	Initial Approval 4 months Later Approvals 6 months If conditions are not met, the request will be sent to a clinical reviewer
PA Review Criteria	**Initial Authorization:** Asthma: • Confirmed diagnosis of one of the following: o Nucala, Fasenra, and Cinqair: Severe Eosinophilic Asthma o Dupixent: Moderate-to-Severe eosinophilic asthma o Tezspire: Severe Asthma • Documentation has been provided of blood eosinophil count within ONE of the following ranges: o Nucala and Dupixent: ≥ 150 cells/mcL (within 6 weeks of request) OR ≥ 300 cells/mcL (within the past 12 months) o Fasenra: ≥ 150 cells/mcL (within the past 12 months) o Cinqair: ≥ 400 cells/mcL (within the past 12 months) o Tezspire: No baseline blood eosinophil counts are required • The member has a documented baseline FEV_1 < 80% of predicted with evidence of reversibility by bronchodilator response. o Tezspire ONLY: If age is < 18 years, the member has a documented baseline FEV_1 < 90% of predicted with evidence of reversibility by bronchodilator response • Documentation has been provided indicating that that the member continues to experience significant symptoms while compliant on a maximally tolerated inhaled corticosteroid with long-acting beta2 agonist (ICS/LABA) AND long-acting muscarinic antagonist (LAMA) (or a documented medical reason must be provided why the member is unable to use these therapies) and ONE of the following: o Nucala: ≥ 2 exacerbations in the past 12 months o Fasenra: ≥ 1 exacerbation in the past 12 months

	○ Cinqair: ≥ 1 exacerbation in the past 12 months requiring systemic corticosteroids ○ Dupixent: ≥ 1 exacerbation in the past 12 months requiring systemic corticosteroids or hospitalization ○ Tezspire: ≥ 2 exacerbations requiring systemic corticosteroids OR ≥ 1 exacerbation in the past 12 months requiring hospitalization • The prescribed dose is within FDA approved dosing guidelines <u>Oral Corticosteroid Dependent Asthma: (Dupixent only)</u> • Confirmed diagnosis of oral corticosteroid (OCS) dependent asthma with at least 5 mg oral prednisone or equivalent per day for at least 4 weeks within the last 3 months • The patient has a documented baseline FEV1 < 80% of predicted with evidence of reversibility by bronchodilator response. • Documentation has been provided indicating patient still is having significant symptoms with ≥ 1 exacerbations in the previous 12 months requiring additional medical treatment, (emergency room visits, hospital admissions) while compliant on a high-dose inhaled corticosteroid with a long-acting B2 agonist AND a long-acting muscarinic antagonist (LAMA). If the patient has not utilized these therapies, a documented medical reason must be provided why patient is unable to do so. • The prescribed dose is within FDA approved dosing guidelines <u>Eosinophilic Esophagitis (EoE) (*Dupixent only):*</u> • Confirmed diagnosis of EoE by endoscopic biopsy indicating ≥15 intraepithelial eosinophils per high-power field (eos/hpf) • Documentation of baseline esophageal intraepithelial eosinophil count and Dysphagia Symptom Questionnaire (DSQ) scores • Member has a history of at least 2 episodes of dysphagia (with intakes of solids) per week in the last 4 weeks • Documented trial and failure, intolerance, or contraindication to one proton pump inhibitor at a maximally tolerated dose for a minimum of 8 weeks • Member has a documented weight greater than or equal to 40 kg • The prescribed dose is within FDA approved dosing guidelines <u>Prurigo Nodularis (PN) (Dupixent only):</u> • Confirmed diagnosis of PN lasting for at least three months prior to request • Member has a Worst-itch Numeric Rating Scale (WI-NRS) score of 7 or higher indicating severe or very severe itching • Member has at least 20 PN lesions in total • Documented trial and failure, intolerance, or contraindication to at least two of the following for a minimum of two weeks: ○ One medium to super-high potency topical corticosteroid ○ One topical calcineurin inhibitor ○ UVB phototherapy or psoralen plus UVA phototherapy • The prescribed dose is within FDA approved dosing guidelines <u>Eosinophilic granulomatosis with polyangiitis (EGPA) (*Nucala only*)</u>: • Confirmed diagnosis of EGPA and eosinophilic asthma lasting for ≥6 months • Member has a history of relapsing disease defined as at least one EGPA relapse requiring additional corticosteroids or immunosuppressant or hospitalization within the past 2 years OR member has a history of refractory disease defined as failure to attain remission in the prior 6 months following induction treatment with standard therapy

	• Member must be on a stable dose of oral corticosteroids for at least 4 weeks prior to request • Member has a blood eosinophil count ≥1,000 cells/mcL OR > 10% of total leukocyte count • Documented trial and failure, intolerance, or contraindication to cyclophosphamide, rituximab, azathioprine, methotrexate, OR mycophenolate mofetil • The prescribed dose is within FDA approved dosing guidelines <u>Hypereosinophilic Syndrome (HES) (*Nucala only*)</u>: • Confirmed diagnosis of FIP1 like 1-platelet derived growth factor receptor alpha (FIP1L1-PDGFRA)-negative HES lasting for ≥6 months without an identifiable non-hematologic secondary cause • Member has a history of two or more HES flares (worsening of HES-related symptoms necessitating therapy escalation or ≥2 courses of rescue oral corticosteroids) within the past 12 months • Member has a blood eosinophil count ≥1,000 cells/mcL • Documented trial and failure, intolerance, or contraindication to oral corticosteroids AND at least one second-line agent (e.g. hydroxyurea, interferon, imatinib, methotrexate, cyclophosphamide, cyclosporine, azathioprine) (member must be on stable dose of at least one agent for at least 4 weeks prior to request) **<u>Criteria for re-authorization</u>**: • Documented submitted indicates the member has had a positive clinical response (e.g. Asthma: improved FEV1, reduced exacerbations; HES: symptomatic improvement, reduced oral corticosteroid dose; EGPA: reduction in relapse frequency or severity, disease remission, symptomatic improvement, reduced oral corticosteroid dose; EoE: histological remission, improvement in DSQ scores; PN: improvement in WI-NRS score, symptomatic improvement) • The prescribed dose is within FDA approved dosing guidelines
Criteria Statement	For asthma, Nucala, Dupixent, Fasenra, and Cinqair are reserved for members who have used (or cannot/should not use) a maximally tolerated inhaled corticosteroid with a long acting B2 agonist (ICS/LABA) AND a long-acting muscarinic antagonist (LAMA), who have eosinophils in the treatment range per package insert, and who have had asthma exacerbations during the previous 12 months. For oral corticosteroid dependent asthma, Dupixent is reserved for members with a diagnosis of oral corticosteroid dependent asthma, who have used (or cannot/should not use) a high-dose inhaled corticosteroid with a long acting B2 agonist (ICS/LABA) AND a long-acting muscarinic antagonist (LAMA), and who have been using oral corticosteroids for at least 4 weeks within the past 3 months and who have had asthma exacerbations during the previous 12 months. For eosinophilic esophagitis (EoE), Dupixent is reserved for members with a diagnosis of eosinophilic esophagitis with a history of at least 2 episodes of dysphagia (with intakes of solids) per week in the last 4 weeks, who have used (or cannot/should not use) one proton pump inhibitor at a maximum dose for 8 weeks, with a weight greater than or equal to 40kg. For prurigo nodularis (PN), Dupixent is reserved for members with a diagnosis of prurigo nodularis with a Worst-itch Numeric Rating Scale (WI-NRS) score of 7 or higher indicating severe or very severe itching AND at least 20 PN lesions in total AND who have used (or cannot/should not use) at least two of the following: one medium to

	super-high potency topical corticosteroid or one topical calcineurin inhibitor or UVB phototherapy or psoralen plus UVA phototherapy. For eosinophilic granulomatosis with polyangiitis (EGPA), Nucala is reserved for members with a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA), with a history of relapsing disease, who have used (or cannot/should not use) cyclophosphamide, rituximab, azathioprine, methotrexate, OR mycophenolate mofetil. For hypereosinophilic syndrome (HES), Nucala is reserved for members with a diagnosis of hypereosinophilic syndrome, who have a history of 2 or more flares within the past 12 months, who have used (or cannot/should not use) oral corticosteroids AND at least one second-line agent (e.g. hydroxyurea, interferon, imatinib, methotrexate, cyclophosphamide, cyclosporine, or azathioprine).
Last P&T Review Date	~~3/2023~~3/2024

Recommendation:

- Minor changes in wording of prescriber restrictions requirement for ease of access

Biologic Agents for Nasal Polyposis	
Therapeutic Classes (AHFS)	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.; RESPIRATORY TRACT AGENTS, MISCELLANEOUS
Medications	Formulary, PA required Dupixent (dupilumab) Xolair (omalizumab) Nucala (mepolizumab)
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	Use of Dupixent, Nucala, or Xolair concomitantly or with another pulmonary biologic (e.g. Fasenra, Cinqair)
Required Clinical Information	See "**PA Review Criteria**" below
Age Restrictions	Patients must be 18 years age or older Check AAH active CCS cases for members < 21 years of age
Prescriber Restrictions	~~Prescriber m~~Must be prescribed by, or in consultation with an allergist/immunologist or otolaryngologist
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 all of the criteria are not met, the request is referred to a clinical reviewer for medical necessity review.
PA Review Criteria	****Xolair: For asthma and urticaria, please refer to the "Xolair for Asthma and Urticaria" policy**** ****Dupixent: For atopic dermatitis, please refer to the "Agents for Atopic Dermatitis" policy; For asthma, please refer to the "Pulmonary Biologics for Asthma and Eosinophilic Conditions**** ****Nucala: For asthma or other eosinophilic conditions, please refer to the "Pulmonary Biologics for Asthma and Eosinophilic Conditions" policy**** **Initial Authorization:** • Diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) • Medication is being prescribed at an FDA approved dosage • Patient is currently using an intranasal corticosteroid and will continue therapy, will be prescribed an intranasal corticosteroid with request, or has a medical reason for not using an intranasal corticosteroid • Documentation of ONE of the following: o Trial and failure or intolerance or has a medical reason for not using ALL of the following therapies: ▪ an intranasal corticosteroid ▪ a systemic corticosteroid o Prior surgery for nasal polyps **Re-authorization:** • Member will continue to use intranasal corticosteroid, or has a medical reason for not using an intranasal corticosteroid • Documentation has been provided that demonstrates a clinical benefit (e.g. improvements in symptom severity, nasal polyp score [NPS], sino-nasal

	outcome test-22 [SNOT-22], nasal congestion score [NCS]), nasal obstruction symptom visual analogue scale [VAS]) • Medication is being prescribed at an FDA-approved dosage
	When used for chronic rhinosinusitis with nasal polyps, Xolair, Nucala, or Dupixent are reserved for members who have used (or cannot/should not use) an intranasal steroid (and will continue using it) and additionally, who have used (or cannot/should not use) all of the following: intranasal corticosteroids and a systemic corticosteroid, OR has had prior surgery for nasal polyps.
Last P&T Review Date	~~9/2023~~3/2024

Alameda PADs for review Q1 2024 P&T

Recommendation:

- Add new medication Rivfloza and change the name of the policy to be inclusive of both medications.
- Separate metabolic testing requirements based on what endpoints drug is approved for. Rivfloza is only approved to reduce urinary oxalate, Oxlumo is approved to reduce urinary oxalate and plasma oxalate.
- Add kidney function requirement for Rivfloza, as it is part of the drug indication.
- Add exclusion for not using both drugs concurrently.

Primary Hyperoxaluria Agents~~Oxlumo (lumasiran)~~	
Medications	Oxlumo (lumasiran) Rivfloza (nedosiran)
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 nephrologist, urologist, hepatologist, or endocrinologist
Coverage Duration	A 6 month duration for initial approval and 12 months for renewal
Maximum Billable Units	Variable

Other Criteria	**Initial Authorization**
	• Diagnosis of primary hyperoxaluria type 1 (PH1) confirmed by one of the following:
	  ○ Genetic testing confirming at least one mutation at the AGXT gene
	  ○ Liver biopsy showing decreased or absent alanine:glyoxylate aminotransferase (AGT) activity
	• Metabolic testing demonstrating one of the following:
	  ○ For Oxlumo (one of the following):
	  ▪ Increased urinary oxalate excretion (≥ 0.5 mmol/1.73 m2 per day[45 mg/1.73 m2 per day])
	  ▪ Increased urinary oxalate:creatinine ratio relative to normative values for age
	  ▪ Increased plasma oxalate level (≥ 20 µmol/L)
	  ○ For Rivfloza (one of the following):
	  ▪ Increased urinary oxalate excretion (≥ 0.5 mmol/1.73 m2 per day[45 mg/1.73 m2 per day])
	  ▪ Increased urinary oxalate:creatinine ratio relative to normative values for age
	  ~~○ Increased urinary oxalate excretion (≥ 0.5 mmol/1.73 m3 per day[45 mg/1.73 m3 per day])~~
	  ~~○ Increased urinary oxalate:creatinine ratio relative to normative values for age~~
	  ~~○ Increased plasma oxalate level (≥20 µmol/L)~~
	• For Rivfloza: member has relatively preserved kidney function (e.g., EGFR ≥ 30 mL/min/1.73 m2)
	• Member is concurrently using pyridoxine or has tried and failed previous pyridoxine therapy for at least 3 months, or has a medical reason for not using pyridoxine
	• Member has no history of liver or kidney transplant

	• Medication is prescribed at an FDA approved dose • Patient is not using Oxlumo and Rivfloza concurrently **Reauthorization** • Members previously using pyridoxine will continue to use it, or have a medical reason for not using it • Documentation has been provided that demonstrates a clinical benefit (e.g. symptomatic improvement, reduction in urinary or plasma oxalate levels from baseline) • Medication is prescribed at an FDA approved dose • Patient is not using Oxlumo and Rivfloza concurrently If all of the above criteria are not met, the request is referred to a Clinical Reviewer for medical necessity review
Last Review Date	3/20233/2024

Recommendation:

- For oncology, add detail to initial authorization and add reauthorization criteria
- For rheumatoid arthritis, add in disease state specific bullet points, as the previous disease-state specific policy, Specialty Biological Agents for Rheumatoid Arthritis, has been retired
- For GPA, EGPA, and MPA add in requirement that that rituximab is being used concurrently with glucocorticoids

Rituximab	
Medications	Ruxience (rituximab-pvvr) - biosimilar Truxima (rituximab-abbs) - biosimilar Riabni (rituximab-arrx) - biosimilar RITUXAN (rituximab) RITUXAN HYCELA (rituximab and hyaluronidase)
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	See "Other Criteria" below
Coverage Duration	See "Other Criteria" below
Maximum Billable Units	Variable
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, in addition to meeting all applicable criteria below, unless 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.** **ONCOLOGY INDICATIONS** **Initial Authorization:** • The medication is being recommended and prescribed by an oncologist. • The medication is being requested for a labeled indication OR ~~Requested~~ an indication ~~must be~~ supported by NCCN category 1 or 2A level of evidence. ○ If the request is for a category 2B recommendation then the medical documentation has been provided as to why member is unable to utilize a treatment regimen with a higher level of evidence (e.g. allergic reaction, contraindication). • The requested indication is CD20 positive • Documentation provided of results of all required laboratory values and patient specific information (e.g. weigh, ALT/AST, creatinine kinase, etc.) when recommended/required per drug package insert. • Documentation indicating that the patient has been screened for HBV (hepatitis B virus) prior to initiation of treatment. • The medication is being prescribed at a dose that is within FDA approved guidelines and/or is supported by the medical compendium as defined by the Social Security Act and/or the National Comprehensive Cancer Network (NCCN) or American Society of Clinical Oncology (ASCO) standard of care guidelines.~~.~~ • For requests for IV medications: attestation medication is administered by a healthcare professional (Medi-Cal only).

If all of the above conditions are met, the request will be approved for up to a 3 month duration

Reauthorization

- The medication is being recommended and prescribed by an oncologist.
- Rituximab is being prescribed at a dose that is within FDA approved guidelines and/or is supported by the medical compendium as defined by the Social Security Act and/or per the NCCN or ASCO standard of care guidelines.

If all of the above conditions are met, the request will be approved for up to a 3 month duration.

RHEUMATOID ARTHRITIS INDICATIONS

Initial Authorization

- The medication is being recommended and prescribed by a rheumatologist.
- The patient is an adult (≥18 y/o) and has a documented clinical diagnosis of rheumatoid arthritis.
- The patient has a documented (consistent with pharmacy claims data, OR for new members to the health plan consistent with medical chart history) adequate trial (including dates and doses) of 3 months or more of therapy with one conventional (non-biologic) DMARD (e.g. methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) or has a documented medical reason (e.g. intolerance, hypersensitivity) for not utilizing any of these therapies to manage their medical condition.
- Documentation indicating that the patient has been screened for Hepatitis B Virus (HBV) prior to initiation of treatment.
- Rituximab is being prescribed at an FDA approved dosage.

If all of the above conditions are met, the request will be approved for up to a 6 month duration.

Reauthorization

- The member has been receiving rituximab and documentation is provided that a rheumatologist has reevaluated the member and recommends continuation of therapy.
- Documentation was provided indicating that the patient had clinical benefit from receiving rituximab therapy.
- Rituximab is being prescribed at an FDA approved dosage.

If all of the above conditions are met, the request will be approved for up to a 1 year duration.

- ~~Refer to "Specialty Biological Agents for Rheumatoid Arthritis"~~

MULTIPLE SCLEROSIS INDICATIONS

- Refer to "Healthcare Professional (HCP) administered/IV Disease Modifying Therapies (DMTs) for Multiple Sclerosis (MS)"

NEUROMYELITIS OPTICA SPECTRUM DISORDER (NMOSD):

- Refer to "Neuromyelitis Optica Spectrum Disorder (NMOSD) Agents"

PEMPHIGUS VULGARIS

Initial Approval

- The medication is being recommended and prescribed by a rheumatologist or dermatologist
- The patient has a diagnosis of moderate to severe pemphigus vulgaris

	• Documentation the patient will be receiving *P. jirovecii pneumonia* (PCP) prophylaxis (ex. TMP/SMX, dapsone, atovaquone) or the prescriber has provided a medical reason for not prescribing PCP prophylaxis • Rituximab is being used in combination with a tapering course of glucocorticoids • Documentation indicating that the patient has been screened for HBV (hepatitis B virus) prior to initiation of treatment. • Rituximab is prescribed at an FDA approved dose/frequency If all of the above conditions are met, the request will be approved for up to a 3 month duration **Reauthorization** • Documentation of clinical benefits (e.g. absence of new lesions) with rituximab therapy was provided by a rheumatologist or dermatologist • Documentation the patient will continue to receive *P. jirovecii pneumonia* (PCP) prophylaxis (ex. TMP/SMX, dapsone, atovaquone) or the prescriber has provided a medical reason for not prescribing PCP prophylaxis • Rituximab is being prescribed at an FDA approved dose/frequency If all of the above conditions are met, the request will be approved for up to a 1 year duration. **GRANULOMATOSIS WITH POLYANGIITIS (GPA) (WEGENER'S GRANULOMATOSIS) AND MICROSCOPIC POLYANGIITIS (MPA)** **Initial Approval** • The medication is being recommended and prescribed by a rheumatologist or nephrologist. • The patient has a documented clinical diagnosis of granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA), or microscopic polyangiitis (MPA) AND the prescriber indicates a diagnosis classification of either severe or non-severe disease. • The patient has a documented (consistent with pharmacy claims data, OR for new members to the health plan consistent with medical chart history) adequate trial (including dates, doses) of glucocorticoid (i.e. prednisone) along with methotrexate OR cyclophosphamide (Cytoxan) or a documented medical reason (intolerance, hypersensitivity, etc.) why patient is not able to use these therapies to manage their medical condition. o If the member has severe GPA/MPA, then this is not required. • Documentation indicating that rituximab is being used concurrently with glucocorticoids. • Documentation the patient will be receiving *P. jirovecii pneumonia* (PCP) prophylaxis (ex. TMP/SMX, dapsone, atovaquone) during treatment or the prescriber has provided a medical reason for not prescribing PCP prophylaxis • Documentation indicating that the patient has been screened for HBV (hepatitis B virus) prior to initiation of treatment. • Rituximab is being prescribed at an FDA approved dosage. If all of the above conditions are met, the request will be approved for up to a 3 month duration. **Reauthorization** • The medication is being recommended and prescribed by a rheumatologist or nephrologist.

	• Documentation the patient will continue to receive *P. jirovecii pneumonia* (PCP) prophylaxis (ex. TMP/SMX, dapsone, atovaquone) or the prescriber has provided a medical reason for not prescribing PCP prophylaxis • Rituxan is being prescribed at an FDA approved dose. If all of the above conditions are met, the request will be approved for up to a 1 year duration. 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	~~3/2023~~3/2024

Recommendation:

- For chronic inflammatory demyelinating polyneuropathy (CIPD): add that the use of corticosteroids is not required for pure motor CIPD. The guidelines recommend IVIG treatment as the first choice for pure motor CIPD.

Immunoglobulin Therapy (IVIG)	
Medications	Bivigam (IV) (Immune Globulin) Cuvitru (SQ) (Immune Globulin) Flebogamma (IV) (Immune Globulin) Gamastan (IM) (Immune Globulin) Gamastan SD (IM) (Immune Globulin) Gammagard liquid (IV or SQ) (Immune Globulin) Gammagard SD (IV) (Immune Globulin) Gammaked (IV or SQ) (Immune Globulin) Gammaplex (IV) (Immune Globulin) Gamunex-C (IV or SQ) (Immune Globulin) Hizentra (SQ) (Immune Globulin) Octagam (IV) (Immune Globulin) Privigen (IV) (Immune Globulin) Asceniv (IV) (Immune Globulin-slra) Cutaquig (SQ) (Immune Globulin-hipp) Panzyga (IV) (Immune Globulin-ifas) Hyqvia (SQ) (Immune Globulin Human/Recombinant Human Hyaluronidase) Xembify (SQ) (Immune Globulin-klhw)
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	See “Other Criteria” below
Coverage Duration	If the criteria are met the request will be approved for a 3 month duration unless otherwise specified in the diagnosis specific “Other Criteria” section below.
Maximum Billable Units	Variable

Other Criteria	**All Requests:**
	• Diagnosis has been confirmed by one of the specialist types, listed below
	  ○ Immunologist
	  ○ Neurologist
	  ○ Oncologist/Hematologist
	• Documentation of patient weight
	• Member has tried and failed, or has a documented medical reason for not using, all other standard of care therapies as defined per recognized guidelines.
	
	Primary Immunodeficiency*:
	• Patient’s IgG level is provided and is below normal for provided indication
	• Clinically significant deficiency of humoral immunity as evidenced by ONE of the following:
	  ○ Inability to produce an adequate immunologic response to specific antigens.
	  ○ History of recurrent infections despite prophylactic antibiotics
	• Dose is consistent with FDA approved package labeling, nationally recognized compendia, or peer-reviewed literature

	• If criteria are met, approve for 6 months. *Primary Immunodeficiency includes, but is not limited to, the following: Congenital agammaglobulinemia. Hypogammaglobulinemia (Common Variable Immunodeficiency, CVID), Severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, X-linked agammaglobulinemia or Bruton's agammaglobulinemia, Hypergammaglobulinemia, X-linked Hyper IgM syndrome **Idiopathic Thrombocytopenic Purpura, acute and chronic**: • Acute: (active bleeding, patients requiring an urgent invasive procedure, to defer splenectomy, or platelet counts < 20,000/ul at risk for intra-cerebral hemorrhage or has life threatening bleeding), or has an adequate increase in platelets from corticosteroids or is unable to tolerate corticosteroids) o Dose does not exceed 1g/kg daily for up to 2 days, or 400mg/kg daily for 5 days • Chronic: o Duration of illness is greater than 12 months o Member has documented trial and failure of corticosteroids and splenectomy, or has a documented medical reason why they are not able to use corticosteroids or member is at high risk for post-splenectomy sepsis. o Dose does not exceed 1g/kg daily for up to 2 days, or 400mg/kg daily for 5 days • If criteria are met, approve for up to 5 days **Kawasaki disease:** • Immunoglobulin is being given with high dose aspirin • Requested dose does not exceed a single 2g/kg dose within 10 days of the diagnosis • If criteria is met, approve for a single dose **Chronic B-cell lymphocytic leukemia:** • Patient's IgG level has been provided, and is < 500mg/dL • The patient has history of severe bacterial infections • Dose does not exceed 400mg/kg every 3-4 weeks • If criteria are met, approve for 3 months. **Bone marrow transplantation:** • Patient requires a bone marrow transplant • Patient's IgG level is < 400mg/dL • Dose does not exceed 500mg/kg/wk for the first 100 days post- transplant or 500 mg/kg/dose every 3-4 weeks for greater than 100 days post- transplant • If criteria are met, approve for 3 months. **Pediatric HIV**: • Diagnosis of HIV • Patient is < 13 years of age • Either patient's IgG level is < 400mg/dL or • If patient's IgG level is ≥ 400 mg/dL than significant deficiency of humoral immunity as evidenced by ONE of the following: o Inability to produce an adequate immunologic response to specific

antigens.
    - History of recurrent bacterial infections despite prophylactic antibiotics
- Dose does not exceed 400mg/kg/dose every 14 days

- If criteria are met, approve for 3 months.

Multifocal motor neuropathy (MMN):
- Duration of symptoms has been at least 1 month with disability.
- Nerve conduction studies were completed to rule out other possible conditions, and confirms the diagnosis of MMN.
- Dose does not exceed 2g/kg/month. This dose can be given over two to five days.

- If criteria is met, approve for up to 5 days for 3 months.

Chronic inflammatory demyelinating polyneuropathy (CIDP):
- Duration of symptoms has been at least 2 months with disability.
- Nerve conduction studies or a nerve biopsy were completed in order to rule out other possible conditions, and confirms the diagnosis of CIDP.
- Patient has tried and failed, or has a medical reason for not using, corticosteroids.
    - If the patient has severe and fulminant CIDP a trial of corticosteroids is not required
    - If the patient has pure motor CIPD a trial of corticosteroids in not required
- Dose is consistent with FDA approved package labeling, nationally recognized compendia, or peer-reviewed literature

- If criteria are met, approve for up to 5 days for 3 months

Guillain-Barre syndrome:
- Patient has severe disease with the inability to walk without aid
- Onset of symptoms within the last 4 weeks
- Dose does not exceed 2g/kg given in divided doses over 2-5 days

- If criteria are met, approve for up to 5 days for 3 months

Myasthenia Gravis (DM):
- Acute:
    - Patient has an acute myasthenic exacerbation (i.e. acute episode of respiratory muscle weakness, difficulty swallowing, etc.) or is in preparation for thymoma surgery to prevent myasthenic exacerbation
    - Dose does not exceed 2 g/kg administered over 2-5 days

    - If criteria are met, approve for up to 5 days for 3 months
- Chronic:
    - Diagnosis of refractory generalized myasthenia gravis
    - Patient has tried and failed, or has a documented medical reason for not using 2 or more immunosuppressive therapies (i.e. corticosteroids, azathioprine, cyclosporine, mycophenolate mofetil)
    - Dose does not exceed 2 g/kg/month administered over 2-5 days

    - If criteria are met, approve for 3 months

	Dermatomyositis (DM):
	• One of the following:
	  ○ Bohan and Peter score of 3 (i.e. definite DM)
	  ○ Bohan and Peter score of 2 (i.e. probable DM) AND concurring diagnostic evaluation by ≥ 1 specialist (e.g. neurologist, rheumatologist, dermatologist)
	• Patient does NOT have any of the following:
	  ○ Cancer (CA) associated myositis defined as myositis within 2 years of CA diagnosis (except basal or squamous cell skin cancer or carcinoma in situ of the cervix that has been excised and cure)
	  ○ Active malignancy
	  ○ Malignancy diagnosed within the previous 5 years
	  ○ Breast CA within the previous 10 years
	• For a diagnosis of DM, one of the following:
	  ○ Patient has tried and failed, or has a documented medical reason for not using both of the following:
	  ▪ methotrexate (MTX) OR azathioprine
	  ▪ rituximab
	  ○ Patient has severe, life-threatening weakness or dysphagia
	• For a diagnosis of cutaneous DM (i.e. amyopathic DM, hypomyopathic DM):
	  ○ Patient has tried and failed, or has a documented medical reason for not using all of the following: MTX and mycophenolate mofetil.
	• Dose does not exceed 2 g/kg administered over 2-5 days every 4 weeks.
	
	• If criteria are met, approve for 3 months
	
	If all of the above criteria are not met per diagnosis, the request is referred to a Clinical Reviewer for medical necessity review.

Last Review Date	~~3/2023~~3/2024

Recommendation:

- Update the myelodysplastic syndrome section to account for the new indication to treat anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require RBC transfusion
- The new indication for ESA-naïve patients (regardless of erythropoietin levels) allows them to have myelodysplastic syndrome with or without ring sideroblasts.

Reblozyl (luspatercept-aamt)	
Medications	Reblozyl (luspatercept-aamt) vial for subcutaneous injection
Covered Uses	Medically accepted indications are defined using the following sources: the Food and Drug Administration (FDA), Micromedex, American Hospital Formulary Service (AHFS), United States Pharmacopeia Drug Information for the Healthcare Professional (USP DI), the Drug Package Insert (PPI), and/or per standard of care guidelines.
Exclusion Criteria	Members are excluded if they have hemoglobin S/beta-thalassemia, isolated alpha-thalassemia~~, or myelodysplastic syndrome without ring sideroblasts.~~
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 for MCAL
Prescriber Restrictions	Prescriber is a hematologist or oncologist
Coverage Duration	Initial requests will be approved for 3 months. Reauthorization requests will be approved for 6 months.
Maximum Billable Units	Variable

Other Criteria	**Criteria for initial approval:**
	• Requested dose is appropriate per labeling
	• The member's weight has been provided with the request
	• The member's most recent hemoglobin level (within the last month) has been provided with the request
	• Diagnosis appropriate per Covered Uses
	• For requests for anemia due to beta thalassemia, documentation of all of the following is required:
	  ○ Member requires regular RBC transfusions (defined as no transfusion-free period of more than 35 days over the last 6 months)
	• For requests for anemia due to myelodysplastic syndrome, documentation of all of the following is required:
	  ~~○ Documentation of 5% or greater ring sideroblasts present in bone marrow~~
	  ○ Myelodysplastic Syndrome Revised International Prognostic Scoring System (IPSS-R) categorization as very low, low, or intermediate risk of progression.
	  ~~○ Member has tried and failed (or medical justification provided for not using) at least one erythropoiesis stimulating agent (ESA) at a dose equivalent to one of the following regimens:~~
	  ~~▪ Recombinant human erythropoietin ≥ 40,000 IU/week of for at least 8 doses~~
	  ~~▪ Darbepoetin ≥ 500 ug every 3 weeks for at least 4 doses~~
	  ~~OR~~
	  ~~▪ If erythropoietin > 500 mU/mL, trial of ESA is not required~~
	  ○ Member has required transfusion of 2 or more red blood cell (RBC) units within an 8 week period in the last 4 months
	  ○ Hemoglobin less than 10 g/dl
	
	Reauthorization:

	• For diagnosis of anemia due to beta thalassemia, documentation of the following:
	  ○ Fewer transfusions compared with baseline
	  AND
	  ○ A reduction in transfusion requirement of at least 2 red-cell units compared with baseline
	• Diagnosis of anemia due to myelodysplastic syndrome: documentation of ONE of the following:
	  ○ Hemoglobin increase of at least 1.5 g/dl from baseline over a period of 3-6 months
	  OR
	  ○ Reduction in red blood cell transfusion by at least 4 units over a period of 3-6 months compared with baseline transfusion requirement
	• Prescriber states that the member did not experience a Grade 3 or 4 hypersensitivity reaction.
	
	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	~~3/2023~~3/2024

ALAMEDA NEW PRODUCT REVIEW Q1 2024 P&T

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Immphentiv	phenylephrine 0.5 mg/5 ml, 1 mg/10 ml intravenous vial	Hikma Pharmaceuticals USA	• For increasing blood pressure in adults with clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia	$10 per vial	Phenylephrine, Norepinephrine, Epinephrine, Ephedrine	Non-formulary
Meropenem	meropenem 2 g intravenous vial	WG Critical Care	Penem antibacterial indicated for the treatment of: • Complicated skin and skin structure infections (adult patients and pediatric patients 3 months of age and older only) • Complicated intra-abdominal infections (adult and pediatric patients) • Bacterial meningitis (pediatric patients 3 months of age and older only)	$33 per vial	Imipenem/cilastatin, Ertapenem	Non-formulary
Adalimumab-aacf	adalimumab-aacf 40 mg/0.8 ml subcutaneous auto-injector	Fresenius	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$899 per dose	Humira, Amjevita, Hulio, Cyltezo, Hyrimoz, Yusimry, Yuflyma, Hadlima, Abrilada	Non-formulary
Augtyro	repotrectinib 40 mg oral capsules	Bristol-Myers Squibb	• Treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)	$29,000	Rozlytrek, Xalkori	Non-formulary
Zemaira	alpha1-proteinase inhibitor (human) 4000 mg, 5000 mg intravenous vials	CSL Behring	• For chronic augmentation and maintenance therapy in individuals with alpha1-proteinase inhibitor (A1-PI) deficiency and clinical evidence of emphysema	$11,200 for a 70 kg adult	Prolastin-C, Aralast NP, Glassia	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Xalkori	crizotinib 20 mg, 50 mg, 150 mg oral pellet capsules	Pfizer	• Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are anaplastic lymphoma kinase (ALK) or ROS1-positive as detected by an FDA-approved test • Treatment of pediatric patients 1 year of age and older and young adults with relapsed or refractory, systemic anaplastic large cell lymphoma (ALCL) that is ALK-positive • Treatment of adult and pediatric patients 1 year of age and older with unresectable, recurrent, or refractory inflammatory myofibroblastic tumor (IMT) that is ALK-positive.	$26,447	Alecensa, Alunbrig, Lorbrena, Rozlytrek, Augtyro	Non-formulary
Cabtreo	clindamycin phosphate/ adapalene/benzoyl peroxide 1.2%-0.15%-3.1% topical gel	Bausch Health US	• For the topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older	$950	Clindamycin phosphate/benzoyl peroxide, Adapalene/benzoyl peroxide, Tretinoin	Non-formulary
Truqap	capivasertib 160 mg, 200 mg oral tablets	AstraZeneca	• To be used in combination with fulvestrant for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy	$22,922	Piqray, Fulvestrant, Everolimus, Anastrozole, Tamoxifen	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Amjevita	adalimumab-atto 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	Amgen	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa, Uveitis	$693 per dose	Humira, Hulio, Idacio, Cyltezo, Hyrimoz, Yusimry, Yuflyma, Hadlima, Abrilada	Non-formulary
Adzynma	ADAMTS13, recombinant-krhn 500 unit, 1500 unit intravenous vials	Takeda Pharmaceuticals	• For prophylactic or on demand enzyme replacement therapy (ERT) in adult and pediatric patients with congenital thrombotic thrombocytopenic purpura (cTTP)	$18,368 for a 70 kg adult	Octaplas	Non-formulary (see new PAD)
Loqtorzi	toripalimab-tpzi 240 mg/6 ml intravenous vial	Coherus BioSciences, Inc.	• In combination with cisplatin and gemcitabine, for first-line treatment of adults with metastatic or with recurrent locally advanced nasopharyngeal carcinoma (NPC) • As a single agent for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy	$17,784 for a 70 kg adult	Keytruda, Opdivo	Non-formulary
Yuflyma	adalimumab-aaty 80 mg/0.8 mL subcutaneous auto-injector	Celltrion	Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Crohn's Disease, Ulcerative Colitis, Plaque Psoriasis, Hidradenitis Suppurativa	$3,288 per dose	Humira, Amjevita, Hulio, Idacio, Cyltezo, Hyrimoz, Yusimry, Hadlima, Abrilada	Non-formulary
Jylamvo	methotrexate 2 mg/ml oral solution	Shorla Oncology	• Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen • Treatment of adults with mycosis fungoides • Treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen • Treatment of adults with rheumatoid arthritis • Treatment of adults with severe psoriasis	$876 per 60 ml bottle	Methotrexate tablets, Xatmep	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Ogsiveo	nirogacestat 50 mg oral tablets	SpringWorks Therapeutics, Inc.	• For adult patients with progressing desmoid tumors who require systemic treatment	$29,000	None	Non-formulary
Bijuva	estradiol/progesterone 0.5 mg-100 mg oral capsule	Mayne Pharma	• To be used in a woman with a uterus for the treatment of moderate to severe vasomotor symptoms due to menopause	$264	Prempro, Estradiol tablets, Progesterone capsules	Non-formulary
Coxanto	oxaprozin 300 mg oral capsules	Solubiomix, LLC	• Relief of signs and symptoms of Osteoarthritis (OA) • Relief of signs and symptoms of Rheumatoid Arthritis (RA) • Relief of signs and symptoms of Juvenile Rheumatoid Arthritis (JRA)	$6,434 for max dose	Oxaprozin tablets, Naproxen, Ibuprofen,	Non-formulary
Fabhalta	iptacopan 200 mg oral capsules	Novartis	• Treatment of adults with paroxysmal nocturnal hemoglobinuria	$45,205	Empaveli, Soliris, Ultomiris	Non-formulary (see new MRG)
Rezipres	ephedrine hydrochloride 47 mg/10 ml intravenous vial	Dr. Reddy's Laboratories	• Treatment of clinically important hypotension occurring in the setting of anesthesia	$40 per vial	Phenylephrine, Norepinephrine, Epinephrine, Ephedrine	Non-formulary
Casgevy	exagamglogene autotemcel intravenous suspension	Vertex	• Treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs) • Treatment of patients aged 12 years and older with transfusion-dependent β-thalassemia (TDT)	$2.2 million per one-time treatment	Lyfgenia, Zynteglo, Adakveo, Oxbryta, Endari, Hydroxyurea	Non-formulary (see new PAD)
Lyfgenia	lovotibeglogene autotemcel intravenous suspension	bluebird bio	• Treatment of patients 12 years of age or older with sickle cell disease and a history of vaso-occlusive events	$3.1 million per one-time treatment	Casgevy, Adakveo, Oxbryta, Endari, Hydroxyurea	Non-formulary (see new PAD)
Vevye	cyclosporine 0.1% ophthalmic solution	Novaliq	• Treatment of the signs and symptoms of dry eye disease	$770	Cyclosporine ophthalmic emulsion, Artificial tears, Xiidra, Miebo	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
iDose TR	travoprost 75 mg intracameral implant	Glaukos Corporation	• For the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT)	$13,950 per implant	Travoprost ophthalmic solution, Latanoprost, Bimatoprost, Brimonidine, Brinzolamide	Non-formulary
Zituvio	sitagliptin 25 mg, 50 mg, 100 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	$520	Januvia, Tradjenta, Saxagliptin, Alogliptin	Non-formulary (see updated MRG)
Zoryve	roflumilast 0.3% topical foam	Arcutis Biotherapeutics	• Treatment of seborrheic dermatitis in adult and pediatric patients 9 years of age and older	$858	Ketoconazole, Triamcinolone, Hydrocortisone, Pimecrolimus	Non-formulary
Breyna	budesonide/formoterol 80 mcg-4.5 mcg, 160 mcg-4.5 mcg inhaler	Mylan	• Treatment of asthma in patients 6 years of age and older[1] [1]Breyna should be used for patients not adequately controlled on a long-term asthma-control medication such as an inhaled corticosteroid (ICS) or whose disease warrants initiation of treatment with both an inhaled corticosteroid and long-acting beta2-adrenergic agonist (LABA).	$250	Budesonide/formoterol, Fluticasone/salmeterol, Symbicort, Dulera, Breo Ellipta, Wixela Inhub	Non-formulary
Penbraya	meningococcal groups A, B, C, W, and Y intramuscular vaccine	Pfizer	• For active immunization to prevent invasive disease caused by Neisseria meningitidis serogroups A, B, C, W, and Y, in individuals 10 through 25 years of age	$462 per two-dose series	Trumenba, Menveo, Bexsero, MenQuadfi	F-QL-AL (0.5ml per dose) (2 fills per lifetime) (max age 25 years) (already added via CRF)
Wainua	eplontersen 45 mg/0.8 ml subcutaneous auto-injector	AstraZeneca	• Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults	$41,583	Onpattro, Amvuttra, Tegsedi	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Ixchiq	chikungunya intramuscular vaccine, live	Valneva	• For the prevention of disease caused by chikungunya virus (CHIKV) in individuals 18 years of age and older who are at increased risk of exposure to CHIKV • This indication is approved under accelerated approval based on anti-CHIKV neutralizing antibody titers. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies.	$275 per one-time dose	None	Non-formulary
Zenpep	pancrelipase 60,000 units (lipase)-189,600 units (protease)-252,600 units (amylase) delayed-release oral capsules	Nestlé HealthScience	• Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, or other conditions	$2,847-$5,693 for a 70 kg adult	Creon, Pancreaze, Pertzye, Viokace,	F-AL (min 21 years) (already added via CRF)
Iwilfin	eflornithine 192 mg oral tablets	US WorldMeds	• To reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy	$21,600 (max dose)	Isotretinoin, Unituxin	Non-formulary
Bosulif	bosutinib 50 mg, 100 mg oral capsules	Pfizer	• Treatment of adult and pediatric patients 1 year of age and older with chronic phase Ph+ chronic myelogenous leukemia (CML), newly-diagnosed or resistant or intolerant to prior therapy • Treatment of adult patients with accelerated, or blast phase Ph+ CML with resistance or intolerance to prior therapy	$30,100 (max dose)	Imatinib, Sprycel, Iclusig, Tasigna	Non-formulary
Zilbrysq	zilucoplan 16.6 mg/0.416 ml, 23 mg/0.574 ml, 32.4 mg/0.81 ml subcutaneous syringe	UCB	• Treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) antibody positive	$31,410 for a 70 kg adult	Soliris, Ultomiris, Rystiggo, Vyvgart, Vyvgart Hytrulo	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
Agamree	vamorolone 40 mg/ml oral suspension	Catalyst Pharmaceuticals	• Treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older.	$12,825 for a 30 kg child	Prednisone, Emflaza	Non-formulary (see updated MRG)
Tramadol	tramadol 25 mg oral tablet	Advagen Pharma	• Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	$132 per 3-day course (50 mg every 4 hours)	Oxycodone, Morphine, Hydrocodone/acetaminophen, Naproxen, Ibuprofen	Non-formulary
Hemlibra	emicizumab-kxwh 300 mg/2 ml subcutaneous vial	Genentech	• For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors	$47,018 for a 70 kg adult	Altuviiio, Eloctate, Advate, Esperoct, Jivi, Novoeight	Non-formulary
Combogesic	ibuprofen/acetaminophen 300 mg-1000 mg/100 ml intravenous vial	Hikma Pharmaceuticals	For adults where an intravenous route of administration is considered clinically necessary for: • Relief of mild to moderate pain • Management of moderate to severe pain as an adjunct to opioid analgesics	$23 per 100 ml vial	Morphine, Fentanyl, Ibuprofen, Acetaminophen, Ketamine	Non-formulary
Rivfloza	nedosiran 128 mg/0.8 ml, 160 mg/ml subcutaneous syringe; nedosiran 80 mg/0.5 ml subcutaneous vial	Novo Nordisk	To lower urinary oxalate levels in children 9 years of age and older and adults with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function, e.g., eGFR $\geq$ 30 mL/min/1.73 m^2	$62,880 for a 70 kg adult	Oxlumo	Non-formulary (see updated PAD)
Udenyca	pegfilgrastim-cbqv 6 mg/0.6 ml subcutaneous syringe with on-body injector	Coherus BioSciences	• Decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia Increase survival in patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome)	$4,175 per 6 mg/0.6 ml injection	Neulasta Onpro, Ziextenzo, Nyvepria, Fulphila, Stimufend, Fylnetra	Non-formulary

BRAND NAME	GENERIC NAME/ DOSAGE FORM	MANUFACTURER	INDICATION	PRICING*	FORMULARY ALTERNATIVES	RECOMMENDATION^
DefenCath	taurolidine/heparin 40.5 mg-3000 units/3 ml instillation vial	CorMedix Inc.	• To reduce the incidence of catheter related bloodstream infections (CRBSI) in adult patients with kidney failure receiving chronic hemodialysis (HD) through a central venous catheter (CVC)[1] • [1]This drug is indicated for use in a limited and specific population of patients.	$250 per vial	None	Non-formulary

*	Pricing reflects Wholesale Acquisition Cost (WAC) per month unless otherwise noted.
†	Pricing based on standard twice-monthly dosing for most indications.
‡	Pricing is per each kit on items listed as a kit.