South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

March 4, 2022

South Dakota Department of Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

March 4, 2022
1:00 – 3:00 PM

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_OTM5NzYxMjMtN2NlYi00N2U4LWJiMmQtNDMxNDhlMDc0NzUz%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
425899727@t.plcm.vc
Video Conference ID: 116 130 791 5

Join by phone
+1 952-222-7450
Phone Conference ID: 337 652 025#

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **Oral oncology drugs**
- **Anticonvulsants – brand utilization review & NTI**
- **Opioid update**

New business
- **Urinary antispasmodics PA review**
- **Musculoskeletal therapy agents PA review**
- **Opioid and muscle relaxant combination**
- **Hypnotics**
- **Vuity & pilocarpine drops**
- **Opzelura**

Public input accepted after individual topic discussion
Next meeting date June 10, 2022 & adjournment

South Dakota Department of Social Services, Division of Medicaid Services
Pharmacy & Therapeutics (P&T) Committee Meeting Minutes

Friday, December 10, 2021
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD	-	Heather Preuss, MD	X
Dana Darger, RPh, Chair	X	Matthew Stanley, DO	-
Mikel Holland, MD	X	Deidre Van Gilder, PharmD	X
Bill Ladwig, RPh	X	Mike Jockheck, DSS Staff	X
Kelley Oehlke, PharmD	X	Matthew Ballard, DSS Staff	X
Lenny Petrik, PharmD	X	Sarah Aker, DSS Staff	X

Administrative Business

Darger called the meeting to order at 1:05 pm. The minutes of the September meeting were presented. Oehlke made a motion to approve. Ladwig seconded the motion. The motion was unanimously approved.

Jockheck made an announcement to the committee welcoming Sarah Aker back as the new Medicaid Director since Bill Synder's departure, the previous Medicaid Director, at the last meeting.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from July 1, 2021 to September 30, 2021. A total of 1,712 PAs were reviewed of which 141 requests (8.2%) were received via telephone and 914 requests (53.4%) were received via fax, and 657 (38.4%) were reviewed via electronically. There was a 17.7% increase of PAs received from the previous quarter. Analgesics-opioids decreased to the fourth spot on the Top Therapeutic Classes reviewed for PA.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from July 1, 2021 to September 30, 2021. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, cystic fibrosis correctors, skin and mucous membrane agents, and anticonvulsants. These top 15 therapeutic classes make up 24.59 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 9.19 % of total claims. Under the top drugs based on number of claims, the top increases were covid vaccines and albuterol utilization. Van Gilder commented the increase in albuterol could be associated with the increase in RSV infections. The big decreases in number of claims were hydrocodone and tramadol. Under the top drugs by paid amount, due to the decrease in HIV utilization of single agent drugs for multi-class combination drugs, there was an increase in utilization of Biktarvy during this quarter. Darger requested Humira pen and Humira combined going forward.

Old Business

Pancreatic enzyme utilization

The committee continued the review on the utilization of pancreatic enzymes specifically the average quantity per prescription. Darger commented on the price increase of these drugs. The utilization looked appropriate.

Review PA forms and criteria
The committee reviewed utilization of drugs on PA that are available as generics now. After review, the committee decided on the following:

- Uloric – keep PA on both brands and generics
- Antihistamines – keep PA on ODT, chewables, and Clarinex syrup since children under 12 years old and patients with dysphagia bypass the PA

Darger inquired if there was any public comment. There were none.

Hepatitis C update
Aker gave an update on the department's efforts to implement the committee's hepatitis C recommendations with consideration of the overall budget and monitoring of community health. Nathan Blake from AbbVie provided public comment. Becky Klemme, RN, from Avera Liver Clinic provided public comment. Tami Hogie-Lorenzen, Chief Medical Officer for South Dakota Urban City and Health, provided public comment. Dr. Doug Lehmann, MD, internal medication pediatric doctor in Rapid City at the Community Health Center at Black Hills provided public comment. Preuss, Petrik, Holland, and Darger also provided feedback.

Opioid update
The committee reviewed 3Q2021 opioid outcomes compared to previous quarters from the opioid initiatives. There was a slight increase in opioid utilization and opioid utilizers during third quarter which corresponds to the increase in total eligible members and total drug utilization, but the number of utilizers exceeding 180 MED/day decreased.

New Business

Antineoplastic oral drugs
Committee reviewed utilization of antineoplastic oral drugs. Nearly half the pipeline of new drugs in development are geared towards oncology related medications. Oral oncology drugs account for 3.3% of total plan paid. Committee also discussed the pros and cons of managing the more expensive oral oncology drugs with a shorter 15 day fill for the first 90 days for new starts only to avoid medication waste if a drug is not well tolerated. The cons entailed the rural nature of the state, some drugs requiring the original container for dispensing, and hardship of some members driving to the pharmacy for two fills in one month.

Anticonvulsants
Committee reviewed utilization of anticonvulsants for appropriate use. Several anticonvulsants had label indications for various mental health disorders. There was an in-depth review for appropriate use for those anticonvulsants without the label indication for mental health disorders. Based on the utilization and available diagnosis codes, utilization seemed appropriate.

Darger inquired if there was any public comment. There were none.

Gastrointestinal drugs
Committee reviewed the utilization of gastrointestinal drugs as a follow up to the in-depth review of Cholbam at the last meeting. Utilization and current PAs all were appropriate.

Insulin quantity
Committee reviewed the utilization of insulins and current quantity limits. Van Gilder provided expertise on utilization and potential quantity limits for the long-acting insulins. Jockheck inquired if setting a limit of 45 ml for pens and 50 ml for vials were appropriate. Van Gilder agreed. Darger inquired since Lantus and Semglee are bio-identical for these to be interchangeable. Jockheck will confirm on MAC pricing.

JAK inhibitor criteria
Committee reviewed the safety updates for increased risk of serious heart-related events and class-wide update and label for all three oral JAK inhibitors: Xeljanz/XR, Olumiant, and Rinvoq. There was discussion to update the PA criteria for all the oral JAK inhibitors for patients who have had an inadequate response to, intolerance to one or more TNF blockers. VanGilder made the motion to update the criteria with the class-wide update to the labeling. Holland seconded the motion. The motion was unanimously approved.

Darger inquired if there was any public comment. There were none.

Trudhesa
Trudhesa clinical information was presented for review. Committee decided to monitor utilization. Darger inquired if there was any public comment. There were none.

Adjournment
The next meeting is scheduled on March 4, 2022. The June meeting is tentatively scheduled on June 10, 2022. Holland made a motion to adjourn the meeting, and everyone seconded the motion. The motion passed unanimously, and the meeting adjourned at 2:30 pm.

PA Report
10/1/2021 – 12/31/2021

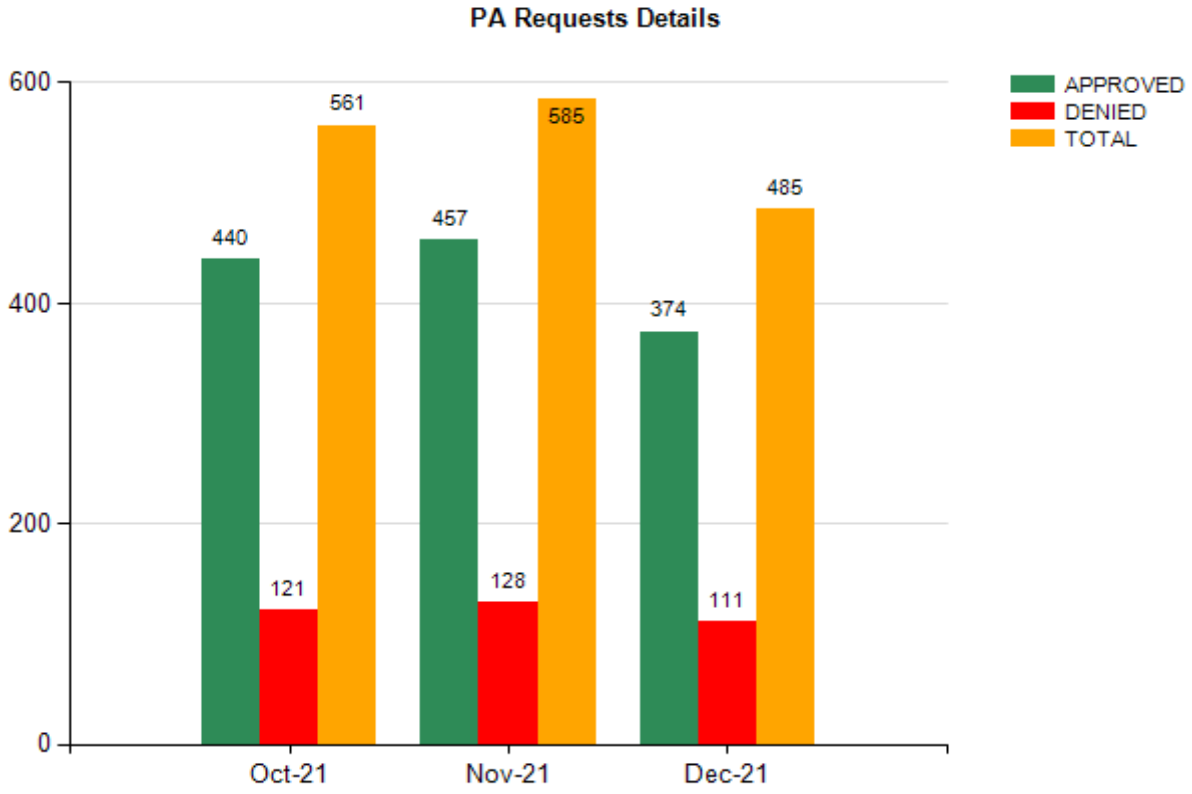
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 hrs Urgent - 24 hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	1,593	1,593	0	100.00%	0.00%
Urgent	38	38	0	100.00%	0.00%
Grand Total	**1,631**	**1,631**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
Total	**1,631**	**133**	**8.2%**	**899**	**55.1%**	**599**	**36.7%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Oct-21	440	121	561
Nov-21	457	128	585
Dec-21	374	111	485
4Q21	1,271	360	1,631
Percent of Total	77.93%	22.07%	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTIC/ANTIMANIC	314	18	332	94.58%	20.36%	, ARIPIPRAZOLE
65 - ANALGESICS - OPIOID*	109	79	188	57.98%	11.53%	HYDROCODONE /APAP, TRAMADOL
27 - ANTIDIABETICS*	169	13	182	92.86%	11.16%	, OZEMPIC
90 - DERMATOLOGICALS*	93	62	155	60.00%	9.50%	IVERMECTIN, DUPIXENT
58 - ANTIDEPRESSANTS*	115	30	145	79.31%	8.89%	, SERTRALINE HCL
OTHERS -	471	158	629	74.88%	38.57%	
3Q21	**1,271**	**360**	**1,631**	**77.93%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	314	18	332	94.58%
27 - ANTIDIABETICS*	169	13	182	92.86%
58 - ANTIDEPRESSANTS*	115	30	145	79.31%
65 - ANALGESICS - OPIOID*	109	79	188	57.98%
90 - DERMATOLOGICALS*	93	62	155	60.00%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	79	16	95	83.16%
52 - GASTROINTESTINAL AGENTS - MISC.*	56	13	69	81.16%
66 - ANALGESICS - ANTI-INFLAMMATORY*	49	4	53	92.45%
67 - MIGRAINE PRODUCTS*	48	23	71	67.61%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	46	17	63	73.02%
41 - ANTIHISTAMINES*	28	2	30	93.33%
16 - ANTI-INFECTIVE AGENTS - MISC.*	22	2	24	91.67%
72 - ANTICONVULSANTS*	21	8	29	72.41%
54 - URINARY ANTISPASMODICS*	18	8	26	69.23%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	13	14	27	48.15%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	11	0	11	100.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	11	3	14	78.57%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	10	2	12	83.33%
33 - BETA BLOCKERS*	8	2	10	80.00%
50 - ANTIEMETICS*	8	1	9	88.89%
12 - ANTIVIRALS*	6	24	30	20.00%
75 - MUSCULOSKELETAL THERAPY AGENTS*	6	3	9	66.67%
39 - ANTIHYPERLIPIDEMICS*	5	1	6	83.33%
36 - ANTIHYPERTENSIVES*	4	0	4	100.00%
03 - MACROLIDES*	3	1	4	75.00%
34 - CALCIUM CHANNEL BLOCKERS*	3	1	4	75.00%
45 - RESPIRATORY AGENTS - MISC.*	3	0	3	100.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	3	5	8	37.50%
83 - ANTICOAGULANTS*	3	3	6	50.00%
01 - PENICILLINS*	1	0	1	100.00%
32 - ANTIANGINAL AGENTS*	1	0	1	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	1	1	2	50.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	0	1	100.00%
74 - NEUROMUSCULAR AGENTS*	1	2	3	33.33%
85 - HEMATOLOGICAL AGENTS - MISC.*	1	1	2	50.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	1	0	1	100.00%
15 - ANTHELMINTICS*	0	1	1	0.00%
4Q21	**1,271**	**360**	**1,631**	
Percent of Total	**77.93%**	**22.07%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Oct-21	20	83.33%	4	16.67%	24
Nov-21	8	72.73%	3	27.27%	11
Dec-21	19	67.86%	9	32.14%	28
4Q21	**47**	**74.60%**	**16**	**25.40%**	**63**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
AIMOVIG	2	0	2	100.00%
AJOVY	2	0	2	100.00%
AMITIZA	4	0	4	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
CLINDAMYCIN/BENZOYL PEROXIDE	1	0	1	100.00%
CLOBAZAM	1	0	1	100.00%
DEXILANT	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
EMGALITY	1	0	1	100.00%
EPCLUSA	1	0	1	100.00%
EVRYSDI	1	1	2	50.00%
GENOTROPIN	2	0	2	100.00%
HARVONI	0	1	1	0.00%
HEMLIBRA	1	0	1	100.00%
HUMIRA PEDIATRIC CROHNS DISEASE STARTER	0	1	1	0.00%
IVERMECTIN	1	1	2	50.00%
LANSOPRAZOLE ODT	1	0	1	100.00%
LINZESS	2	0	2	100.00%
LUBIPROSTONE	4	0	4	100.00%
MALATHION	1	0	1	100.00%
MAVYRET	2	7	9	22.22%
MODAFINIL	1	0	1	100.00%
MYRBETRIQ	1	0	1	100.00%
NIFEDIPINE ER	0	1	1	0.00%
NORDITROPIN FLEXPRO	3	0	3	100.00%
NUCYNTA	1	0	1	100.00%
NURTEC	3	0	3	100.00%
NUTROPIN AQ NUSPIN 10	1	0	1	100.00%
ONFI	1	0	1	100.00%
OXYCONTIN	1	0	1	100.00%
OZEMPIC	0	1	1	0.00%
REPATHA SURECLICK	1	0	1	100.00%
SOFOSBUVIR/VELPATASVIR	0	3	3	0.00%
STELARA	1	0	1	100.00%
TRACLEER	1	0	1	100.00%
TRAMADOL HCL	2	0	2	100.00%
4Q21	**47**	**16**	**63**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 10/1/2021 – 12/31/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	14,682	$185,824.10	$12.66	6.54%
2	ANTICONVULSANTS, MISCELLANEOUS	11,680	$1,034,840.68	$88.60	5.20%
3	ATYPICAL ANTIPSYCHOTICS	9,163	$2,614,268.87	$285.31	4.08%
4	SELECTIVE BETA-2-ADRENERGIC AGONISTS	9,073	$528,202.45	$58.22	4.04%
5	AMINOPENICILLIN ANTIBIOTICS	8,787	$132,147.32	$15.04	3.91%
6	SECOND GENERATION ANTIHISTAMINES	7,623	$86,504.57	$11.35	3.40%
7	ADRENALS	7,298	$678,860.26	$93.02	3.25%
8	RESPIRATORY AND CNS STIMULANTS	7,205	$524,034.45	$72.73	3.21%
9	AMPHETAMINES	7,154	$1,203,867.53	$168.28	3.19%
10	PROTON-PUMP INHIBITORS	6,411	$203,947.86	$31.81	2.86%
11	OPIATE AGONISTS	5,714	$167,168.71	$29.26	2.55%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	4,549	$86,502.50	$19.02	2.03%
13	CONTRACEPTIVES	4,078	$123,628.35	$30.32	1.82%
14	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,826	$219,998.43	$57.50	1.70%
15	THYROID AGENTS	3,693	$72,351.26	$19.59	1.65%
Total		**110,936**	**$7,862,147.34**	**$70.87**	**49.43%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 10/1/2021 – 12/31/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	ATYPICAL ANTIPSYCHOTICS	9,163	$2,614,268.87	$285.31	4.08%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	311	$1,898,870.65	$6,105.69	0.14%
3	CYSTIC FIBROSIS (CFTR) CORRECTORS	75	$1,687,969.88	$22,506.27	0.03%
4	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	563	$1,680,410.80	$2,984.74	0.25%
5	AMPHETAMINES	7,154	$1,203,867.53	$168.28	3.19%
6	HEMOSTATICS	55	$1,148,279.67	$20,877.81	0.02%
7	ANTICONVULSANTS, MISCELLANEOUS	11,680	$1,034,840.68	$88.60	5.20%
8	ANTINEOPLASTIC AGENTS	293	$750,766.95	$2,562.34	0.13%
9	ADRENALS	7,298	$678,860.26	$93.02	3.25%
10	INCRETIN MIMETICS	839	$678,480.23	$808.68	0.37%
11	LONG-ACTING INSULINS	1,372	$678,169.50	$494.29	0.61%
12	RAPID-ACTING INSULINS	1,333	$573,331.57	$430.11	0.59%
13	SELECTIVE BETA-2-ADRENERGIC AGONISTS	9,073	$528,202.45	$58.22	4.04%
14	RESPIRATORY AND CNS STIMULANTS	7,205	$524,034.45	$72.73	3.21%
15	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	140	$413,386.43	$2,952.76	0.06%
Total		**56,554**	**$16,093,739.92**	**$284.57**	**25.20%**

Total Rx Claims from 10/1/2021 – 12/31/2021	**224,452**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 10/1/2021 – 12/31/2021						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	6,584	$87,429.60	$13.28	2.93%
2	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	5,082	$260,063.55	$51.17	2.26%
3	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	4,609	$186,563.07	$40.48	2.05%
4	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE HYDROCHLORIDE	4,372	$46,269.87	$10.58	1.95%
5	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,733	$43,125.99	$11.55	1.66%
6	AMPHETAMINES	VYVANSE	3,582	$1,087,540.27	$303.61	1.60%
7	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE	3,553	$44,186.58	$12.44	1.58%
8	AMPHETAMINES	AMPHETAMINE/DEXTROAM	3,399	$90,169.41	$26.53	1.51%
9	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,357	$45,152.81	$13.45	1.50%
10	SEROTONIN MODULATORS	TRAZODONE	3,303	$33,735.53	$10.21	1.47%
11	ANTICONVULSANTS, MISCELLANEOUS	GABAPENTIN	3,282	$55,593.98	$16.94	1.46%
12	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	3,264	$41,729.39	$12.78	1.45%
13	THYROID AGENTS	LEVOTHYROXINE SODIUM	2,922	$47,940.01	$16.41	1.30%
14	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE NEBS	2,616	$48,476.97	$18.53	1.17%
15	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HCL	2,572	$30,075.59	$11.69	1.15%
16	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	2,474	$41,009.46	$16.58	1.10%
17	CENTRAL ALPHA-AGONISTS	CLONIDINE	2,458	$23,638.12	$9.62	1.10%
18	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION HCL 24HR	2,334	$47,486.11	$20.35	1.04%
19	OPIATE AGONISTS	HYDROCODONE BITARTRATE	2,333	$34,919.22	$14.97	1.04%
20	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANATE	2,200	$44,423.71	$20.19	0.98%
21	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,177	$34,004.99	$15.62	0.97%
22	ANGIOTENSIN-CONVERTING ENZYME INHIBITOR	LISINOPRIL	2,138	$19,910.25	$9.31	0.95%
23	ADRENALS	PREDNISONE	2,118	$20,381.93	$9.62	0.94%
24	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	2,038	$23,988.35	$11.77	0.91%
25	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	2,025	$24,601.96	$12.15	0.90%
26	3RD GENERATION CEPHALOSPORIN ANTIBIOTIC	CEFDINIR	1,988	$41,910.78	$21.08	0.89%
27	ANTICONVULSANTS, MISCELLANEOUS	LAMOTRIGINE	1,859	$26,583.58	$14.30	0.83%
28	5-HT3 RECEPTOR ANTAGONISTS	ONDANSETRON ODT	1,846	$27,722.80	$15.02	0.82%
29	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,815	$22,861.83	$12.60	0.81%
30	SECOND GENERATION ANTIHISTAMINES	LORATADINE	1,759	$19,268.98	$10.95	0.78%
31	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,728	$20,794.81	$12.03	0.77%
32	VACCINES	PFIZER-BIONTECH COVID-19	1,724	$67,994.38	$39.44	0.77%
33	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	CEPHALEXIN	1,715	$27,606.03	$16.10	0.76%
34	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE ER	1,703	$29,875.19	$17.54	0.76%
35	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONATE	1,681	$24,785.83	$14.74	0.75%
36	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,637	$20,761.51	$12.68	0.73%
37	SEL.SEROTONIN, NOREPI REUPTAKE INHIBITOR	DULOXETINE	1,560	$24,176.88	$15.50	0.70%
38	BIGUANIDES	METFORMIN	1,494	$14,282.52	$9.56	0.67%
39	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,488	$16,409.20	$11.03	0.66%
40	COMPOUNDS	-	1,392	$35,914.32	$25.80	0.62%
41	ANTICONVULSANTS, MISCELLANEOUS	LEVETIRACETAM	1,338	$28,439.40	$21.26	0.60%
42	ADRENALS	PREDNISOLONE SOD PHOSP	1,273	$20,576.80	$16.16	0.57%
43	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPRINE	1,247	$12,938.85	$10.38	0.56%
44	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRAN)	TRIAMCINOLONE ACETONID	1,237	$18,872.03	$15.26	0.55%
45	PROTON-PUMP INHIBITORS	PANTOPRAZOLE SODIUM	1,228	$15,923.80	$12.97	0.55%
46	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS	HYDROXYZINE	1,224	$14,341.29	$11.72	0.55%
47	ANTICONVULSANTS, MISCELLANEOUS	TOPIRAMATE	1,224	$16,769.98	$13.70	0.55%
48	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,214	$17,387.38	$14.32	0.54%
49	DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,204	$11,892.84	$9.88	0.54%
50	VITAMIN D	VITAMIN D	1,131	$11,474.06	$10.15	0.50%
	Total Top 50 Drugs		**116,234**	**$3,051,981.79**	**$26.26**	**51.79%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 10/1/2021 – 12/31/2021						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	57	$1,362,657.66	$23,906.27	0.03%
2*	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA **&** PEN	155	$1,221,569.62	$7,881.09	0.07%
3	AMPHETAMINES	VYVANSE	3,582	$1,087,540.27	$303.61	1.60%
4	SKIN AND MUCOUS MEMBRANE AGENTS	STELARA	35	$734,119.71	$20,974.85	0.02%
5	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	306	$707,568.99	$2,312.32	0.14%
6	ATYPICAL ANTIPSYCHOTICS	LATUDA	378	$478,012.75	$1,264.58	0.17%
7*	ATYPICAL ANTIPSYCHOTICS	ARISTADA **&** INITIO	157	$393,816.10	$2,508.38	0.07%
8*	SKIN/MUCOUS, INTERLEUKIN ANTAGONISTS	DUPIXENT	127	$391,750.32	$3,084.65	0.06%
9	HEMOSTATICS	HEMLIBRA	6	$357,443.44	$59,573.91	0.00%
10	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	305	$355,311.11	$1,164.95	0.14%
11	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	18	$325,312.22	$18,072.90	0.01%
12	INCRETIN MIMETICS	OZEMPIC	373	$298,704.40	$800.82	0.17%
13	MUCOLYTIC AGENTS	PULMOZYME	68	$296,096.82	$4,354.37	0.03%
14	HEMOSTATICS	ADVATE	8	$268,284.52	$33,535.57	0.00%
15	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE HCL	5,082	$260,063.55	$51.17	2.26%
16	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	56	$255,468.35	$4,561.93	0.02%
17*	SKIN AND MUCOUS MEMBRANE AGENTS	COSENTYX**/**SENSORDY PEN	40	$243,799.45	$6,094.99	0.02%
18*	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SURECLICK **&** MINI	42	$231,299.08	$5,507.12	0.02%
19	ADRENALS	FLOVENT HFA	962	$229,170.43	$238.22	0.43%
20	LONG-ACTING INSULINS	LANTUS SOLOSTAR	537	$227,867.48	$424.33	0.24%
21	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	69	$223,730.84	$3,242.48	0.03%
22	ANTICONVULSANTS, MISCELLANEOUS	EPIDIOLEX	91	$221,882.23	$2,438.27	0.04%
23	ANTICONVULSANTS, MISCELLANEOUS	VIMPAT	231	$217,727.25	$942.54	0.10%
24	INCRETIN MIMETICS	TRULICITY	267	$216,306.76	$810.14	0.12%
25	ATYPICAL ANTIPSYCHOTICS	REXULTI	189	$209,226.53	$1,107.02	0.08%
26	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	411	$206,361.43	$502.10	0.18%
27	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	4,609	$186,563.07	$40.48	2.05%
28	VESICULAR MONOAMINE TRANSPORT2 INHIBIT	INGREZZA	27	$180,679.12	$6,691.82	0.01%
29	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	288	$174,504.62	$605.92	0.13%
30	RIFAMYCIN ANTIBIOTICS	XIFAXAN	73	$160,595.70	$2,199.94	0.03%
31	HEMOSTATICS	HUMATE-P	15	$148,469.27	$9,897.95	0.01%
32	HEMOSTATICS	RECOMBINATE	3	$145,659.75	$48,553.25	0.00%
33	VASODILATING AGENTS (RESPIRATORY TRACT)	UPTRAVI	9	$142,994.44	$15,888.27	0.00%
34	GI DRUGS, MISCELLANEOUS	CHOLBAM	7	$140,973.85	$20,139.12	0.00%
35	ENZYMES	PALYNZIQ	7	$137,200.85	$19,600.12	0.00%
36	RAPID-ACTING INSULINS	INSULIN ASPART FLEXPEN	368	$136,839.19	$371.85	0.16%
37	SKIN AND MUCOUS MEMBRANE AGENTS	TALTZ	21	$131,615.45	$6,267.40	0.01%
38	HEMOSTATICS	XYNTHA SOLOFUSE	3	$127,715.01	$42,571.67	0.00%
39	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	354	$127,403.62	$359.90	0.16%
40	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	278	$125,786.68	$452.47	0.12%
41	DIGESTANTS	CREON	75	$117,376.08	$1,565.01	0.03%
42	DIRECT FACTOR XA INHIBITORS	ELIQUIS	263	$117,349.44	$446.20	0.12%
43	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	53	$117,288.21	$2,212.99	0.02%
44	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	34	$112,525.28	$3,309.57	0.02%
45	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	220	$110,090.21	$500.41	0.10%
46	RAPID-ACTING INSULINS	NOVOLOG FLEXPEN	178	$106,453.30	$598.05	0.08%
47	GI DRUGS, MISCELLANEOUS	LINZESS	242	$106,294.02	$439.23	0.11%
48	ANTINEOPLASTIC AGENTS	JAKAFI	5	$105,903.85	$21,180.77	0.00%
49	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	XYREM	7	$99,851.39	$14,264.48	0.00%
50	HEMOSTATICS	ALPROLIX	8	$97,779.40	$12,222.43	0.00%
	Total Top 50 Drugs		**20,646**	**$13,933,495.15**	**$674.88**	**9.20%**

Old Business

Antineoplastic oral drugs

Time frame: 1/1/2021 to 1/31/2022

Cancer Indication	Drug Name	Total Rx	Amount Paid	Paid/Rx	Utilizer
mTOR inhibitors	**AFINITOR TAB 10 MG (everolimus)**	1	$3,013.01	$3,013.01	1
	everolimus tab 2.5 mg	1	$3,210.55	$3,210.55	
Patient 1: • Afinitor 10mg: 1/4/21 (#28 per 28 days) • everolimus 2.5mg: 2/9/22 (#28 per 28 days)					
mTOR inhibitors	**AFINITOR DIS TAB 2 MG (everolimus)**	11	$328,825.28	$29,893.23	1
	everolimus tab 2 mg	1	$12,905.53	$12,905.53	
Patient 1: • Afinitor DIS 2mg: 1/27/21, 2/24, 3/30, 5/4, 6/8, 7/12, 8/13, 9/24 (#56 per 28 days) • everolimus 2mg: 11/3 (#28 per 14 days) • Afinitor DIS 2mg: 11/16, 12/16, 1/13/22 (#56 per 28 days)					
GIST, Renal, Hepatic, Colorectal, Thyroid, Bladder	**CABOMETYX TAB 40 MG (cabozantinib)**	2	$43,346.70	$21,673.35	1
Patient 1: Cabometyx 40mg: 11/15/21, 12/15 (#30 per 30 days)					
Skin Cancers	**ODOMZO CAP 20 MG (sonidegib)**	3	$36,220.80	$12,073.60	1
Patient 1: Odomzo 200mg: 1/18/21, 2/26, 4/5 (#30 per 30 days)					
Chronic Myeloid Leukemia (CML)	**SPRYCEL TAB 20 MG (dasatinib)**	15	$184,755.29	$12,317.02	1
	BOSULIF TAB 400 MG (bosutinib)	1	$17,372.25	$17,372,25	
Patient 1: • Sprycel 20mg: 2/5/21, 3/2, 3/23, 4/16, 5/11, 6/2, 6/27, 7/20, 8/12, 9/7, 10/4, 11/1, 12/1/21 (#90 per 30 days) • Sprycel 20mg: 12/20/21 (#84 per 28 days) • Sprycel 20mg: 1/10/22 (#60 per 20 days) • Bosulif 400mg: 1/14/22 (#30 per 30 days) • Sprycel 20mg: 2/2/22 (#60 per 20 days) • Bosulif 400mg: 2/14/22 (#30 per 30 days)					
Chronic Myeloid Leukemia	**SPRYCEL TAB 70 MG (dasatinib)**	4	$34,067.88	$8,516.97	2
Patient 1: • Sprycel 70mg: 4/30/21 Patient 2: • Sprycel 70mg: 7/2/21, 8/5, 1/20/22, 2/16 (#30 per 30 days)					
Chronic Myeloid Leukemia	**SPRYCEL TAB 100 MG (dasatinib)**	14	$231,280.85	$16,520.06	3
Patient 1: • Sprycel 100mg: 1/8/21, 2/10, 3/12, 4/7, 5/7, 6/7, 7/6, 8/5, 9/3, 10/4, 11/3, 12/2, 1/3/22, 2/2 (#30 per 30 days) Patient 2: • Spyrcel 100mg: 2/17/21, 4/22 (#30 per 30 days) Bill to Medicare after 6/4/21 Patient 3: • Sprycel 100mg: 2/10/21, 1/24/22 (#30 per 30 days) – no claims after 1/24/22					
Breast cancer – CDKIs	**VERZENIO TAB 100 MG (abemaciclib)**	5	$65,290.40	$13,058.08	1
Patient 1: • capecitabine tab 500mg (Xeloda): 1/12/21, 2/9, 3/9 (#84 per 21 days) • Verzenio 100 mg: 4/8, 5/19, 7/30, 9/1, 10/1 (#56 per 28 days) • Piqray tab 300mg: 11/5, 12/3, 1/5/22					

Cancer Indication	Drug Name	Total Rx	Amount Paid	Paid/Rx	Utilizer
NSCLC – KRAS Inhibitor	**LUMAKRAS TAB 120 MG (sotorasib)**	5	$89,542.85	$17,908.57	2
Patient 1: Lumakras 120mg: 7/15/21, 8/19, 9/20 (#240 per 30 days) – no claims after 11/5/21 Patient 2: Lumakras 120mg: 12/14/21, 1/19/22, 2/4/222 (#240 per 30 days)					
Multiple Myeloma oral TNF	**POMALYST CAP (pomalidomide)**	5	$96,209.39	$19,241.88	1
Patient 1: • Pomalyst 4mg: 7/6/21 (#21 per 28 days) • Pomalyst 3mg: 7/29, 9/20 (#21 per 28 days) • Pomalyst 2 mg: 12/10, 1/13, 2/11 (#21 per 28 days)					
Breast, Ovarian & Prostate Cancers – PARP inhibitors	**LYNPARZA TAB (olaparib)**	5	$36,161.58	$7,232.32	2
Patient 1: Lynarza 150mg and 100mg: 1/8, 2/5 (#30 per 30 days and #60 per 30 days) Patient 2: Lynarza 150mg: 10/18/21 (#120 per 30 days)					
Breast Cancer – HER2	**TUKYSA TAB 150 MG (tucatinib)**	2	$39,611.05	$19,805.53	1
Patient 1: Tukysa 150mg: 3/25/21, 7/19 (#120 per 30 days) – no claims after 8/11/21					
Breast Cancer – CDKIs	**IBRANCE CAP (palbociclib)**	17	$300,861.32	$17,697.73	3
Patient 1: Ibrance 75mg: 1/25, 2/23, 3/23, 4/22, 5/19, 6/11, 7/9, 8/9, 9/7, 9/30, 10/28, 11/30, 12/28, 1/21 (#21 per 28 days) Patient 2: Ibrance 125mg: 8/19 (#21 per 28 days) – no claims after 8/19 Patient 3: Ibrance 100mg: 1/4/21, 2/2, 3/2, 4/1, 4/29, 5/27, 6/24, 8/2, 8/26 (#21 per 28 days) – no claims after 8/26					
Lymphomas	**IMBRUVICA TAB 420 MG (ibrutinib)**	14	$196,089.95	$14,006.43	1
Patient 1: Imbruvica 425mg: 1/25, 2/18, 3/26, 4/20, 5/21, 6/15, 7/13, 8/9, 9/8, 10/6, 11/2, 11,24, 12/28, 1/24 (#28 per 28 days)					
GIST, Renal, Hepatic, Colorectal, Thyroid, Bladder	**LONSURF TAB (trifluridine-tipiracil)**	6	$50,232.40	$8,372.07	2
Patient 1: Lonsurf 20-8.19 and Lonsurf 15-6.14: 10/5, 11/10 (#40 per 28 days for each drug) – no claims after 11/10 Patient 2: Lonsurf 20-8.19 and Lonsurf 15-6.14: 9/27 (#40 per 28 days for each drug)					
Myelofibrosis	**JAKAFI TAB (ruxolitinib)**	17	$355,127.90	$20,889.88	2
Patient 1: Jakafi 20mg: 2/3, 2/24, 4/22, 5/24, 6/17, 7/26, 8/26, 9/24, 10/28, 11/30, 12/27, 2/3 (#60 per 30 days) Patient 2: Jakafi 20mg: 8/4, 9/13, 11/12, 12/27 (#120 per 15 days) – no claims after 12/27					
Leukemias	**ONUREG TAB 300 MG (azacitidine)**	1	$21,158.12	$21,158.12	1
Patient 1: Onureg 300mg: 12/23, 2/4 (#14 per 28 days)					
Misc agents/Rare Cancers	**KOSELUGO CAP (selumetinib)**	14	$133,715.44	$9,551.10	2
Patient 1: Koselugo 25mg: 11/29, 1/21/22 (#60 per 30 days) Patient 2: Koselugo 10mg: 3/8, 4/13, 5/17, 6/9, 7/6, 8/5, 9/3, 9/29, 11/29, 12/27, 1/19/22 (#120 per 30 days) – no claims after 1/19/22					
Skin Cancers	**ZELBORAF TAB 240 MG (vemurafenib)**	1	$10,134.62	$10,134.62	1
	COTELLIC TAB 20 MG (cobimetinib)	1	$7,012.17	$7,012.17	
	BRAFTOVI CAP 75 MG (encorafenib)	6	$76,799.71	$12,799.95	
	MEKTOVI TAB 15 MG (binimetinib)	6	$50,248.83	$8,374.81	
Patient 1: • Zelboraf 240mg: 5/6 (#224 per 28 days) • Cotellic 20mg: 5/6 (#63 per 21 days) • Braftovi 75mg and Mektovi 15mg: 8/11, 9/8, 10/5, 11/2, 12/1, 1/4/22, 2/7 (#120 per 30 days for each drug)					
Breast Cancer – P13K inhibitor	**PIQRAY TAB 300 MG (alpelisib)**	3	$133,715.44	$9,551.10	1
See member taking Verzenio above					

Anticonvulsants – brand utilization

Time Frame: 10/1/2021 to 12/3/2021 – 4,002 members taking anticonvulsant

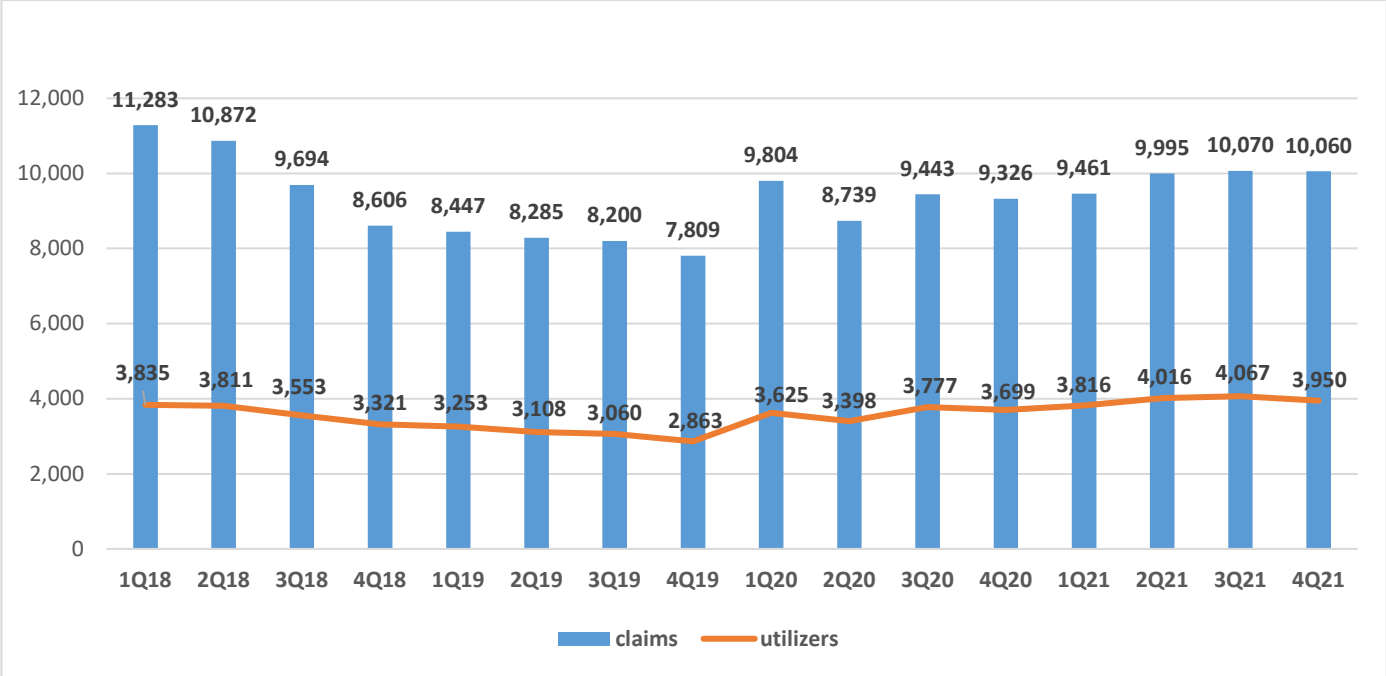
Generic Name	Drug Name	Total Rxs	Paid Amount	Paid/Rx	Utilizers
carbamazepine (NTI) bipolar disorder, mania	EPITOL TAB 200MG	4	$195.19	$48.80	2
	TEGRETOL-XR TAB 100 MG	2	$148.98	$74.49	1
clonazepam panic disorder	KLONOPIN TAB	6	$1,261.23	$210.21	3
divalproex (NTI) bipolar disorder, mania	DEPAKOTE TAB DR	3	$1,554.78	$518.26	1
	DEPAKOTE ER TAB 500MG	8	$4,923.73	$615.47	3
	DEPAKOTE SPRIKLE CAP 125MG	18	$4,978.32	$276.57	6
felbamate	FELBATOL TAB 400MG	3	$8,045.40	$2,681.80	1
lamotrigine (NTI) bipolar disorder	LAMICTAL TAB	17	$29.383.46	$1,728.44	6
	LAMICTAL XR TAB	3	$1,052.08	$350.69	1
levetiracetam (NTI)	KEPPRA SOL 100MG/ML	6	$10,910.52	$1,818.42	2
	KEPPRA TAB	7	$3,202.93	$457.56	2
	KEPPRA XR TAB	7	$9,258.76	$1,322.68	2
	SPRITAM TAB 250MG	2	$1,134.04	$567.02	1
oxcarbazepine	OXTELLAR XR TAB	13	$15,349.14	$1,180.70	5
	TRILEPTAL SUSP 300MG/5ML	3	$1,714.01	$571.34	1
phenytoin (NTI)	DILANTIN CHW 50MG	6	$1,081.58	$180.26	2
	DILANTIN CAP 30MG	6	$592.75	$98.79	3
pregabalin Off-label: GAD, social phobia	LYRICA CAP	7	$4,021.64	$574.52	3
rufinamide Lennox-Gastaut	BANZEL SUSPENSION 40MG/ML	4	$8,187.76	$2,046.94	2
	BANZEL TAB	11	$31,787.16	$2,889.74	4
topiramate (NTI) Off label: bipolar, binge-eating, bulimia	TOPAMAX SPR CAP 25MG	3	$4,568.91	$1,522.97	1
	TOPAMAX TAB	7	$8,558.49	$1,222.64	2
	TROKENDI XR CAP	20	$15,299.03	$764.95	8

NTI – Narrow Therapeutic Index drug

Generic Name	Drug Name	Total Rxs	Paid Amount	Paid/Rx	Utilizers
brivaracetam	BRIVIACT SOL 10MG/ML	6	$8,248.40	$1,374.73	1
	BRIVIACT TAB	21	$28,723.15	$1,367.77	8
cannabidiol Lennox-Gastaut. Dravet, tuberous sclerosis	EPIDIOLEX SOL 100MG/ML	91	$221,882.23	$2,438.27	26
clobazam Lennox-Gastaut Off label: Dravet	ONFI SUSP 2.6MG/ML	14	$10,621.43	$758.67	7
	ONFI TAB	3	$8,366.16	$8,366.16	1
	SYMPAZAN MIS	16	$23,501.90	$1,468.87	4
diazepam	DIASTAT GEL	5	$1,744.28	$348.86	5
	VALTOCO NASAL SPRAY	10	$8,851.47	$885.15	7
eslicarbazepine	APTIOM TAB 400MG	2	$2,061.68	$1,030.84	1
fenfluramine	FINTEPLA SOL 2.2MG/ML	3	$51,253.35	$17,084.45	1
lacosamide	VIMPAT SOL 10MG/ML	53	$45,512.55	$858.73	13
	VIMPAT TAB	178	$172,214.70	$967.50	57
perampanel	FYCOMPA TAB	12	$13,025.01	$1,085.42	5

Red font denotes drug is on PA

Opioid Summary



- 1Q2018 to 4Q2019 excludes IHS
- 1Q2020 to current includes IHS
- 2Q2020 pandemic closure

Total Eligibility and Utilizers

Quarter	Avg eligible members	Avg utilizing members of all drugs	% utilizing members of all drugs
1Q2020	123,573	27,089	21.9%
2Q2020	126,777	20,747	16.4%
3Q2020	132,373	23,417	17.7%
4Q2020	136,262	23,488	17.2%
1Q2021	139,748	24,405	17.5%
2Q2021	142,872	26,162	18.3%
3Q2021	146,023	27,847	19.1%
4Q2021	149,034	29,257	19.3%

Opioid Utilization Snapshot

SDM 4Q2021

Sep 21 to Dec 21

Opioid Claims **10,060**

3.0% prescription claims filled for an opioid

0.5% higher than Medicaid FFS benchmark

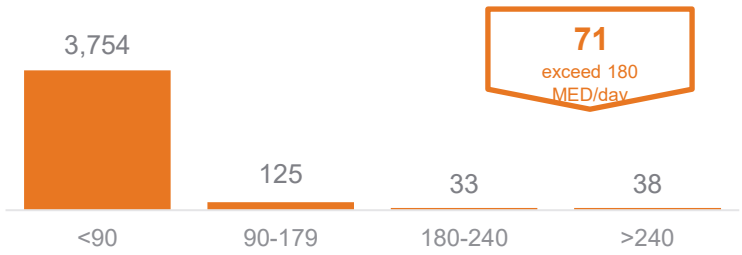
Utilizers **3,950**

31.6% are high utilizers [1]

-3.3% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

41 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

273 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

3Q2021

Jun 21 to Sep 21

Opioid Claims **10,070**

3.1% prescription claims filled for an opioid

0.5% higher than Medicaid FFS benchmark

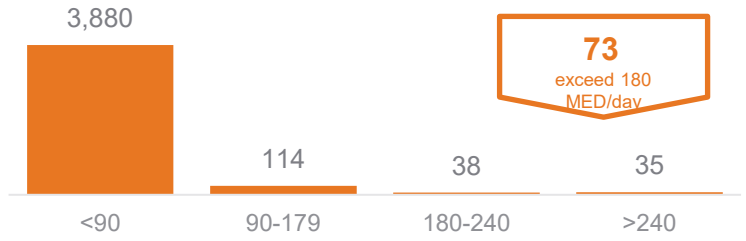
Utilizers **4,067**

29.8% are high utilizers [1]

-4.5% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

Current CDC Guidelines[5] urge doses of 90 MME[6] or less in chronic opioid utilizers[5]



Shoppers: Poly Pharmacy

50 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

262 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUMRx®

[1]Defined as 3+ opioid scripts within 120 days period; [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization

SDM 4Q2021
Opportunities date range: Sep - Dec 2021
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 3,950

3.0% of all Rx claims are filled for an Opioid

Opioid dependence can start in just a few days, and the risk of chronic opioid use increases with each additional day of opioid supplied, starting with the third day. Our Opioid Risk Management program, which includes point of sale, utilization management and retrospective drug utilization edits, are tightly aligned with CDC opioid prescribing guidelines which can help reduce exposure to excessive doses and prevent more members from transitioning from acute to chronic use.

- Opioid prescriptions account for 3.0% of all prescriptions this period, which is 0.5% higher than the benchmark
- 1,250 high opioid utilizers were identified this period, which is -3.3% lower than the benchmark

Opioid claims

PERCENT OPIOID CLAIMS
3.0%

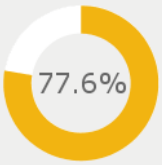
Opioid utilizers

HIGH UTILIZERS
31.6%
1,250 high utilizers

-3.3% under benchmark

High utilizers – Defined as 3+ opioid scripts within 120 day period

Claim breakdown



short acting opioids

77.6% of all opioid Rxs were filled for short acting opioids. **1,587** Rxs were for medication assisted therapy (MAT) and **124** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

MAT – Medication Assisted Therapy (buprenorphine, etc)
Overdose rescue therapy – opioid overdose reversals w/naloxone
MME – relative potency of an opioid to a morphine dose

Utilizers by cumulative MED

71 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,754	125	33	38

MED – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period

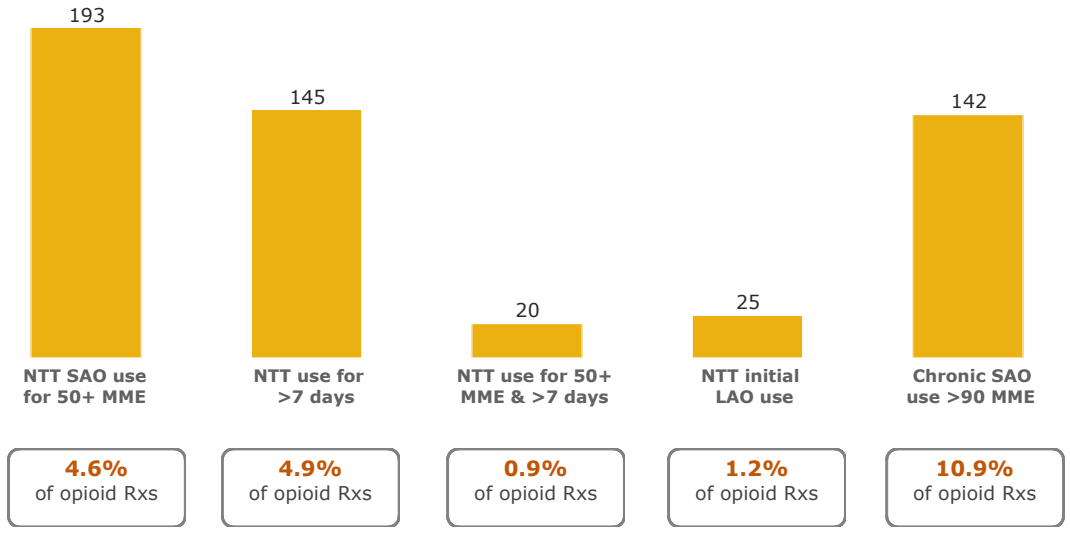
Opioid Opportunity Assessment

SDM 4Q2021
Opportunities date range: Sep - Dec 2021
Benchmark: MEDICAID FEE FOR SERVICE

Percent non-compliant: 9.4%

Utilizers non-compliant to opioid Rx CDC guidelines

(new to therapy and chronic use)



NTT - view definition | SAO - view definition | LAO - view definition | MME - view definition

41 opioid utilizing members use 3 or more pharmacies and 273 opioid utilizing members use 3 or more prescribers.

NNT - New to Therapy
SAO - Short Acting Opioid
LAO - Long Acting Opioid
MME - Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
722	562	688	N/A	150

Anticonvulsants – Gabapentin, Pregabalin, Anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

New Business

PA Drug Class Summary 4Q2021

Drug Class	Approved	Denied	Total	Approval Rate
URINARY ANTISPASMODICS*	18	8	26	69.23%
APPEALS	1	0	1	100%
MUSCULOSKELETAL THERAPY AGENTS*	6	3	9	66.67%

Urinary Antispasmodics PA Approval Review

Detrol, Detrol LA, Enablex, Myrbetriq/Granules, Toviaz, trospium ER, Vesicare/LS, Oxytrol, Gelnique:

1. Diagnosis of overactive bladder, urinary incontinence, urinary urgency, neurogenic bladder
2. Patient has had a 30-day trial of oxybutynin or oxybutynin ER within the last 4 months
3. Gelnique/Oxytrol/Vesicare LS/Mybetriq Granules only – patient has a diagnosis which confirms difficulty in swallowing

Drug Name	Total Manual Reviews	Approvals	Denials
Myrbetriq	14	7	7
APPEAL	1	1	0
Toviaz	2	1	1
tolterodine tartrate ER	1	1	0
trospium ER 24 hour	2	2	0

20 reviewed manually
6 reviewed electronically

Utilization

Time frame: 10/1/2021 to 12/31/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/DS	Utilizers	Age Range
bethanechol tab	14	$356.16	$25.44	#58 per 29	5	18 – 53
darifenacin tab (Enablex)	12	$1,279.49	$106.62	#24 per 24	3	40 – 60
oxybutynin tab	119	$1,703.47	$14.31	#60 per 31	57	9 – 65
oxybutynin tab ER	368	$5,686.79	$15.45	#32 per 30	156	5 – 64
oxybutynin syrup	27	$487.89	$18.07	#258 per 26	17	2 – 41
tolterodine tab (Detrol)	10	$313.05	$31.31	#40 per 23	3	18 – 40
tolterodine cap ER	45	$2,145.96	$47.69	#33 per 31	19	7 – 65
trospium tab (Sanctura)	5	$108.21	$21.64	#33 per 27	2	58 – 59
trospium cap ER	12	$1,177.78	$98.15	#30 per 30	6	11 - 39
Myrbetriq tab (mirabegron)	118	$43,484.82	$368.52	#28 per 29	40	10 – 65
Mybetriq Granules	0					
solifenacin tab (Vesicare)	45	$815.64	$54.38	#18 per 32	10	12 – 63
Vesicare LS oral suspension	0					
Gelnique 10% topical gel	0					
Oxytrol transdermal patch	0					
Toviaz tab (fesoterodine)	12	$4,250.24	$354.19	#31 per 31	4	29 – 55
Gemtesa tab (viberon)	2	$896.28	$448.14	#30 per 30	2	34, 58

*Red font denotes drug is on PA

Musculoskeletal Therapy Agents PA Approval Review

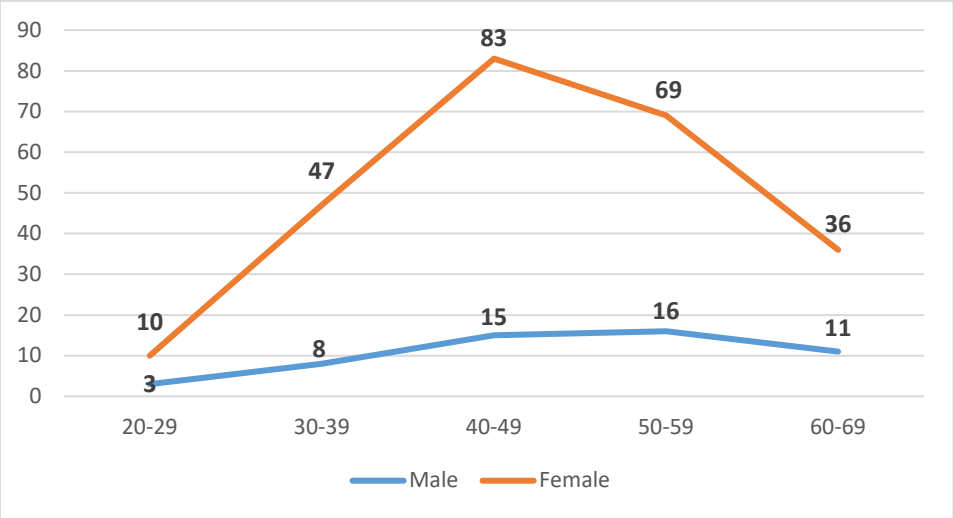
Drug Name	Total Manual Reviews	Approvals	Denials
cyclobenzaprine tab • QLL – 2 per day	8	5 • 3 PAs for 3 per day • 2 PAs for 6 per day	3 • 1 Rx for 6 per day • 2 Rx for 3 per day
methocarbamol • QLL – 4 per day	1	1 • 1 PA for 6 per day but all claims for #30 per 10 days	0

Opioid and Muscle Relaxant combination

Time frame: 10/1/2021 to 1/31/2022

All claims including IHS

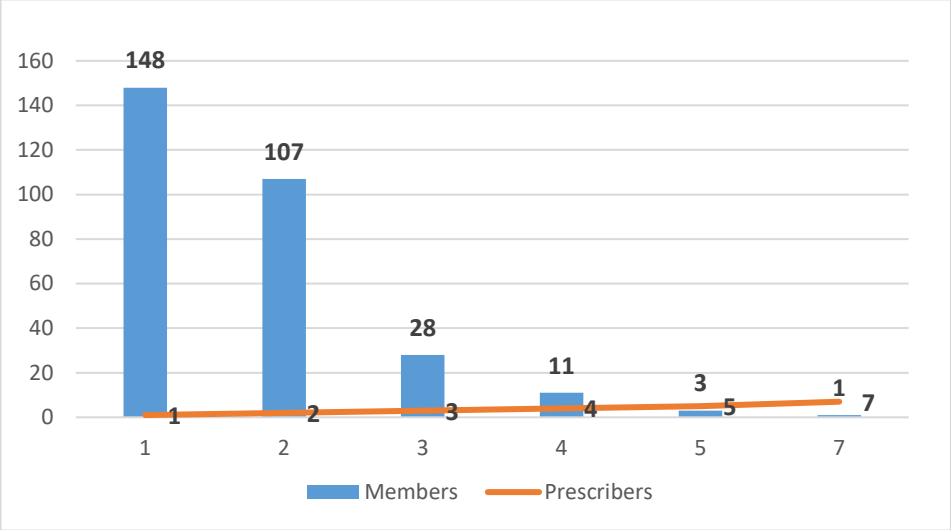
- 606 members taking opioid and muscle relaxant from Oct 2021 to Jan 2022
- 298 member taking opioid and muscle relaxant from Jan to Feb 11, 2022 (chronically)
  - Member demographics
    - Females: 245 members (20 to 66 years old)
    - Males: 53 members (21 to 64 years old)



  - Number of different drugs per member during Jan to Feb 11, 2022
    - 208 members – 2 different drugs (opioid and muscle relaxant)
    - 71 members – 3 different drugs
    - 16 members – 4 different drugs
    - 3 members – 5 different drugs

  - Number of pharmacies filling for opioids and muscle relaxants for each member
    - 248 members – using 1 pharmacy
    - 45 members – using 2 different pharmacies
    - 5 members – using 3 different pharmacies

- Number of prescribers for opioids and muscle relaxant prescriptions for each member



Sedative Hypnotics

Time frame: 10/1/2021 to 12/31/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range
buspirone	1,324	$17,256.27	$13.03	#69 per 29 days	674	9 – 68
doxepin (Silenor)	14	$3,662.03	$261.57	#30 per 30 days	7	18 – 61
doxylamine	1	$8.89	$8.89	#28 per 14 days	1	18
estazolam	3	$74.79	$24.93	#30 per 30 days	1	62
temazepam	66	$1,301.93	$19.73	#30 per 28 days	26	15 – 62
triazolam	9	$95.58	$10.62	#2.5 per 1.4 days	8	15 – 43
trazodone	3,303	$33,735.53	$10.21	#36 per 30 days	1,450	0 – 64
ramelteon (Rozerem)	23	$1,165.41	$50.69	#28 per 30 days	10	9 – 61
eszopiclone (Lunesta)	113	$1,663.56	$14.72	#29 per 29 days	45	18 – 64
zaleplon (Sonata)	4	$63.21	$15.80	#36 per 26 days	3	31 – 42
Ambien	3	$1,608.51	$536.17	#28 per 28 days	1	64
zolpidem tab	580	$6,148.08	$10.60	#28 per 38 days	249	12 – 64
Ambien CR	6	$3,397.32	$566.22	#30 per 30 days	2	60, 64
zolpidem CR	84	$1,511.38	$17.99	#30 per 30 days	31	21 – 62
Edluar SL	0					
Intermezzo SL	0					
Zolpimist lingual spray	0					
Dual Orexin Receptor Agonist						
Belsomra (suvorexant)	52	$18,579.97	$357.31	#29.5 per 27 days	20	23 – 62
Dayvigo (lemborexant)	11	$3,897.59	$354.33	#37 per 29 days	5	19 – 41
Quviviq (daridorexant)	0					

*Red font denotes drug is on ST

PA criteria:

- 14-day trial of zolpidem IR in the last 365 days

Vuity & pilocarpine drops

Time frame: 12/1/2021 to 2/8/2022

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range	Taxonomy
Vuity sol 1.25%	3	$242.22	$80.74	2.5 ml per 21 days $32.30 per ml	2	47	Optometrist
pilocarpine sol 2%	2	$142.12	$71.06	15 ml per 22.5 days $4.74 per ml	1	60	Optometrist
pilocarpine sol 1%	0		*~$67.00*	15 ml per bottle $4.47 per ml			
pilocarpine sol 4%	0		*~$76.00*	15 ml per bottle $5.07 per ml			

Indications:

- pilocarpine 1%, 2%, 4% solution
  - Reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension
  - Induction of miosis
  - Prevention of postoperative elevated IOP associated with laser surgery
- Vuity 1.25% solution
  - Treatment of presbyopia in adults

Opzelura & Atopic Dermatitis

Time frame: 10/1/2021 to 12/31/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity/DS	Utilizers	Age Range
Opzelura cream 1.5% (**ruxolitinib**)	1	$1,960.55	$1,960.55	60 gm per 30 days	1	19
*Opzelura cream 1.5% (**ruxolitinib**)*			*~$11,000*	*340 gm per 30 days*		
pimecrolimus cream 1% (Elidel)	43	$11,863.33	$275.89	56 gm per 26 days	36	0 – 58
Eucrisa ointment 2% (crisaborole)	48	$34,356.75	$715.77	69 gm per 27 days	39	0 – 57
tacrolimus ointment 0.03% (Protopic)	12	$1,165.39	$97.12	40 gm per 23 days	10	1 – 17
tacrolimus ointment 0.1% (Protopic)	43	$4,968.94	$115.56	52.8 gm per 25 days	32	0 – 59
mometasone cream 0.1%	31	$717.47	$23.14	38 gm per 22 days	25	0 – 61
mometasone ointment 0.1%	52	$1,005.45	$19.34	42 gm per 22 days	47	0 – 62
Systemic agent						
Dupixent inj (dupilumab)	127	$391,750.32	$3,084.65	3.5 per 28 days	44	5 – 61
Adbry inj (tralokinumab)	0					
Rinvoq tab ER (upadacitinib)	4	$20,542.32	$5,135.58	30 per 30 days	2	40, 46
Cibinqo tab (abrocitinib)	0					

*Red font denotes drug is on PA

Indications:

1. Opzelura – Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥ 12 years whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
2. Elidel – Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children aged ≥ 2 years, who have failed to respond adequately to other topical prescription treatments
3. Eucrisa – Topical treatment of mild to moderate atopic dermatitis in patients aged ≥ 3 months.
4. Protopic – Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis
5. Mometasone – Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses (medium potency topical corticosteroid).
6. Dupxient (SC) – Treatment of patients ≥ 6 years of age with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies; *Annual ~$43,000*
7. Adbry (SC) – Interleukin-13 antagonist; treatment for adults with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable. Can be used with or without topical corticosteroids (TCS). *Annual ~$43,000*
8. Cibinqo (oral) – JAK inhibitor is limited to certain patients with refractory AD whose disease is not adequately controlled with other systemic drug products, including biologics; *Annual ~$60,000*
9. Rinvoq (oral) – JAK inhibitor is limited to certain patients with refractory AD whose disease is not adequately controlled with other systemic drug products, including biologics; *Annual ~$62,000*

Opzelura PA criteria consideration:
Initial Authorization: 12 weeks to 6 months
Must meet the following:

1. Diagnosis of mild to moderate atopic dermatitis
2. Member is 12 years of age or older
3. One of the following:
   3.1. Greater than or equal to 3% body surface area involvement
   3.2. Involvement of sensitive body areas (e.g., face, hands, feet, scalp, groin)
4. Prescribed by or in consultation with Dermatologist or Allergist/Immunologist
5. *One of the following:*
   *5.1. ≥90 days of topical drug therapy with **each** of the following: corticosteroids, pimecrolimus and/or tacrolimus, crisaborole*
   5.2. Prescriber has provided valid medical justification for the use of Opzelura over topical corticosteroids, tacrolimus, pimecrolimus, and crisaborole
6. *Trial and failure of a minimum 30-day supply (14-day supply for topical corticosteroids), contraindication, or intolerance to at least TWO of the following:*
   6.1. Medium or higher potency topical corticosteroid
   6.2. Elidel (pimecrolimus) cream
   6.3. Tacrolimus ointment
   6.4. Eucrisa (crisaborole) ointment
7. Member is not using concurrently with therapeutic biologics, other Janus kinase inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine
8. Requested quantity does not exceed 240g/30 days

Reauthorization: 6 months to 1 year

1. History of the requested agent within the past 180 days
2. Opzelura will only be used for short-term and/or non-continuous chronic treatment

INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. As a chronic inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus exacerbated by various environmental stimuli, it is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2 to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States (US). Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of 5 years. It can manifest at different sites depending on the age at onset. The prevalence appears to be increasing especially in Western societies *(Berke et al 2012, Eichenfield et al 2014a, Food and Drug Administration [FDA] presentation 2015, Sidbury et al 2014, Weston and Howe 2021)*.
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier, resulting in water loss, xerosis, microbial colonization, and secondary infection. The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces. The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities *(Castro 2008, Eichenfield et al 2014a, Weston and Howe 2021)*.
- Diagnosis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment of the disease and there is no cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical and/or systemic agents *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*.
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine). However, evidence supporting their use is weak due to lack of controlled trials *(Eichenfield et al 2014b)*.
- Topical emollients and topical corticosteroids are first-line treatments for atopic dermatitis. Second- and subsequent-line topical treatment options include topical calcineurin inhibitors and a topical Janus kinase (JAK) inhibitor. The use of systemic therapies is reserved for patients with moderate to severe disease and can include phototherapy, oral cyclosporine or other systemic immunosuppressants, and a biologic interleukin inhibitor, Dupixent (dupilumab) *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014, Weston and Howe 2021)*.
  - Low- to high-potency topical corticosteroids are utilized 1 or more times daily for the treatment of acute flares, as well as intermittently to prevent relapses. There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck *(Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013)*.
  - Eucrisa (crisaborole) is a non-steroidal, topical treatment for mild to moderate atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis. Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines *(Paller et al 2016, Zane et al 2016)*.
  - Opzelura (ruxolitinib) is a JAK inhibitor, non-steroidal, topical treatment for mild to moderate atopic dermatitis; however, use is limited to those patients who are not adequately controlled with other topical prescription therapies, or when those therapies are not advisable. Ruxolitinib is available as an oral tablet and a topical cream; only the cream is indicated for atopic dermatitis. As a kinase inhibitor, ruxolitinib inhibits inflammation-causing JAK1 and JAK2

enzymes, responsible for signaling several cytokines and growth factors. It is not completely known how inhibiting JAK enzymes is responsible for the efficacy in atopic dermatitis (*Clinical Pharmacology 2021*).

- Topical immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Protopic and Elidel provide immunosuppression via inhibition of T-cell activation *(Clinical Pharmacology 2021)*.
- Dupixent (dupilumab) is a human monoclonal antibody that inhibits signaling of interleukin (IL)-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for controlling symptoms of moderate to severe atopic dermatitis *(Clinical Pharmacology 2021)*.

- The scope of this review includes agents FDA-approved for the treatment of atopic dermatitis. General anti-inflammatory agents such as the corticosteroids are not included. Only information pertaining to the indication of atopic dermatitis is included within this document.
- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical; Macrolide Immunosuppressants – Topical; Atopic dermatitis – Monoclonal Antibodies; Atopic dermatitis – Janus Kinase (JAK) Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Systemic agents	
Dupixent (dupilumab)	-
Topical agents	
Elidel (pimecrolimus)	✔
Protopic (tacrolimus)	✔
Eucrisa (crisaborole)	-
Opzelura (ruxolitinib)	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA-approved indications for topical agents

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)	Opzelura (ruxolitinib)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children aged ≥ 2 years, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.	✔			
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✔ *		
Topical treatment of mild to moderate atopic dermatitis in patients aged ≥ 3 months.			✔	
Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in				✔ †

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)	Opzelura (ruxolitinib)
non-immunocompromised patients aged ≥ 12 years whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable				

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age.
†Limitation of use: Use of Opzelura in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

(*Prescribing information: Elidel 2020, Eucrisa 2020, Opzelura 2021, Protopic 2019*)

Table 3. FDA-approved indications for systemic agents

Indication	Dupixent (dupilumab)
Treatment of patients ≥ 6 years of age with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable	✔ *

*Dupixent can be used with or without topical corticosteroids.

(*Prescribing information: Dupixent 2021*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Elidel and Protopic

- The FDA approval of pimecrolimus cream was based on 3 randomized, double-blind (DB), vehicle-controlled, Phase 3 studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (n = 589). Two of these 3 trials support the use of pimecrolimus cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-week, vehicle-controlled, Phase 3 trials were conducted in pediatric patients 2 to 17 years of age (n = 403). These studies showed significant clinical response based on physician's global evaluation for pimecrolimus-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.
- The FDA approval of tacrolimus ointment was based on 3 randomized, DB, vehicle-controlled, Phase 3 studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (n = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (n = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the tacrolimus group compared to the vehicle group ($p < 0.001$). There was some evidence that tacrolimus 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the tacrolimus strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Pimecrolimus and tacrolimus have been directly compared in clinical trials. One trial compared pimecrolimus 1% to tacrolimus 0.03% in patients 2 to 17 years of age (n = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the tacrolimus group. In 2 other clinical trials, tacrolimus 0.1% was compared to pimecrolimus in adult patients over 6 weeks. Patients treated with tacrolimus had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with pimecrolimus. The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the tacrolimus group in both studies. There were no differences in adverse effects (AEs) between the groups *(Abramovits et al 2008, Fleischer et al 2007)*.

- A total of 3 randomized controlled trials (RCTs) showed that both adults and children in the tacrolimus-treated group had a significantly greater improvement in EASI score at week 6 as compared to the pimecrolimus group. The most common AEs in all studies were local application site reactions including burning and stinging *(Paller et al 2005)*.
- A meta-analysis (MA) of 25 RCTs (n = 6897) showed that tacrolimus 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis. Additionally, pimecrolimus was found to be less effective than potent topical corticosteroids *(Ashcroft et al 2005)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A MA and systematic review (SR) assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (n = 7378). In terms of overall comparison, pimecrolimus was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 weeks) than pimecrolimus in the treatment of moderate to severe atopic dermatitis. Although this MA showed that pimecrolimus seems to be less effective than topical corticosteroids, Pimecrolimus would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of tacrolimus trials demonstrated that tacrolimus was more effective than vehicle. When compared to mild potency topical corticosteroids like hydrocortisone acetate, tacrolimus was more efficacious. However, when compared to moderate potency topical corticosteroids, tacrolimus 0.03% was significantly less effective than topical corticosteroids, and tacrolimus 0.1% was equal in effectiveness to the topical corticosteroids. Overall, tacrolimus was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- A SR of 20 RCTs (n = 6288) showed that tacrolimus was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis. Additionally, pimecrolimus was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, 3 trials comparing pimecrolimus to tacrolimus were identified. While 2 of the trials did find tacrolimus to be significantly more efficacious, no significant difference was found in the third trial *(Chen et al 2010)*.
- The following studies outlines data regarding the potential risk for malignancies with topical calcineurin inhibitor use:
  - A 5-year, OL, multicenter (MC) study evaluated the use of pimecrolimus in 2418 infants compared to topical corticosteroids. The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of 0 to 5 on the IGA. Topical corticosteroids included low-potency such as hydrocortisone 1% or medium-potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More pimecrolimus-treated patients reported bronchitis ($p = 0.02$), infected eczema ($p < 0.001$), impetigo ($p = 0.045$), and nasopharyngitis ($p = 0.04$). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the pimecrolimus-treated group. Over the 5-year period, 88.7% and 92.3% of the pimecrolimus- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of pimecrolimus- and corticosteroid-treated patients completing the study *(Sigurgeirsson et al 2015)*.
  - A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to pimecrolimus or tacrolimus was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to tacrolimus and not pimecrolimus ($p < 0.001$, $p = 0.086$, respectively) *(Hui et al 2009)*.
  - A recent MA of observational studies (N = 11 studies, including 8 cohort studies in which 408,366 patients were treated with topical calcineurin inhibitors) published up to October 2020, evaluated the association between topical calcineurin inhibitor use and risk of malignant neoplasms vs controls (non-active comparator or topical corticosteroids). There was no association between topical calcineurin inhibitor use and cancer overall vs non-active comparators (RR, 1.03; 95% CI, 0.92 to 1.16). However, the lymphoma risk was elevated with topical calcineurin inhibitors compared to both the non-active comparators (RR, 1.86; 95% CI, 1.39 to 2.49) and the topical corticosteroids (RR, 1.35; 95% CI, 1.13 to 1.61). No significant association was found between topical calcineurin inhibitor use and increased skin cancer (melanoma and keratinocyte carcinoma) (*Lam et al 2021*).

Eucrisa

- The safety and efficacy of crisaborole were demonstrated in 2 identically designed, randomized, Phase 3, DB, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable BSA. The primary

endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2-grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving crisaborole vs vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8 vs 25.4%, p = 0.038; Study AD-302: 31.4 vs 18.0%, p < 0.001), with a greater percentage achieving clear/almost clear overall (51.7 vs 40.6%, p = 0.005; 48.5 vs 29.7%, p < 0.001). In addition, crisaborole-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both p < 0.001) *(Eucrisa dossier 2018, Paller et al 2016)*.
    - An open-label (OL) extension trial of AD-301 and AD-302 evaluated the safety of crisaborole in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs (TEAEs) were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with crisaborole (93.1%). The most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).
- The CrisADe CARE 1 trial (n = 137) was a Phase 4, OL trial which demonstrated that crisaborole was tolerated and effective in children aged 3 to 24 months with mild to moderate atopic dermatitis. Crisaborole systemic exposures in infants were comparable with those of patients aged ≥ 2 years. TEAEs were reported for 88 (64.2%) patients (98.9% were mild/moderate). The most frequently reported TEAEs were application site pain (3.6%), application site discomfort (2.9%), and erythema (2.9%). ISGA clear/almost clear scores with ≥ 2-grade improvement at day 29 were achieved by 30.2% of patients. From baseline to day 29, mean percentage change in EASI score was -57.5%, and mean change in Patient-Oriented Eczema Measure (POEM) total score was -8.5 (*Schlessinger et al 2020*).
- One SR and network MA (NMA) of 9 RCTs evaluated crisaborole vs other topical treatments for mild to moderate atopic dermatitis. Patients were more likely to achieve ISGA 0 to 1 with crisaborole than with pimecrolimus 1% cream (hazard ratio [HR], 1.62; 95% credible interval [CrI], 1.04 to 2.48; probability treatment was better vs comparator = 98.3%). There was weak evidence of a difference between crisaborole and tacrolimus 0.03% (HR, 1.35; 95% CrI, 0.95 to 1.84; probability treatment was better vs comparator = 95.7%) and no evidence of a difference vs tacrolimus 0.1% (HR, 1.18; 95% CrI, 0.64 to 1.96; probability treatment was better vs comparator = 71.6%). The NMA for safety was not feasible due to data limitations (*Fahrbach et al 2020*).

Opzelura

- The safety and efficacy of Opzelura were demonstrated in 2 identically designed, randomized, Phase 3, DB, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2) in a total of 1249 patients aged ≥ 12 years with atopic dermatitis and 3 to 20% affected BSA and a baseline Investigator's Global Assessment (IGA) score of 2 or 3. The primary endpoint was defined as the proportion of patients at week 8 with an IGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline. Patients were randomized (2:2:1) to ruxolitinib 0.75% cream twice daily (n = 500), ruxolitinib 1.5% cream twice daily (n = 499; FDA-approved dose), or vehicle cream twice daily (n = 250) for 8 weeks. A total of 11.5% of patients in TRuE-AD1 and 9.2% of patients in TRuE-AD2 did not complete the 8-week trials. In TRuE-AD1 and TRuE-AD2, more ruxolitinib-treated patients achieved IGA treatment success with ruxolitinib 0.75% (50.0 vs 39.0%, respectively) and ruxolitinib 1.5% (53.8 vs 51.3%, respectively), vs the vehicle (15.1 vs 7.6%, respectively; p < 0.0001) at week 8. In addition, both ruxolitinib strengths demonstrated significant reductions in itch (as measured by daily itch numerical rating scale scores) and an increase in patients achieving a 75% improvement in EASI (EASI-75) compared to the vehicle. A larger proportion of vehicle-treated patients reported TEAE(s) vs patients treated with the ruxolitinib 1.5% cream (33.2 vs 26.5%, respectively). A total of 15 patients discontinued from both studies due to TEAEs (n = 8 [3.2%] with vehicle and 7 with ruxolitinib [0.6% in the ruxolitinib 1.5% cream group) (*Papp et al 2021*).
    - The long-term safety of ruxolitinib cream was presented at the Revolutionizing Atopic Dermatitis Symposium in June 2021, with data yet to be published. Although available data are limited, ruxolitinib cream appeared to be well tolerated through 1 year of treatment, with no AEs suggestive of a relationship to systemic exposure (*Blauvelt et al 2021*).
    - The TRuE-AD3 trial, an 8-week efficacy trial followed by a 44-week long-term safety trial, is currently evaluating approximately 250 children with atopic dermatitis aged 2 to 11 years (*Clinicaltrials.gov [NCT04921969] 2021*).
- One, dose-ranging, DB/OL, Phase 2 trial evaluated the effectiveness of ruxolitinib vs triamcinolone. The DB phase evaluated ruxolitinib (doses ranging from 0.15 to 1.5% once to twice daily) cream (n = 50 administered ruxolitinib 1.5% twice daily cream) vs triamcinolone 0.1% cream twice daily (n = 51) vs a vehicle cream twice daily (n = 52) in 307 adults with atopic dermatitis, an IGA score of 2 or 3 (mild-to-moderate disease), and 3 to 20% affected BSA at baseline. Treatment continued for 8 weeks, except the triamcinolone group which was treated for only 4 weeks. Therapeutic

benefit was demonstrated with ruxolitinib as early as week 4, regardless of dose. The ruxolitinib 1.5% twice daily cream demonstrated the greatest improvement in IGA responses vs the vehicle at week 4 (38.0 vs 7.7%, respectively; p < 0.001) and week 8 (48.0 vs 9.6%, respectively; p < 0.001). Ruxolitinib 1.5% twice daily cream was not statistically different from the triamcinolone 0.1% twice daily cream for IGA responses at week 4 (38.0 vs 25.5%, respectively). Of note, no comparisons between ruxolitinib and triamcinolone could be made at week 8, because triamcinolone treatment was stopped at week 4 (*Kim et al 2020*).

Dupixent

- The efficacy and safety of dupilumab compared to placebo in adults with moderate-to-severe atopic dermatitis was evaluated in two Phase 3 trials, SOLO 1 (n = 671) and SOLO 2 (n = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to either placebo, dupilumab 300 mg subcutaneously (SC) weekly or every other week for 16 weeks. The proportion of patients with an IGA score of 0 or 1 (indicating clear or almost clear skin) and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome. In both studies between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo (p < 0.001 for all comparisons). Significantly more patients who received dupilumab achieved EASI-75 compared to those who received placebo (p < 0.001). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common AEs with dupilumab compared to placebo were conjunctivitis and injection-site reactions (*Simpson et al 2016*).
- The long-term efficacy and safety of dupilumab were compared to placebo in 740 patients with moderate to severe atopic dermatitis not adequately controlled with topical corticosteroids in the LIBERTY AD CHRONOS study. Patients received either dupilumab 300 mg once weekly, once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and ≥ 2-point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group (p < 0.0001). Similar efficacy results were reported at week 52. At 1 year, the most common AEs associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab while herpes zoster and eczema herpeticum were more common in the placebo group (*Blauvelt et al 2017*).
- A variety of studies with dupilumab have been conducted in pediatric patients:
  - The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis in a DB, MC, RCT. Patients < 60 kg received dupilumab 400 mg initially then 200 mg every 2 weeks and patients ≥ 60 kg received 600 mg initially then 300 mg every 2 weeks for 16 weeks. Compared with placebo, dupilumab resulted in significantly higher proportions of patients achieving EASI-75 at week 16 (41.5% vs 8.2%; p < 0.001) and IGA score of 0 or 1 with 2 or more points improvement at week 16 (24.4% vs 2.4%; p < 0.001) (*Dupixent prescribing information 2021, Simpson et al 2020*).
  - The efficacy of dupilumab plus topical corticosteroids was compared to topical corticosteroids alone in 367 patients 6 to 11 years of age with moderate-to-severe atopic dermatitis in a 16-week DB, MC, RCT. Patients < 30 kg received dupilumab 200 mg initially then 100 mg every 2 weeks and patients ≥ 30 kg received 400 mg initially then 200 mg every 2 weeks. Patients in a third group were dosed regardless of weight at 600 mg initially and 300 mg every 4 weeks thereafter. The primary endpoint was the proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at Week 16. In patients who received dupilumab 300 mg every 4 weeks plus topical corticosteroids, 30% achieved the primary outcome vs 13% with topical corticosteroids alone. In patients who received dupilumab 200 mg every 2 weeks, 39% achieved the primary outcome vs 10% with topical corticosteroids alone (*Dupixent prescribing information 2021, Paller et al 2020*).
  - One OL extension in 33 children aged 6 to 11 years with severe atopic dermatitis evaluated dupilumab 2 mg/kg or 4 mg/kg for a duration of 16 weeks. TEAEs were mostly mild to moderate in nature, and none led to treatment discontinuation. The most commonly reported TEAEs for the 2 mg/kg and 4 mg/kg doses were nasopharyngitis (47 and 56%, respectively) and atopic dermatitis exacerbation (29 and 13%, respectively). Single-dose dupilumab improved atopic dermatitis, with further improvements with continued treatment through week 52 in children with severe disease (*Cork et al 2021*).
  - It was recently announced that treatment with dupilumab, via the LIBERTY AD PRESCHOOL trial, demonstrated significant reductions in the signs and symptoms of moderate-to-severe atopic dermatitis in children aged 6 months to 5 years of age. Data has yet to be presented or FDA-approved (*Sanofi press release 2021*).

- An NMA of 74 studies (n = 8177), with 11 trials comparing dupilumab vs placebo, examined the comparative effectiveness of systemic immunosuppressive treatments for moderate to severe atopic dermatitis. Dupilumab was associated with an increased proportion of patients achieving EASI-75 at ≤ 16 weeks (risk ratio [RR], 3.04; 95% CI, 2.53 to 3.65; 8 trials; n = 3150) and at > 16 weeks (RR, 2.59; 95% CI, 1.87 to 3.60; 2 trials; n = 1162). An EASI-75 was achieved by 18 to 20% of placebo-treated patients. An increased proportion of dupilumab-treated patients had an IGA score of 0 to 1 point at ≤ 16 weeks (RR, 3.58; 95% CI, 3.00 to 4.26; 10 trials; n = 3634). Dupilumab was more effective than placebo in achieving improvement in POEM score (mean difference, 7.30; 95% CI, 6.61 to 8.00) at short-term follow-up. Dupilumab had a decreased risk of serious AEs at ≤ 16 weeks (RR, 0.35; 95% CI, 0.19 to 0.64; 9 trials; n = 2628), but no significant difference in serious AEs at > 16 weeks (3 trials; n = 1541). Overall, the authors suggested that dupilumab ranks first for effectiveness compared with other biological treatments for atopic dermatitis (*Sawangjit et al 2020*). Another MA of 50 RCTs (n = 6681) examined systemic agents for atopic dermatitis. Results indicated that for EASI-75, the efficacy of off-label baricitinib (risk difference [RD], 0.16; 95% CI, 0.10 to 0.23) and FDA-approved dupilumab (RD, 0.37; 95% CI, 0.32 to 0.42; I^2 = 19%) demonstrated superiority vs placebo for < 16 weeks (*Siegels et al 2020*). Other biologics are in development for the treatment of atopic dermatitis, but are investigational at this time.

CLINICAL GUIDELINES

- According to the American Academy of Dermatology, interventions that provide effective control of atopic dermatitis for a majority of patients include non-pharmacologic interventions with emollients, topical treatment with corticosteroids and calcineurin inhibitors, and avoidance of environmental triggers. Phototherapy is the next option for children and adults with moderate to severe atopic dermatitis not controlled with the first-line interventions. A third-line treatment recommended for patients who fail phototherapy is treatment with systemic immunomodulators, such as cyclosporine and methotrexate. The guidelines did not provide a recommendation on use of topical crisaborole, topical ruxolitinib, or injectable dupilumab due to limited data available at the time of publication (*Sidbury et al 2014*).

Topical agents

- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc.) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low- to high-potency topical corticosteroids are the standard of care, and strength is selected based on severity, duration of treatment, location of exacerbation, and age of the patient. Pimecrolimus and tacrolimus are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids. Crisaborole and ruxolitinib have not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.
  - The use of a topical calcineurin inhibitor is recommended for flares associated with specific clinical situations. Specific recommended uses for topical calcineurin inhibitors include any of the following: recalcitrance to steroids, sensitive areas (face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use (*Eichenfield et al 2014a).*
  - For patients with recurrent flares of disease, proactive maintenance treatment with topical steroid (1 to 2 times/week) or topical calcineurin inhibitor (2 to 3 times/week) at sites that typically flare are recommended to help prevent relapses, and are more effective than emollients alone. Combination topical steroid plus topical calcineurin inhibitor, concomitantly or sequentially, may be considered as a steroid-sparing regimen (*Eichenfield et al 2014a)*.
- In May 2021, the National Institute for Health and Care Excellence (NICE) announced it was unable to make a recommendation for the use of crisaborole in treating children aged ≥ 2 years for mild to moderate atopic dermatitis, because Pfizer withdrew its evidence submission. Pfizer stated they did not want to submit for evidence appraisal, because the technology would not be launched in the United Kingdom (*NICE 2021*).

Systemic agents

- A 2018 European consensus guideline from a variety of organizations on treatment of atopic dermatitis includes dupilumab as a treatment option for patients with moderate-to-severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on pediatric treatment was provided due to lack of data (*Wollenberg et al 2018*).
- The International Eczema Council 2017 provides similar guidance as the American Academy of Dermatology as well as additional steps to be taken before initiation of systemic treatment. These include consideration of an alternative

diagnosis, ensuring patient compliance with topical treatment, a trial of intensive topical therapy, treatment of infection, identification and avoidance of all potential triggers, and use of phototherapy if possible. The guidance does not comment on use of biologic agents due to limited data (*Simpson et al 2017*). The International Eczema Council also published a position statement on conjunctivitis in atopic dermatitis with and without dupilumab therapy based on an opinion survey and roundtable discussion of its members. Based on expert opinion, a consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior to treatment, and treatment should be continued after referral to an ophthalmologist should new-onset conjunctivitis occur *(Thyssen et al 2019).*

SAFETY SUMMARY

Elidel and Protopic

- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents. This updated labeling was a result of cancer-related AEs with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established *(FDA press release 2006)*.
  - A number of analyses have evaluated the risk of malignancy in patients administered topical calcineurin inhibitors. Long-term exposure to pimecrolimus or tacrolimus may not be associated with an increase in overall cancer rates; however, exposure to these agents may be associated with an increased risk of lymphoma. Further data may be warranted to validate this potential issue (*Hui et al 2009, Lam et al 2021, Sigurgeirsson et al 2015).*
- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
  - Avoid continuous long-term use in any age group, and limit application to areas of involvement with atopic dermatitis.
  - Both agents are not indicated for use in children less than 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Protopic 0.1% and Elidel are indicated for children 2 years and older and adults.
- Key warnings and precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - While using avoid exposure to sunlight.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.

Eucrisa

- Contraindications: Known hypersensitivity to Eucrisa or any component of the formulation
- Key warnings and precautions:
  - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately, and appropriate therapy initiated.
- AEs:
  - In pivotal studies AD-301 and AD-302, the AE reported by ≥ 1% of Eucrisa-treated patients (45/1012 [4%] vs 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with Eucrisa included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Eucrisa dossier 2018, Paller et al 2016)*.

Opzelura

- Boxed warnings include serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. Further details are described below.
- Key warnings and precautions:
  - Serious infections, including fatal, have been reported with the oral JAK inhibitors (including tuberculosis, bacterial, mycobacterial, invasive fungal, viral or opportunistic infections). Serious lower respiratory tract infections have been

reported with topical Opzelura. Avoid Opzelura in cases of active, serious infections, including localized infections. Herpes viral reactivations have been reported with Opzelura; discontinue treatment until the episode resolves. Do not use Opzelura in patients with active hepatitis B or C.
  - Thrombocytopenia, anemia, and neutropenia have been reported with Opzelura. Should signs and/or symptoms of these occur, discontinue treatment.
  - The following events have been observed with JAK inhibitors prescribed for inflammatory conditions:
    - Mortality, including a higher rate of all-cause mortality and sudden cardiovascular (CV) death.
    - Malignancy and lymphoproliferative disorders, with an increased risk observed in patients who are past or current smokers.
    - MACE defined as CV death, non-fatal myocardial infarction, and non-fatal stroke has been observed at a higher rate.
    - Thrombosis including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have been observed at a higher rate; some cases resulted in death. Opzelura should be used with caution in patients at an increased risk of thrombosis.
  - Lipid elevations (eg, total cholesterol, low-density lipoprotein cholesterol, triglycerides) have been reported with oral ruxolitinib.
- AEs: The most common AEs (incidence ≥ 1%) were nasopharyngitis (13%), diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea (1% for each).

Dupixent
- Contraindications: Known hypersensitivity to Dupixent or any component of the formulation
- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - Conjunctivitis and keratitis occurred more often with Dupixent than placebo in atopic dermatitis clinical trials (conjunctivitis was the most frequently reported eye disorder). New or worsening eye symptoms should be reported to a healthcare provider.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- AEs: The most common adverse reactions in patients with atopic dermatitis included injection-site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Systemic agents				
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Adults: Initial, Two injections; Maintenance, One injection every other week Pediatric: Initial, Two injections; Maintenance for 15 to 29 kg, One injection every 4 weeks; Maintenance for ≥ 30 kg, One injection every other week	Safety and efficacy in pediatric patients < 6 years of age have not been established.* May be administered by a healthcare professional or self-administered via pre-filled syringe or pen. The pre-filled pen is only for use in adults and adolescents aged ≥ 12 years. Concomitant topical corticosteroids may be used. Concomitant topical calcineurin inhibitors (Elidel or Protopic) may be used, but reserved

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				for problem areas only (eg, face, neck, intertriginous or genital areas).
Topical agents				
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	Safety and effectiveness in pediatric patients below the age of 3 months have not been established.
Opzelura (ruxolitinib)	Cream (1.5%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 12 years of age. Do not use > 60 grams per week. Apply only up to 20% of BSA. If signs and symptoms persist beyond 8 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.

See the current prescribing information for full details
*Safety and effectiveness of Dupixent has been established in patients aged ≥ 12 years of age for asthma and ≥ 18 years of age for chronic rhinosinusitis with nasal polyposis.

CONCLUSION

- Topical treatments for atopic dermatitis include the topical calcineurin inhibitors, Elidel (pimecrolimus) and Protopic (tacrolimus); a topical JAK inhibitor, Opzelura (ruxolitinib); and topical PDE-4 inhibitor, Eucrisa (crisaborole). Therapy is often a stepwise approach to improve symptoms and achieve long-term disease control based on disease severity.
  - The use of a topical calcineurin inhibitor is recommended for flares associated with specific clinical situations. Specific recommended uses for topical calcineurin inhibitors include any of the following: recalcitrance to steroids, sensitive areas (face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use (*Eichenfield et al 2014a).*
  - For patients with recurrent flares of disease, proactive maintenance treatment with topical steroid (1 to 2 times/week) or topical calcineurin inhibitor (2 to 3 times/week) at sites that typically flare are recommended to help prevent relapses, and are more effective than emollients alone. Combination topical steroid plus topical calcineurin inhibitor, concomitantly or sequentially, may be considered as a steroid-sparing regimen (*Eichenfield et al 2014a)*. Eucrisa and Opzelura have not been added to guidelines at the time of review.
  - For patients with severe atopic dermatitis refractory to other treatments, systemic therapy with either dupilumab or off-label treatments such as cyclosporine or azathioprine is recommended. These therapies may be administered concomitantly with topical treatments (*Wollenberg et al 2018*). Dupixent has not been added to US guidelines at the time of review.
- The topical atopic dermatitis agents may be prescribed in combination with systemic agents to improve disease control. Elidel and Protopic are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age). Eucrisa has proven effectiveness in mild to moderate atopic dermatitis in patients aged ≥ 3 months. Opzelura (ruxolitinib) has proven effectiveness in short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥ 12 years; however, use is limited to those patients who are not adequately controlled with other topical prescription therapies, or when those therapies are not advisable.
  - Eucrisa demonstrated short-term efficacy over vehicle ointment in 2 identically designed, 28-day, Phase 3, DB, randomized trials; more patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Data gleaned from the 48-week, long-term study revealed no significant safety signals (*Fahrbach et al 2020)*. Similar efficacy was demonstrated in children aged 3 to 24 months (*Schlessinger et al, 2020*).
  - Opzelura demonstrated efficacy and safety over a vehicle cream in 2 identically designed, 8-week, Phase 3, DB, randomized trials (TRuE-AD1 and TRuE-AD2); more patients receiving Opzelura vs vehicle achieved the primary endpoint of IGA success, with a greater percentage of Opzelura-treated patients achieving clear/almost clear skin. A larger proportion of vehicle-treated patients reported TEAE(s) vs patients treated with the ruxolitinib 1.5% cream. The most common AE was nasopharyngitis (*Papp et al 2021*). The long-term safety of ruxolitinib cream was presented at the Revolutionizing Atopic Dermatitis Symposium in June 2021, with data yet to be published (*Blauvelt et al 2021*).
    - The labeling for Opzelura does include the significant safety concerns including Boxed warnings for the JAK inhibitor class (eg, risks for serious infection, mortality, malignancy, MACE, and thrombosis). Serious lower respiratory tract infections, thrombocytopenia, anemia, and neutropenia have been reported with topical Opzelura. Further data are needed to confirm whether events described in the other JAK inhibitor class warnings may occur with Opzelura.
  - Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. Three studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment. Results favored treatment with Protopic, and AEs between the groups were similar *(Paller et al 2005)*. A MA evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease *(Ashcroft et al 2005)*. Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
    - Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the

potential risk of cancer of these products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies *(FDA press release 2006)*. A recent MA evaluated observational studies published up to October 2020 and the authors concluded there may be an association between topical calcineurin inhibitor use and the risk of lymphoma vs topical corticosteroids or non-active comparators (*Lam et al 2021*).

- Dupixent is the only FDA-approved systemic therapy for the treatment of moderate-to-severe atopic dermatitis in patients ≥ 6 years of age when not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent is an IL-4/IL-13 antagonist which may be administered by a healthcare professional or self-administered SC. It may be used with or without topical corticosteroids. The use of Dupixent in atopic dermatitis should be determined by its approved indication and clinician judgment.
  - Comparative effectiveness reviews examined systemic treatments for moderate to severe atopic dermatitis. Dupixent was associated with an increased proportion of patients achieving EASI-75 at short- and long-term follow up. Dupixent also had a decreased risk of serious AEs at short-term follow up, but no significant difference after long-term follow up. Overall, one author suggested that Dupixent ranks first for effectiveness compared with other biological treatments for atopic dermatitis; however, biologic therapies other than Dupixent are investigational at this time (*Sawangjit et al 2020; Siegels et al 2020*).
  - Possible AEs or safety concerns associated with Dupixent include injection-site reactions, serious allergic reactions, and ophthalmic issues, such as conjunctivitis or keratitis.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical treatments upfront in therapy and systemic agents when not adequately controlled with topical prescription therapies or when those topical therapies are not advisable *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

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INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, with an estimated 6.9 million people with severe visual impairment or blindness due to glaucoma (*WHO 2019*). Open-angle glaucoma is the most common form in those of European or African descent; other forms include angle-closure, developmental, and secondary glaucoma (*Jacobs 2020a*). Patients with open-angle glaucoma do not typically have symptoms, and it is usually detected with a comprehensive eye exam. If left untreated, progression to visual field loss and blindness can occur. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia (*Ellis et al 2000, Gedde et al 2021, Girkin et al 2004, Lesk et al 2007*).
- Elevated IOP is the only major risk factor for glaucoma that is directly treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage (*Jacobs 2020b*). Treatment may be initiated in patients with an elevated IOP despite having no visual field loss or optic nerve damage. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression (*Jacobs 2020a*). In general, a target IOP that is 25 to 30% lower than baseline is reasonable (*Jacobs 2020b*). The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life.
- The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 20 to 30% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further vis0ual loss and optic nerve damage will be prevented (*Gedde et al 2021*).
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). Medical intervention or laser therapy is generally used as initial therapy prior to surgical treatment (*Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors (*Gedde et al 2021, Jacobs 2020b*). These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow.
- The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*). Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents (*Jacobs 2020b*).
- Presbyopia ("aging sight") is a common, non-refractive and irreversible error of the eye that affects visual acuity, occurring normally due to aging, and usually begins at ≥ 40 years of age. The average age of those first reporting symptoms is between 42 to 44 years of age. Presbyopia has most commonly been treated with use of lenses, including convex lenses ("reading glasses") or in combination with lens with correction for distance viewing (eg, bifocals, trifocals, etc.). In the United States (U.S.), presbyopia is the most common cause of visual impairment, with 76 million Americans born between 1946 and 1964 (*AAO 2021, Katz et al 2021, Mian 2021*).
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha-Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03%, which is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1%*	-
Alphagan P (brimonidine tartrate ophthalmic solution) 0.15%*	✔
brimonidine tartrate ophthalmic solution 0.2% ‡	✔
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	-
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
levobunolol hydrochloride ophthalmic solution 0.5% ††	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	✔
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%§§	✔
Vuity (pilocarpine ophthalmic solution) 1.25%	-
Prostaglandin Analogues¥	
bimatoprost ophthalmic solution 0.03% **	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% **	-
Travatan Z (travoprost ophthalmic solution) 0.004%	✔
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	- ‡‡
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	✔
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Rocklatan (latanoprost/netarsudil ophthalmic solution) 0.005%/0.02%	-
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is available as a branded product only.
‖ Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
¥ A bimatoprost 10 mcg ocular implant for intracameral administration (Durysta) was approved in March 2020 for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Due to its method of administration, this product is outside the scope of this review and will not be discussed further.

** Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
†† Brand Betagan is no longer available.
‡‡ A generic is approved by the Food and Drug Administration (FDA) but is not currently marketed.
§§ Brand Isopto Carpine 4% is no longer available.

(*Drugs@FDA 2022, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2022*)

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate)*	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol hydrochloride	✔ ‡			
Istalol (timolol maleate)	✔			
levobunolol hydrochloride	✔ ‡			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	✔			
Trusopt (dorzolamide)	✔			
Prostaglandin Analogues				
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Xalatan (latanoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Rhopressa (netarsudil)	✔			
Combinations				
Combigan (brimonidine/timolol) ‖				✔
Rocklatan (latanoprost/netarsudil)	✔			
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(*Prescribing information: Alphagan P 2013, apraclonidine 2022, Azopt 2021, betaxolol hydrochloride ophthalmic solution 2022, Betimol 2018, Betoptic S 2021, bimatoprost ophthalmic solution 0.03% 2020, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2012, Combigan 2015, Cosopt 2020, Cosopt PF 2017, levobunolol ophthalmic solution 2016, Iopidine 2021, Istalol 2019, Lumigan 2020, Rocklatan 2020, Rhopressa 2019, Simbrinza 2021, Timoptic 2020, Timoptic in Ocudose 2020, Timoptic-XE 2021, Travatan Z 2020, Trusopt 2020, Vyzulta 2019, Xalatan 2020, Xelpros 2021, Zioptan 2021*)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Presbyopia
Miotics					
Isopto Carpine (pilocarpine)	✔	✔	✔	✔	
Vuity (pilocarpine)					✔

(*Prescribing information: Isopto Carpine 2020, Vuity 2021*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient-reported outcomes, or visual impairment. Very little direct comparative evidence is available (*Boland et al 2012, Boland et al 2013*).
- A network meta-analysis included 114 randomized controlled trials (N = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma (*Li et al 2016*). All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- Another network meta-analysis of 106 trials (N = 18,523) that compared single agents to each other or placebo and reported 3-month IOP outcomes did not find significant differences between latanoprostene bunod and latanoprost, tafluprost, or bimatoprost (both 0.01% and 0.03%). Bimatoprost 0.03% was ranked highest for likelihood of being the most effective, followed by latanoprostene bunod and then bimatoprost 0.01% (*Harasymowycz et al 2021*).
- A network meta-analysis evaluated 72 randomized controlled trials (N = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia except the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (N = 6841) and trough (N = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol (*Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008*). Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6-week crossover trial ($p = 0.03$) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3-month study (*Coleman et al 2003*). However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period ($p = 0.48$) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open-angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol ($p < 0.001$) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy (*Barnes et al 1999, Chen et al 2001, Chen 2005, Sterk et al 1998*).
- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% ($p \leq 0.025$). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% ($p = 0.014$). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient ($p < 0.001$) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (N = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma (*Zhang et al 2017*). Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs apraclonidine (3 randomized controlled trials), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether 1 medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline (*Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989*).
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) (*Vogel et al 1989*).
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP (*Berry et al 1984, Stewart et al 1986*).
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant (*Berry et al 1984, Vogel et al 1989*).
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p

values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) (*Watson et al 2001*).

- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% (*Berson et al 1985, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998*).
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) (*Krieglstein et al 1987*).
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event ($p = 0.024$). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group ($p < 0.001$) (*Halper et al 2002*).
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) (*Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002*). The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% ($p < 0.05$) and also caused more stinging and burning ($p = 0.001$) (*Mundorf et al 2004*).
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing ($p = 0.04$ for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS ($p = 0.04$). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment ($p = 0.024$); however, this was not found to be significant at 24 weeks of treatment (*Shedden et al 2001*).

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect (*Cantor et al 2001, Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004*).
  - In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
  - Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*Haneda et al 2006, March et al 2000, Varma et al 2009*).
  - In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) (*Walters et al 2004*).
  - In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) (*Ikeda et al 2008*).

Carbonic Anhydrase Inhibitors

- Trials that support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2021, Trusopt prescribing information 2014*). However, the efficacy of ophthalmic carbonic anhydrase inhibitors appears to be inferior to other newer pharmacologic options for treating open-angle glaucoma (*Jacobs 2020b*).
- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel-group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) (*Silver 1998*). In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide

compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event (*Silver 2000*).
- Similar reductions in IOP were also observed when the agents were used in combination with timolol (*Michaud et al 2001*).

Carbonic Anhydrase Inhibitors compared to other classes
- The single agent carbonic anhydrase inhibitors were compared to beta-blockers (*March et al 2000, Rusk et al 1998, Strahlman et al 1995*). Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel-group, randomized controlled trial, timolol 0.5% was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily ($p = 0.0002$) (*March et al 2000*).
  - When dorzolamide 2% was compared to betaxolol 0.5% or timolol 0.5% in a 1 year, double-blind, parallel-group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) (*Strahlman et al 1995*).
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) (*Rusk et al 1998*).
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy ($p < 0.001$ for both groups) (*Bournias et al 2009*).

Miotics
- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics (eg, pilocarpine products) are very limited. These agents have been available for many years and are recognized as an established treatment option (*Jacobs 2021b*).
- The safety and efficacy of Vuity (pilocarpine) were evaluated in 2 multicenter, parallel-group, randomized controlled trials (GEMINI 1 and GEMINI 2), which included a total of 750 adults (n = 375 administered Vuity) aged 40 to 55 years diagnosed with presbyopia. The proportion of patients gaining ≥ 3 lines in high contrast, binocular distance corrected near visual acuity (DCNVA), without losing ≥ 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was significantly greater with pilocarpine vs vehicle (31% vs 8% in GEMINI 1; 26% vs 11% in GEMINI 2; $p < 0.01$ in each trial) at Day 30 (hour 3). A total of 6 (1.6%) patients and 4 (1.1%) patients treated with Vuity or vehicle, respectively, discontinued due to treatment-emergent adverse events (*Vuity prescribing information 2021, Waring et al 2021*).

Miotics compared to other drug classes
- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues (*Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999*). A trial evaluated pilocarpine plus a beta-blocker and found that pilocarpine was an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues (*Diestelhorst et al 2000*).
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery (*Ren et al 1999*).

Prostaglandin Analogues
- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost (*Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012, Tang et al 2019*).
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72),

and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk (*Lin et al 2014*).
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 PM (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point (*Aptel et al 2008*).
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patients with open-angle glaucoma or ocular hypertension (*Li et al 2006*).
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) (*Honrubia et al 2009*).
  - A meta-analysis (17 trials, N = 2433) comparing latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% found that bimatoprost 0.03% was associated with greater IOP reduction after 3 and 6 months of therapy compared to latanoprost 0.005% and after 3 months of therapy compared to travoprost 0.004%. Latanoprost 0.005% had the lowest rates of conjunctival hyperemia (*Tang et al 2019*).
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data have not been included in many meta-analyses. Available trials and meta-analyses suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost (*Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010b, Yang et al 2020*).
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) (*Traverso et al 2010*).
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups (*Schnober et al 2010*).
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments (*Uusitalo et al 2010b*).
  - A randomized trial compared IOP fluctuations among patients with newly diagnosed open-angle glaucoma who received latanoprost 0.005%, travoprost 0.004%, and tafluprost 0.0015%. Patients underwent IOP measurement at 8 AM, 2 PM, and 8 PM at baseline and weeks 2 and 6. At all time points, IOP reductions and fluctuations were similar between treatment groups. Tolerability was also similar between groups (*Faseeh et al 2021*).
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; p = 0.049) (*Uusitalo et al 2010a*).
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) (*Chabi et al 2012*).
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; n = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016, Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% (*Weinreb et al 2015*).

- Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
- A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in three Phase 3, randomized, double-masked, active control, parallel-group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points (*Rhopressa Prescribing Information 2019, Serle et al 2018*).
  - Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
  - In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Serle et al 2018*).
  - In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Serle et al 2018*).
  - In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg in the per-protocol population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 27 mmHg and < 30 mmHg in the per-protocol population (*Khouri et al 2019*).
  - Safety analyses have demonstrated that the drug is well-tolerated, with conjunctival hyperemia as the most frequent adverse event, and maintains consistently lowered IOP through 12 months of therapy (*Kahook et al 2019*).
- In a pooled analysis of data from the ROCKET-1 to 4 studies, efficacy of netarsudil 0.02% (n = 494) demonstrated non-inferiority to timolol 0.5% (n = 510) in patients with open-angle glaucoma or ocular hypertension with an IOP < 25 mmHg. The mean IOP through 3 months of treatment was 16.4 to 18.1 mmHg with netarsudil compared to 16.8 to 17.6 mmHg with timolol. Conjunctival hyperemia occurred more often with netarsudil (54.4%) compared to timolol (10.4%) (*Singh et al 2020*).
- Netarsudil was also evaluated in a 28-day, Phase 2, dose-response, double-masked, active control, parallel-group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline (*Craven et al 2005, Goñi et al 2005, Sherwood et al 2006*). In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study (*Katz et al 2012*). The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to

2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.

- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3-month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group (*Katz et al 2013, Nguyen et al 2013, Realini et al 2013*).
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months (*Whitson et al 2013*). Another trial evaluating twice daily dosing was conducted after the U.S. approval of the thrice daily dosing. Results were similar to those previously observed (*Aung et al 2014*).
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks (*Kozobolis et al 2017*).
- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment (*Clineschmidt et al 1998*).
  - One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation (*Renieri et al 2010*). Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.
- Rocklatan (netarsudil/latanoprost)
  - The efficacy and safety of the combination of netarsudil/latanoprost were established in 2 double-masked, multicenter, randomized controlled trials. In both, the fixed-dose combination was compared to its individual components, and patients were followed for 12 months and 3 months, respectively. Both trials found that netarsudil/latanoprost significantly lowered the mean IOP compared to either monotherapy (eg, netarsudil and latanoprost) at all time points through month 3. The IOP reductions were maintained for 12 months in the longer duration trial. Adverse events were mostly ocular in nature, and the combination group experienced higher rates of conjunctival hyperemia, eye pruritis, and cornea verticillata compared to each monotherapy group (*Asrani et al 2019, Asrani et al 2020, Rocklatan Prescribing Information 2020*).
- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) (*Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012*). However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; $p = 0.03$) (*Garcia-Feijoo et al 2010*). In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; $p < 0.001$). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol ($p = 0.03$ and $p = 0.012$, respectively) (*Konstas et al 2012*). It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Gedde et al 2021)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, are relatively safe, and are used once daily. They are often considered as initial medical therapy

unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)
- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open-angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

American Optometric Association (AOA) – Care of the Patient with Visual Impairment (*AOA 2007*)

The 2007 AOA guideline defines presbyopia as a reduction in accommodative ability that occurs normally with age and necessitates a plus lens addition for satisfactory seeing at near states. The AOA recommend that all visually impaired patients should undergo refraction to ensure optimal correction for best visual acuity and to determine the amount of magnification needed for certain tasks.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entities or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events. Beta-blockers may mask symptoms of hyperthyroidism such as tachycardia, and thyroid storm can occur with abrupt beta-blocker discontinuation.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

- Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including fundoscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
- Caution is advised when administering ophthalmic pilocarpine solution (Isopto Carpine) for control of IOP in pediatric patients with primary congenital glaucoma.
- Ophthalmic pilocarpine solution (Vuity) is not recommended when iritis is present because adhesions (synechiae) may form between the iris and lens. Contact lenses should be removed prior to drug instillation, and 10 minutes should be allowed to pass prior to reinserting contact lenses.

- Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.
- ROCK inhibitor
  - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.

- Adverse reactions
  - Alpha-Agonists
    - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
    - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
    - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
  - Beta-blockers
    - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
  - Carbonic Anhydrase Inhibitors
    - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
    - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste that have been reported in up to 30% of patients.
  - Miotics
    - Most adverse events reported with the miotics are associated with the eye. The most common adverse events reported with ophthalmic pilocarpine solutions were blurred vision, eye irritation, eye pain, accommodative change, and/or visual impairment with Isopto Carpine and headache and conjunctival hyperemia with Vuity.
  - Prostaglandin Analogues
    - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
  - ROCK inhibitor
    - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
      - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

- Drug interactions
  - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.

- Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy: Unclassified†
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
levobunolol hydrochloride	Ophthalmic solution	Ophthalmic	Once or twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	Ophthalmic suspension	Ophthalmic	Three times daily	A 3-month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy: Unclassified†
Trusopt (dorzolamide)	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active-control trial.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Miotics				
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30-minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Vuity (pilocarpine)	Ophthalmic solution	Ophthalmic	Once daily	Studies did not include patients aged ≥ 65 years; it is unknown if they respond differently from younger patients. Presbyopia does not occur in children. There are no adequate studies of Vuity in pregnant women. If > 1 topical ophthalmic products are being used, products should be administered ≥ 5 minutes apart.
Prostaglandin Analogues				
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xalatan (latanoprost)	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				16 years of age; contraindicated in pediatric patients < 2 years. Pregnancy: Unclassified†
Cosopt/Cosopt PF (dorzolamide /timolol)	Ophthalmic solution Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy: Unclassified†
Rocklatan (latanoprost/netarsudil)	Ophthalmic solution Contains benzalkonium chloride 0.02% as a preservative	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). A target IOP between 25 and 30% lower than baseline is reasonable (*Gedde et al 2021, Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*).
  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory (*Gedde et al 2021*). Combination therapy can be given as separate drops or in fixed-dose combinations, which include brimonidine/timolol, brimonidine/brinzolamide, dorzolamide/timolol, and latanoprost/netarsudil.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Gedde et al 2021, Jacobs 2020b*).
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues (*Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018, Tang et al 2019*).
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma (*Jacobs 2020b*).
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy that require additional IOP reduction. Ophthalmic pilocarpine, more specifically Isopto Carpine, is indicated for the control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension; Vuity is indicated for presbyopia, which is an additional treatment option to reading glasses.

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