South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

December 7, 2018

DSS

Strong Families - South Dakota's Foundation and Our Future

Table of Contents

DEPARTMENT OF SOCIAL SERVICES
OFFICE OF THE SECRETARY
700 GOVERNORS DRIVE
PIERRE, SD 57501-2291
PHONE: 605-773-3165
FAX: 605-773-4855
WEB: dss.sd.gov

Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

December 7, 2018
1:00 – 3:00 PM

DDN Locations:
Sioux Falls
University Center
DDN Room FADM145
4801 North Career Avenue

Pierre
Capitol Building
DDN Room CAP A
500 East Capitol

Rapid City
Black Hills State University
DDN Room UC113
4300 Cheyenne Boulevard

Call to order

Approval of minutes of previous meeting

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **CGRP utilization/PA fax form**
- **Onfi utilization**
- **PPI utilization/PA fax form**
- **PDL/Formulary 101**

New business
- **Respiratory drugs utilization review**
- **SUPPORT Act**
- **Anticonvulsants**
- **Antiasthmatic monoclonal antibodies**

Public comment accepted after individual topic discussion

Next meeting date 3/7/19 & adjournment

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

Friday, September 7, 2018
1:00 – 3:00 pm CT

Members and DSS Staff

Michelle Baack, MD		Kelley Oehlke, PharmD	X
Dana Darger, RPh, Chair	X	Lenny Petrik, PharmD	X
James Engelbrecht, MD	X	Timothy Soundy, MD	
Deidre Van Gilder, PharmD	X	Mike Jockheck, DSS Staff	X
Mikal Holland, MD	X	Sarah Akers, DSS Staff	
Richard Holm, MD	X	Bill Snyder, DSS Staff	X
Bill Ladwig, RPh	X		

Administrative Business
The meeting was called to order by Darger at 1:03 PM. The minutes of the June meeting were presented. Ladwig made a motion to approve. Oehlke seconded the motion. Motion was approved unanimously.

New Committee Member Introduction
The committee welcomed new committee member Deidra Van Gilder, PharmD.

Prior Authorization Update (PA) and Statistics
The committee reviewed the PA activity report for April 1, 2018 to June 30, 2018. There were a total of 1,136 PAs reviewed during this time period. There were 254 requests (22%) received via telephone and 882 requests (78%) received via fax. PA appeals information were also reviewed.

Analysis of the Top 15 Therapeutic Classes and Drug Spend
The committee reviewed the top 15 therapeutic classes by total cost of claims from April 1, 2018 to June 30, 2018. The top five classes were atypical antipsychotics, insulins, amphetamines, respiratory and CNS stimulants, and anticonvulsants. The top 15 therapeutic classes make up 27.64% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 11.97% of total claims. Darger noted Onfi is the 6th drug on the top 50 drug list. Darger requested in-depth utilization such as diagnosis codes, prescribers, & general member profiles (age, etc) to review at the next meeting.

Old business
Committee reviewed mometasone utilization data compared to the other nasal steroids. No changes were recommended at this time.

Committee reviewed utilization data on proton pump inhibitor packets/suspensions/ODTs. Committee requested PA form separating packets/suspensions/ODTs vs tabs/caps to review at the next meeting.

Committee reviewed the Lyrica PA fax form which included two additional diagnoses and reauthorization criteria. Ladwig motioned to approve. Oehlke seconded the motion. Motion was approved unanimously.

Committee reviewed the PCSK9 PA fax form which included a criteria change and reauthorization criteria. Ladwig motioned to approve. Holm seconded the motion. Motion was approved unanimously.

Committee reviewed new PA criteria for Aimovig. Engelbrecht motioned to approve PA as presented and review utilization at the next meeting. Ladwig seconded the motion. Motion was approved unanimously.

New business
Committee discussed the advantages and disadvantages of a preferred drug list (PDL). Committee requested more information.

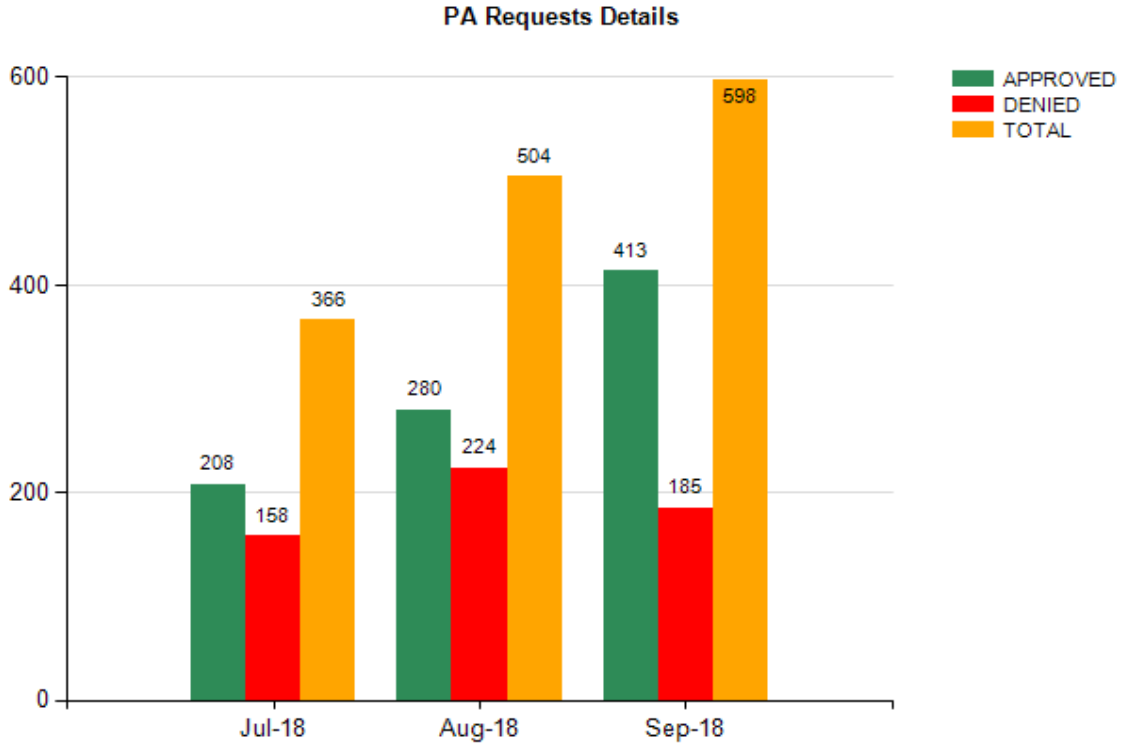
The next meeting is scheduled for December 7, 2018. Tentative meeting date for March 2019 date is March 7, 2019. Ladwig made a motion to adjourn. Holm seconded the motion. The meeting adjourned at 2:30 PM.

South Dakota Medicaid Quarterly Report
7/1/2018 to 9/30/2018

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
URGENT	43	43	0	100.00%	0.00%
STANDARD	1425	1425	0	100.00%	0.00%
GRAND TOTAL	**1468**	**1468**	**0**		

Prior Authorization Initial Requests Summary

Month	Approved	Denied	Total
Jul-18	208	158	366
Aug-18	280	224	504
Sep-18	413	185	598
3Q18	901	567	1468
Percent of Total	61.38%	38.62%	



Top 5 Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
65 - ANALGESICS - OPIOID*	186	134	320	58.13%	21.80%	HYDROCODONE-APAP, TRAMADOL
90 - DERMATOLOGICALS*	86	92	178	48.31%	12.13%	SKLICE, CLINDAMYCIN/ BENZOYL PEROXIDE
72 - ANTICONVULSANTS*	66	61	127	51.97%	8.65%	LYRICA, ONFI
59 ANTIPSYCHOTICS/ ANTIMANIC AGENTS*	104	22	126	82.54%	8.58%	INVEGA SUSTENNA, LATUDA,
49 - ULCER DRUGS/ ANTISPASMODICS/ ANTICHOLINERGIC	93	27	120	77.50%	8.17%	ESOMEPRAZOLE MAGNESIUM, DEXILANT
Others -	366	231	597	61.31%	40.67%	
3Q18	901	567	1468	61.38%		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
02 - CEPHALOSPORINS*	5	1	6	83.33%
03 - MACROLIDES	1	0	1	100.00%
12 - ANTIVIRALS*	7	15	22	31.82%
16 - ANTI-INFECTIVE AGENTS - MISC.*	4	3	7	57.14%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	0	1	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	7	3	10	70.00%
25 - CONTRACEPTIVES*	1	0	1	100.00%
27 - ANTIDIABETICS*	20	3	23	86.96%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	11	13	24	45.83%
33 - BETA BLOCKERS*	3	3	6	50.00%
34 - CALCIUM CHANNEL BLOCKERS*	2	3	5	40.00%
39 - ANTIHYPERLIPIDEMICS*	2	4	6	33.33%
40 - CARDIOVASCULAR AGENTS - MISC.*	2	1	3	66.67%
41 - ANTIHISTAMINES*	15	6	21	71.43%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	2	5	7	28.57%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	11	5	16	68.75%
45 - RESPIRATORY AGENTS - MISC.*	2	1	3	66.67%
48 - ANTACIDS*	0	1	1	0.00%
49 - ULCER DRUGS/ ANTISPASMODICS/ ANTICHOLING	93	27	120	77.50%
50 - ANTIEMETICS*	13	5	18	72.22%
52 - GASTROINTESTINAL AGENTS - MISC.*	19	14	33	57.58%
54 - URINARY ANTISPASMODICS*	18	19	37	48.65%
58 - ANTIDEPRESSANTS*	81	24	105	77.14%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	104	22	126	82.54%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	5	0	5	100.00%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	23	29	52	44.23%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	15	2	17	88.24%
65 - ANALGESICS - OPIOID*	186	134	320	58.13%

66 - ANALGESICS - ANTI-INFLAMMATORY*	34	11	45	75.56%
67 - MIGRAINE PRODUCTS*	3	18	21	14.29%
68 - GOUT AGENTS*	3	0	3	100.00%
72 - ANTICONVULSANTS*	66	61	127	51.97%
75 - MUSCULOSKELETAL THERAPY AGENTS*	7	4	11	63.64%
82 - HEMATOPOIETIC AGENTS*	0	1	1	0.00%
83 - ANTICOAGULANTS*	44	11	55	80.00%
86 - OPHTHALMIC AGENTS*	3	23	26	11.54%
88 - MOUTH/THROAT/DENTAL AGENTS*	0	1	1	0.00%
89 - ANORECTAL AGENTS*	0	1	1	0.00%
90 - DERMATOLOGICALS*	86	92	178	48.31%
94 - DIAGNOSTIC PRODUCTS*	1	1	2	50.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	1	0	1	100.00%
3Q18	901	567	1468	
Percent of Total	61.38%	38.62%		

Opiate Agonist & Opiate-Partial Agonist Summary

Drug Name	# of PA
ACETAMINOPHEN/CODEINE	9
BUPRENORPHINE HCL	19
BUPRENORPHINE HCL/NALOXONE HCL	8
BUTALBITAL/ACETAMINOPHEN/CAFFEINE/CODEINE	1
BUTALBITAL/ASPIRIN/CAFFEINE/CODEINE	1
FENTANYL	4
HYDROCODONE BITARTRATE/ACETAMINOPHEN	8
HYDROCODONE/ACETAMINOPHEN	104
HYDROMORPHONE HCL	8
METHADONE HCL	8
METHADOSE	1
MORPHINE SULFATE	11
MORPHINE SULFATE ER	3
NORCO	1
NUCYNTA	8
OXYCODONE HCL	26
OXYCODONE/ACETAMINOPHEN	26
SUBOXONE	5
TRAMADOL HCL	49
TRAMADOL HCL ER	1
Total	**301**

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jul-18	10	55.56%	8	44.44%	18
Aug-18	17	53.13%	15	46.88%	32
Sep-18	10	71.43%	4	28.57%	14
3Q18	37	57.81%	27	42.19%	64

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
ADAPALENE	0	1	1	0.00%
AMITIZA	1	1	2	50.00%
CABERGOLINE	1	0	1	100.00%
DULOXETINE HCL	3	0	3	100.00%
ENBREL	1	0	1	100.00%
FENTANYL	1	0	1	100.00%
HARVONI	0	1	1	0.00%
HUMIRA PEN-CD/UC/HS STARTER	0	1	1	0.00%
HYDROCODONE BITARTRATE/ACETAMINOPHEN	0	1	1	0.00%
HYDROCODONE/ACETAMINOPHEN	5	1	6	83.33%
LANSOPRAZOLE	1	0	1	100.00%
LIDOCAINE	0	2	2	0.00%
LINZESS	2	0	2	100.00%
LYRICA	5	2	7	71.43%
MALATHION	1	0	1	100.00%
MAVYRET	0	8	8	0.00%
MODAFINIL	1	1	2	50.00%
MONTELUKAST SODIUM	1	0	1	100.00%
MORPHINE SULFATE	1	0	1	100.00%
NORCO	1	0	1	100.00%
NORDITROPIN FLEXPRO	3	1	4	75.00%
OLOPATADINE HCL	0	1	1	0.00%
ONFI	1	0	1	100.00%
ORKAMBI	1	0	1	100.00%
OXYCODONE HCL	2	0	2	100.00%
QUETIAPINE FUMARATE ER	1	1	2	50.00%
STELARA	0	1	1	0.00%
SUBOXONE	1	0	1	100.00%
TALTZ	1	0	1	100.00%
TROSPIUM CHLORIDE	1	0	1	100.00%
VICTOZA	1	1	2	50.00%
VIIBRYD STARTER PACK	0	1	1	0.00%
VYVANSE	0	1	1	0.00%
XOLAIR	0	1	1	0.00%
3Q18	37	27	64	

South Dakota Medicaid

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 07/01/2018 - 09/30/2018				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
ATYPICAL ANTIPSYCHOTICS	7,399	$1,740,973.32	$235.30	3.77%
INSULINS	2,828	$1,282,174.78	$453.39	1.44%
RESPIRATORY AND CNS STIMULANTS	6,174	$1,037,738.72	$168.08	3.14%
AMPHETAMINES	5,981	$1,036,822.10	$173.35	3.05%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	246	$1,031,056.07	$4,191.28	0.13%
MISCELLANEOUS ANTICONVULS	10,302	$996,914.27	$96.77	5.25%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,562	$705,727.82	$93.33	3.85%
ADRENALS	5,410	$555,146.01	$102.61	2.76%
ANTINEOPLASTIC AGENTS	330	$529,959.83	$1,605.94	0.17%
SKIN AND MUCOUS MEMBRANE	384	$465,783.70	$1,212.98	0.20%
HEMOSTATICS	27	$460,289.28	$17,047.75	0.01%
SOMATOTROPIN AGONISTS	82	$285,164.49	$3,477.62	0.04%
BENZODIAZEPINES (ANTICONV	1,891	$278,277.25	$147.16	0.96%
PROTON-PUMP INHIBITORS	5,727	$260,129.33	$45.42	2.92%
IMMUNOMODULATORY AGENTS	43	$257,046.21	$5,977.82	0.02%
TOTAL TOP 15 THERAPEUTIC CLASSES	54,386	$10,923,203.18	$200.85	27.70%

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 07/01/2018 - 09/30/2018				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	10,842	$129,025.86	$11.90	5.52%
MISCELLANEOUS ANTICONVULS	10,302	$996,914.27	$96.77	5.25%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,562	$705,727.82	$93.33	3.85%
SECOND GENERATION ANTIHIS	7,431	$77,913.29	$10.48	3.78%
ATYPICAL ANTIPSYCHOTICS	7,399	$1,740,973.32	$235.30	3.77%
OPIATE AGONISTS	7,304	$237,243.23	$32.48	3.72%
AMINOPENICILLIN ANTIBIOTICS	6,364	$88,868.04	$13.96	3.24%
RESPIRATORY AND CNS STIMULANTS	6,174	$1,037,738.72	$168.08	3.14%
AMPHETAMINES	5,981	$1,036,822.10	$173.35	3.05%
PROTON-PUMP INHIBITORS	5,727	$260,129.33	$45.42	2.92%
ADRENALS	5,410	$555,146.01	$102.61	2.76%
THYROID AGENTS	3,594	$67,227.18	$18.71	1.83%
LEUKOTRIENE MODIFIERS	3,505	$48,737.51	$13.91	1.79%
OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	3,305	$50,136.99	$15.17	1.68%
MISC. ANXIOLYTICS, SEDATI	3,204	$116,578.61	$36.39	1.63%
TOTAL TOP 15 THERAPEUTIC CLASSES	94,104	$7,149,182.28	$75.97	47.93%

Total Rx Claims from 07/01/2018 - 09/30/2018	**196,355**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 07/01/2018 - 09/30/2018					
Drug Brand Name	**AHFS Description**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/ Rx**	**%Total Claims**
VYVANSE	AMPHETAMINES	3,089	$844,761.26	$273.47	1.57%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	3,132	$520,805.67	$166.29	1.60%
LATUDA	ATYPICAL ANTIPSYCHOTICS	433	$489,191.72	$1,129.77	0.22%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	74	$448,411.21	$6,059.61	0.04%
INVEGA SUSTENNA	ATYPICAL ANTIPSYCHOTICS	189	$392,627.21	$2,077.39	0.10%
NOVOLOG FLEXPEN	INSULINS	537	$284,039.60	$528.94	0.27%
ONFI	BENZODIAZEPINES (ANTICONV	190	$261,237.32	$1,374.93	0.10%
METHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,171	$251,517.45	$214.79	0.60%
KALYDECO	CYSTIC FIBROSIS (CFTR) POTENTIATORS	10	$242,659.62	$24,265.96	0.01%
LANTUS SOLOSTAR	INSULINS	621	$219,391.45	$353.29	0.32%
ENBREL SURECLICK	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	46	$219,124.43	$4,763.57	0.02%
LYRICA	MISCELLANEOUS ANTICONVULS	429	$217,710.10	$507.48	0.22%
PULMOZYME	MUCOLYTIC AGENTS	55	$206,973.64	$3,763.16	0.03%
FLOVENT HFA	ADRENALS	851	$198,034.63	$232.71	0.43%
STELARA	SKIN AND MUCOUS MEMBRANE	13	$195,321.24	$15,024.71	0.01%
ADVAIR DISKUS	SELECTIVE BETA-2-ADRENERGIC AGONISTS	465	$188,142.62	$404.61	0.24%
RECOMBINATE	HEMOSTATICS	4	$170,271.43	$42,567.86	0.00%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,742	$169,270.19	$61.73	1.40%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,087	$165,153.54	$151.94	0.55%
BEXAROTENE	ANTINEOPLASTIC AGENTS	3	$162,104.05	$54,034.68	0.00%
HARVONI	HCV REPLICATION COMPLEX INHIBITORS	5	$153,890.55	$30,778.11	0.00%
EPCLUSA	HCV POLYMERASE INHIBITOR ANTIVIRALS	6	$147,783.98	$24,630.66	0.00%
VIMPAT	MISCELLANEOUS ANTICONVULS	196	$142,042.08	$724.70	0.10%
ARISTADA	ATYPICAL ANTIPSYCHOTICS	66	$141,351.42	$2,141.69	0.03%
ADVATE	HEMOSTATICS	7	$136,202.66	$19,457.52	0.00%
BANZEL	MISCELLANEOUS ANTICONVULS	65	$135,144.64	$2,079.15	0.03%
JANUVIA	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	322	$130,977.10	$406.76	0.16%
NORDITROPIN FLEXPRO	SOMATOTROPIN AGONISTS	47	$128,411.26	$2,732.15	0.02%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	23	$126,919.71	$5,518.25	0.01%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,046	$124,933.00	$61.06	1.04%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,854	$123,514.70	$66.62	0.94%
VRAYLAR	ATYPICAL ANTIPSYCHOTICS	113	$113,646.79	$1,005.72	0.06%
LEVEMIR FLEXTOUCH	INSULINS	269	$113,191.03	$420.78	0.14%
NOVOLOG	INSULINS	241	$112,497.14	$466.79	0.12%
ADVAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	294	$108,443.42	$368.86	0.15%
XOLAIR	RESPIRATORY TRACT AGENTS, MISCELLANEOUS	29	$105,870.85	$3,650.72	0.01%
IMBRUVICA	ANTINEOPLASTIC AGENTS	9	$105,835.87	$11,759.54	0.00%
ORKAMBI	CYSTIC FIBROSIS (CFTR) CORRECTORS	5	$105,563.00	$21,112.60	0.00%
TRESIBA FLEXTOUCH	INSULINS	195	$103,465.07	$530.59	0.10%
INGREZZA	-	16	$102,597.54	$6,412.35	0.01%
GENOTROPIN	SOMATOTROPIN AGONISTS	19	$102,221.80	$5,380.09	0.01%
VICTOZA	INCRETIN MIMETICS	131	$98,994.11	$755.68	0.07%
ABILIFY MAINTENA	ATYPICAL ANTIPSYCHOTICS	46	$96,177.82	$2,090.82	0.02%
INVEGA TRINZA	ATYPICAL ANTIPSYCHOTICS	14	$92,308.50	$6,593.46	0.01%
NOVOLOG PENFILL	INSULINS	216	$89,922.57	$416.31	0.11%
REXULTI	ATYPICAL ANTIPSYCHOTICS	95	$88,654.32	$933.20	0.05%
TRACLEER	VASODILATING AGENTS (RESPIRATORY TRACT)	9	$87,888.91	$9,765.43	0.00%
CIPRODEX	CORTICOSTEROIDS	387	$82,308.11	$212.68	0.20%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,643	$81,710.63	$49.73	0.84%
SYMBICORT	ADRENALS	264	$80,374.36	$304.45	0.13%
TOTAL TOP 50 DRUGS		**23,773**	**$9,209,591.32**	**$387.40**	**12.11%**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 07/01/2018 - 09/30/2018					
Drug Brand Name	**AHFS Description**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	5,009	$56,193.95	$11.22	2.55%
CETIRIZINE HCL	SECOND GENERATION ANTIHIS	4,256	$41,019.20	$9.64	2.17%
FLUOXETINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,579	$33,521.04	$9.37	1.82%
SERTRALINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,561	$36,460.37	$10.24	1.81%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	3,494	$47,459.76	$13.58	1.78%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,168	$33,254.01	$10.50	1.61%
LEVOTHYROXINE SODIUM	THYROID AGENTS	3,144	$50,799.92	$16.16	1.60%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	3,132	$520,805.67	$166.29	1.60%
GABAPENTIN	MISCELLANEOUS ANTICONVULS	3,114	$50,899.01	$16.35	1.59%
VYVANSE	AMPHETAMINES	3,089	$844,761.26	$273.47	1.57%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,742	$169,270.19	$61.73	1.40%
HYDROCODONE/ACETAMINOPHEN	OPIATE AGONISTS	2,647	$36,203.91	$13.68	1.35%
LISINOPRIL	ANGIOTENSIN-CONVERTING EN	2,317	$16,684.98	$7.20	1.18%
GUANFACINE ER	MISC. CENTRAL NERVOUS SYS	2,176	$51,999.20	$23.90	1.11%
AZITHROMYCIN	OTHER MACROLIDE ANTIBIOTICS	2,168	$40,093.81	$18.49	1.10%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,046	$124,933.00	$61.06	1.04%
FLUTICASONE PROPIONATE	CORTICOSTEROIDS	2,025	$24,875.02	$12.28	1.03%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	2,008	$19,355.49	$9.64	1.02%
LORATADINE	SECOND GENERATION ANTIHIS	1,893	$17,866.09	$9.44	0.96%
CEPHALEXIN	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	1,889	$31,339.81	$16.59	0.96%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,854	$123,514.70	$66.62	0.94%
TRAZODONE HYDROCHLORIDE	SEROTONIN MODULATORS	1,829	$18,781.57	$10.27	0.93%
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,771	$37,784.62	$21.34	0.90%
ESCITALOPRAM OXALATE	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	1,731	$19,784.80	$11.43	0.88%
POLYETHYLENE GLYCOL 3350	CATHARTICS AND LAXATIVES	1,676	$34,629.55	$20.66	0.85%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,643	$81,710.63	$49.73	0.84%
COMPOUNDS	-	1,643	$58,413.02	$35.55	0.84%
TRAMADOL HCL	OPIATE AGONISTS	1,595	$14,056.36	$8.81	0.81%
PREDNISONE	ADRENALS	1,594	$14,657.56	$9.20	0.81%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBIT	1,588	$16,814.54	$10.59	0.81%
CLONAZEPAM	BENZODIAZEPINES (ANTICONV	1,556	$13,564.23	$8.72	0.79%
RISPERIDONE	ATYPICAL ANTIPSYCHOTICS	1,437	$17,912.87	$12.47	0.73%
QUETIAPINE FUMARATE	ATYPICAL ANTIPSYCHOTICS	1,384	$19,894.82	$14.37	0.70%
LAMOTRIGINE	MISCELLANEOUS ANTICONVULS	1,376	$21,442.04	$15.58	0.70%
SULFAMETHOXAZOLE/TRIMETHO	SULFONAMIDES (SYSTEMIC)	1,364	$25,229.30	$18.50	0.69%
AMOXICILLIN/CLAVULANATE P	AMINOPENICILLIN ANTIBIOTICS	1,352	$32,068.63	$23.72	0.69%
TRIAMCINOLONE ACETONIDE	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRANE)	1,306	$16,706.64	$12.79	0.67%
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	1,285	$12,938.07	$10.07	0.65%
MUPIROCIN	ANTIBACTERIALS (SKIN & MU	1,281	$40,506.80	$31.62	0.65%
BUPROPION HCL XL	ANTIDEPRESSANTS, MISCELLANEOUS	1,254	$28,964.46	$23.10	0.64%
MIRTAZAPINE	ANTIDEPRESSANTS, MISCELLANEOUS	1,219	$15,579.07	$12.78	0.62%
LEVETIRACETAM	MISCELLANEOUS ANTICONVULS	1,177	$28,651.96	$24.34	0.60%
METHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,171	$251,517.45	$214.79	0.60%
DULOXETINE HCL	SEL.SEROTONIN,NOREPI REUPTAKE INHIBITOR	1,167	$19,517.51	$16.72	0.59%
TOPIRAMATE	MISCELLANEOUS ANTICONVULS	1,157	$15,235.93	$13.17	0.59%
METFORMIN HCL	BIGUANIDES	1,136	$7,284.04	$6.41	0.58%
RANITIDINE HCL	HISTAMINE H2-ANTAGONISTS	1,120	$12,658.81	$11.30	0.57%
FOLIC ACID	VITAMIN B COMPLEX	1,118	$8,486.26	$7.59	0.57%
CEFDINIR	3RD GENERATION CEPHALOSPORIN ANTIBIOTICS	1,118	$32,513.71	$29.08	0.57%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYT	1,114	$10,400.39	$9.34	0.57%
TOTAL TOP 50 DRUGS		**99,473**	**$3,299,016.03**	**$33.16**	**50.66%**

Utilization and PA Information

Time frame: 7/1/2018 – 9/30/2018
Red font denotes drug is on prior authorization

CGRP Inhibitors (PA)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Aimovig	16	$9,355.06	$584.69	9	31 – 57
Ajovy	0				
Emgality	0				

Onfi (SilentAuth)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Onfi (clobazam)	190	$261,237.32	$1,374.93	68	1- 51

1. Diagnosis:
    a. Seizures associated with Lennox-Gastaut syndrome (LGS) or
    b. Intractable treatment-resistant seizure disorder
2. Must be prescribed by or in consultation with a neurologist

Proton Pump Inhibitors (SilentAuth)

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Nexium 2.5 mg packet	0				
Nexium 5 mg packet	2	$427.81	$70.24	2	0 - 1
Nexium 10 mg packet	18	$5,738.19	$318.79	9	0 - 11
Nexium 20 mg packet	22	$7,576.30	$344.38	13	0 - 74
Nexium 40 mg packet	28	$6,393.01	$228.32	10	6 - 39
lansoprazole suspension 3mg/ml	70	$5,065.56	$72.37	33	0 - 37
lansoprazole 15 mg tab	97	$35,832.99	$369.41	54	0 - 56
lansoprazole 30 mg tab	19	$6,405.33	$337.12	12	3 - 26
Prevacid 15 mg Solutab	35	$18,544.99	$529.86	18	0 - 22
Prevacid 30 mg Solutab	61	$32,749.04	$536.87	28	5 - 54
omeprazole 2mg/ml suspension	101	$7501.00	$74.26	55	0 - 29
Prilosec 2.5 mg pack (delayed release granules for suspension)	2	$2,372.60	$1,186.30	1	0
Prilosec 10 mg pack (delayed release granules for suspension)	4	$1,901.29	$475.32	4	5 - 43
Protonix Pak	0				
Aciphex Sprinkles	0				
Zegerid Oral Packet	0				

1. Aciphex sprinkles, Nexium oral packet, Protonix Pak, Zegerid oral packet, Prevacid Solutab, lansoprazole & omeprazole suspension
    a. Patient is less than 13 years of age OR
    b. Patient has diagnosis swallowing difficulty
2. Nexium, Dexilant, esomeprazole, Prevpac, Zegerid
    a. Diagnosis of erosive esophagitis, Barrett's esophagitis, or Zollinger-Ellison Syndrome OR
    b. Trial & failure of omeprazole, pantoprazole, rabeprazole, or lansoprazole

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Aimovig™, Ajovy™, Emgality™ Prior Authorization Request Form (Page 1 of 2)

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Chronic migraines
❑ Episodic migraines
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Clinical information:

Is the requested medication prescribed by or in consultation with a neurologist or pain/headache specialist? ❑ **Yes** ❑ **No**

Will the requested medication be used in combination with another CGRP inhibitor? ❑ **Yes** ❑ **No**

Select the prophylactic therapies the patient has had a trial and failure, (defined as at least 2 months of therapy with greater than 80% adherence), or an intolerance/contraindication to:

❑ Antidepressants (i.e., venlafaxine or tricyclic antidepressant such as amitriptyline or nortriptyline)
Please specify: _____
❑ Anti-epileptics (i.e., topiramate or divalproex sodium). Please specify: _____
❑ Beta-blockers (i.e., atenolol, propranolol, nadolol, timolol, or metoprolol). Please specify: _____

For chronic migraines, also answer the following:

Has the patient been evaluated for rebound headaches caused by medication overuse (more than 12 doses per month of narcotics, triptans, caffeine, or NSAIDs)? ❑ **Yes** ❑ **No**

If diagnosed, will treatment include a plan to taper off the offending medication? ❑ **Yes** ❑ **No**

Does the patient have greater than or equal to 15 headache days per month, of which at least 8 must be migraine days for at least 3 months? ❑ **Yes** ❑ **No**

For episodic migraines, also answer the following:

Does the patient have 4 to 14 migraines per month (but no more than 14 headache days per month)? ❑ **Yes** ❑ **No**

Reauthorization:

If this is a reauthorization request, answer the following:

Has the patient experienced a positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity? ❑ **Yes** ❑ **No**

Has the use of acute migraine medications (e.g., NSAIDs, triptans, narcotics) decreased since the start of CGRP therapy? ❑ **Yes** ❑ **No**

Is the requested medication prescribed by or in consultation with a neurologist or pain/headache specialist? ❑ **Yes** ❑ **No**

DSS
Strong Families - South Dakota's Foundation and Our Future

Aimovig™, Ajovy™, Emgality™ Prior Authorization Request Form (Page 2 of 2)

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Proton Pump Inhibitor Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:
❑ Barrett's esophagitis ❑ Erosive esophagitis ❑ Zollinger-Ellison Syndrome
❑ Other diagnosis: _____ ICD-10 Code(s): _____

For Aciphex sprinkle, First-lansoprazole suspension compounding kit, First omeprazole suspension compounding kit, Nexium pack, omeprazole suspension compounding kit, Prevacid solutab, Protonix pack, and Zegerid pack (omeprazole-sodium bicarbonate pack) requests, answer the following:
Does the patient have a diagnosis that confirms a difficulty in swallowing? ❑ **Yes** ❑ **No**

For Aciphex tablet, Dexilant, esomeprazole strontium capsule, Nexium capsule (esomeprazole magnesium capsule), Prevacid capsule, Prevpack (lansoprazole-amoxicillin-clarithromycin), Prilosec capsule, Protonix tablet, and Zegerid capsule (omeprazole-sodium bicarbonate capsule) requests, answer the following:
Has the patient had a trial and failure (after a minimum of 14 days) in the past year with at least one of the following generics: Lansoprazole, omeprazole, pantoprazole, or rabeprazole? ❑ **Yes** ❑ **No**

Has the patient experienced an adverse reaction (must be documented on a MedWatch form), allergy or contraindication to **ALL** of the following: Lansoprazole, omeprazole, pantoprazole, and rabeprazole? ❑ **Yes** ❑ **No**

Quantity limit requests:
What is the quantity requested per DAY? _____
What is the reason for exceeding the plan limitations?
❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Other: _____

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: ProtonPumpInhibitors_SouthDakotaMedicaid_2017May-P

South Dakota Medicaid

Preferred Drug List/Formulary 101

A formulary is a list of prescription drugs available to members. Formularies are developed based on evaluations of efficacy, safety, and cost-effectiveness of drugs. Tiered copay formularies provide financial incentives for patients to select lower-cost drugs in commercial health plans. Since Medicaid precludes tiering of copays, a preferred drug list (PDL) can be developed instead to incentivize prescribers. A PDL is a list of medications that Medicaid will cover the cost for without the need to request prior authorization (PA).[1] PDLs are comprised of medications that either are generic formulations or are the result of price negotiations between the pharmaceutical companies and Medicaid.[1] PDLs create incentives for a provider to prescribe a drug on the PDL if possible or receive PA to do otherwise.[2] Utilization management tools such as prior authorization, step therapy, and quantity limits can still be utilized with a PDL.

Pros/Cons

Preferred Drug List would allow management of drug classes that are currently not managed, for example allow short acting bronchodilators or insulins to be managed via PDL vs clinical PA thus moving members to the most cost effective, clinically appropriate product.

Supplemental rebate negotiations vs multi-state purchasing pools

- Hiring rebate contractor for supplemental rebate negotiations & ongoing maintenance of contracts
- Using internal resources to negotiate supplemental rebates & ongoing maintenance of contracts
- Joining a multi-state purchasing pool, would require internal resources to manage this program and deciding which purchasing pool to join

P&T sessions to review financials

- 4 extra meetings per year for P&T
- Add independent meetings to existing meetings (could entail a session to discuss clinical component of drug, then another session to review financials, then another session to announce decisions made in the financial review session)

Grandfathering members vs moving members to preferred drugs

- Grandfathering members for therapy classes such as multiple sclerosis drugs and targeted immune modulator therapies; new starts to use preferred drug(s)
- For therapy classes such as short acting bronchodilators or insulins, move members to preferred drugs – member/physician/pharmacy notification sent XX days in advance
- Increased PA rejects for non-preferred drugs causing member disruption and increased calls to prescribers by pharmacies to switch members to preferred drugs
- If all therapy classes are grandfathered, there will be no savings

Member/Physician/Pharmacy impact

- Member disruption and possible gaps in care
- Prescriber burden to prescribe the preferred drug for Medicaid
- Prescriber burden to submit PA requests to prescribe non-preferred drugs

- Increased PA rejects at pharmacy point-of-sale, outbound calls to prescribers to switch to preferred drug or continue to use non-preferred drugs

More administrative work/burden

- Quarterly maintenance of PDL document that will need to be updated and posted along with sending physician/pharmacy communications
- Therapy classes currently not managed will require UM criteria for preferred vs non-preferred status (increase in the number of PA criteria to manage)
- Updating existing UM criteria based on preferred vs non-preferred status
- Implementing and updating all system PA coding for preferred/non-preferred drugs

Closed formulary or closed certain therapeutic classes to have greater leverage to obtain supplemental rebates

- Massachusetts submitted an application to CMS that included a provision to amend its Section 1115 Medicaid demonstration waiver to create a closed formulary[2]
- Potential for greater supplemental rebates for closed therapy classes
- No clinical PA reviews of non-preferred drugs in closed therapy classes

Estimated PDL-Supplemental Rebate Savings

2Q2018	Estimated State Plan Cost	Estimated PDL Savings
SABA	$324,434.45	-
Atypical Antipsychotics – Oral	$1,102,720.65	-
Anti-glaucoma Agents	$28,141.89	-
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors	$168,302.96	-
Growth Hormone Modifiers	$273,199.33	-
Total	**$2,111,151.20**	**~ $90,000.00**

References:

1. Ovsag K, Hydery S, Mousa S. Preferred drug list: Potential impact on healthcare economics. *Vascular Health and Risk Management.* 2008; 4(2): 403-413
2. Young K, Garfield R. Snapshots of Recent State Initiatives In Medicaid Prescription Drug Cost Control. *The Henry J. Kaiser Family Foundation*. 2018

Respiratory Drugs Utilization

Time frame: 7/1/2018 – 9/30/2018

Inhaled Anticholinergics (short & long acting)

Drug Name	Total Rx	Paid Amount	Paid/Rx
Atrovent HFA (ipratropium bromide)	32	$10,910.30	$340.95
ipratropium bromide solution	28	$517.29	$18.47
Incruse Ellipta (umeclidinium bromide)	32	$9,615.41	$300.48
Lonhala Magnair (glycopyrrolate)	1	$1,143.30	$1,143.30
Seebri Neohaler (glycopyrrolate)	0		
Spiriva Handihaler (tiotropium bromide)	151	$60,501.74	$400.67
Spiriva Respimat (tiotropium bromide)	44	$16,785.25	$381.48
Spiriva Aero (tiopropium bromide)	62	$21,951.80	$354.06
Tudorza Pressair (aclidinium bromide)	2	$697.42	$348.71

Inhaled Corticosteroids

Drug Name	Total Rx	Paid Amount	Paid/Rx
Alvesco 160 mcg (ciclesonide)	1	$252.64	$252.64
Alvesco 80 mcg (ciclesonide)	3	$159.48	$53.16
ArmonAir RespiClick (fluticasone propionate)	0		
Arnuity Ellipta 100 mcg (fluticasone furoate)	5	$862.79	$172.56
Arnuity Ellipta 200 mcg (fluticasone furoate)	6	$1,368.16	$228.03
Asmanex HFA 100 mcg (mometasone furoate)	11	$1,611.23	$146.48
Asmanex HFA 200 mcg (mometasone furoate)	8	$1,849.50	$231.19
Asmanex Twisthaler 120 AER 220 mcg (mometasone furoate)	1	$337.37	$337.37
Asmanex Twisthaler 30 AER 110 mcg (mometasone furoate)	9	$1,288.56	$143.17
Asmanex Twisthaler 30 AER 220 mcg (mometasone furoate)	9	$1,414.98	$157.22
Asmanex Twisthaler 60 AER 220 mcg (mometasone furoate)	37	$7,772.31	$210.06
Flovent Diskus 100 mcg (fluticasone propionate)	12	$2,243.34	$186.95
Flovent Diskus 250 mcg (fluticasone propionate)	8	$1,994.40	$249.30
Flovent Diskus 50 mcg (fluticasone propionate)	6	$1,067.50	$177.92
Flovent HFA 110 mcg (fluticasone propionate)	486	$118,144.98	$243.10
Flovent HFA 220 mcg (fluticasone propionate)	85	$29,459.78	$346.59
Flovent HFA 44 mcg (fluticasone propionate)	280	$50,429.87	$180.11
Pulmicort Flexhaler 180 mcg (budesonide)	34	$7,451.80	$219.17
Pulmicort Flexhaler 90 mcg (budesonide)	16	$2,827.92	$176.75
Pulmicort Respules (budesonide)	1	$1,187.61	$1,187.61
QVAR RediHaler 80 mcg (beclomethasone dipropionate)	93	$19,923.35	$214.23
QVAR RediHaler 40 mcg (beclomethasone dipropionate)	74	$11,319.25	$152.96
Qvar 40 mcg (beclomethasone dipropionate)	10	$1,748.90	$174.89
Qvar 80 mcg (beclomethasone dipropionate)	12	$2,458.52	$204.88

Beta2-Agonist & Anticholinergic combinations

Drug Name	Total Rx	Paid Amount	Paid/Rx
Anoro Ellipta (umeclidinium/vilanterol)	42	$16,765.74	$399.18
Bevespi Aerosphere (glycopyrrolate formoterol fumarate)	6	$2,135.22	$355.87
Combivent Respimat (ipratropium albuterol)	69	$25,829.22	$374.34
ipratropium/albuterol solution	328	$7,769.34	$23.69
Stiolto Respimat (tiotropium/olodaterol)	48	$17,815.85	$371.16
Utibron Neohaler (glycopyrrolate/indacaterol)	0		

Beta2-Agonist & Corticosteroid combinations

Drug Name	Total Rx	Paid Amount	Paid/Rx
Advair Diskus 100/50 (fluticasone propionate/salmeterol)	90	$28,959.94	$321.78
Advair Diskus 250/50 (fluticasone propionate/salmeterol)	252	$96,287.06	$382.09
Advair Diskus 500/50 (fluticasone propionate/salmeterol)	123	$62,895.62	$511.35
Advair HFA 45/21 (fluticasone propionate/salmeterol	58	$17,805.47	$306.99
Advair HFA 115/21 (fluticasone propionate/salmeterol)	163	$56,640.54	$347.49
Advair HFA 230/21 (fluticasone propionate/salmeterol	73	$33,997.41	$465.72
AirDuo RespiClick (fluticasone propionate/salmeterol)	0		
Breo Ellipta 100-25 (fluticasone furoate/vilanterol)	70	$21,216.10	$303.09
Breo Ellipta 200-25 (fluticasone furoate/vilanterol)	70	$23,886.91	$341.24
Dulera 100-5mcg (mometasone furoate/formoterol fumarate dihydrate)	80	$23,050.46	$288.13
Dulera 200-5mcg (mometasone furoate/formoterol fumarate dihydrate)	106	$32,658.92	$308.10
Symbicort 160-4.5 (budesonide/formoterol fumarate dihydrate)	189	$59,047.53	$312.42
Symbicort 80-4.5 (budesonide/formoterol fumarate dihydrate)	75	$21,326.83	$284.36

Triple combination

Drug Name	Total Rx	Paid Amount	Paid/Rx
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	5	$2,665.03	$533.01

Short-Acting Beta2-Agonists Inhaled (SABA)

Drug Name	Total Rx	Paid Amount	Paid/Rx
ProAir HFA (albuterol sulfate)	1,853	$123,447.01	$66.62
ProAir Resp Aerosol (albuterol sulfate)	30	$1,913.54	$63.78
Proventil HFA (albuterol sulfate)	304	$27,282.50	$89.75
Ventolin HFA (albuterol sulfate)	2,046	$124,933.00	$61.06
Xopenex HFA (levalbuterol tartrate)	20	$1,623.24	$81.16

Long-Acting Beta2-Agonists Inhaled (LABA)

Drug Name	Total Rx	Paid Amount	Paid/Rx
Arcapta Neohaler (indacaterol)	0		
Brovana (arformoterol)	35	$28,669.33	$819.12
Perforomist (formoterol)	3	$2,474.94	$824.98
Serevent Diskus (salmeterol)	11	$4,193.58	$381.23
Striverdi Respimat (olodaterol)	0		

Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (SUPPORT Act)

President Trump signed into law H.R. 6 – SUPPORT Act, in the fight against the opioid epidemic.

Medicaid provisions include:

- Requirements that State Medicaid programs have drug utilization and safety edits for opioid refills and an automated claims review process to identify refills in excess of state limits, monitor concurrent prescribing of opioids, benzodiazepines or antipsychotics, and require managed care plans to have these in place by **October 1, 2019**.

- Requires State Medicaid programs to ensure providers check the PDMP for enrollee's prescription drug history before prescribing.

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2014*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2018*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2018*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1). Of these agents, mephobarbital and ezogabine are not currently marketed as either brand or generic formulations, but are included in this review for informational and historical purposes.
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. It is pending a Drug Enforcement Administration (DEA) scheduling designation (*GW Pharmaceuticals News Release).*
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Mephobarbital* (Mebaral)‡	-‡
Pentobarbital (Nembutal†)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi)	-
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium§)	✔ ‖
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)***	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔

Drug	Generic Availability
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Ezogabine (Potiga)‡	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	- #
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	-
Rufinamide (Banzel)	- #
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid (Depacon, Depakene, Stavzor DR‡)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
‡ No brand or generic currently marketed
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
# Generic is FDA-approved for at least 1 strength or formulation, but not currently marketed
** Branded generic
†† Branded generic; not currently marketed
*** Cannabidiol is not yet available as DEA schedule designation is pending (anticipated by Fall 2018) (*GW Pharmaceuticals News Release 2018*)

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *			A		✔, A*	✔, A*		✔ *		A*	✔, A*		A*	✔ *	✔, A*	A*
Primary generalized tonic-clonic seizure (grand mal)			✔								✔				✔ *			A*	A*
Absence seizure (petit mal)					✔ *			✔, A*		✔									
Multiple seizure types that include absence seizures								A											
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *		A*	✔, A									A*				A*	
Seizures of Dravet syndrome		✔ *																	
Juvenile myoclonic epilepsy (JME)																			A*
Emergency/acute/short-term use for seizure control (see notes)							✔ *								✔ *				
Akinetic and myoclonic seizures					✔, A														
Convulsive disorders (see notes)							A*												
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																
Migraine prophylaxis								✔ *											
Trigeminal neuralgia			✔ *																
Postherpetic neuralgia																✔ *			
Bipolar disorder			✔ *					✔ *										✔ *	
Panic disorder, with or without agoraphobia					✔														
Anxiety disorder; short-term relief of anxiety symptoms						✔	✔												
Symptomatic relief of acute alcohol withdrawal						✔	✔												

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Ezogabine	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome							A												
Partial-onset seizures associated with tuberous sclerosis complex (TSC)												A*							

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✓, A*		✓*		✓*	A*	✓, A*			A*	✓, A*	✓, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)	✓				A*		✓*		✓, A*				✓, A*			
Absence seizure (petit mal)	✓	✓*												✓, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/short-term use for seizure control (see notes)				✓*			✓*									
Infantile spasms															✓*	
Convulsive disorders (see notes)						✓*										
Migraine prophylaxis													✓*	✓*		

Indications	Mephobarbital†	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension	✔															
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Mephobarbital and phenobarbital are not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- **Brivaracetam**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- **Cannabidiol**
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- **Carbamazepine**:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- **Clobazam**:
  - Seizures associated with LGS in patients aged ≥ 2 years
- **Clonazepam**:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- **Diazepam**:
  - Oral diazepam may be used adjunctively in convulsive disorders
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
- **Divalproex sodium**:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (age ≥ 10 years for all formulations)
- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (age ≥ 10 years for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- **Eslicarbazepine:**
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- **Ethotoin**:
  - Complex partial (psychomotor) seizures
- **Everolimus**
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- **Ezogabine**:
  - Adjunctive treatment of partial-onset seizures in patients ≥18 years of age who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity
- **Felbamate**:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- **Fosphenytoin**:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- **Gabapentin**:
  - Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- **Lacosamide**:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- **Lamotrigine immediate-release formulations**:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- **Lamotrigine extended-release tablets**:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- **Levetiracetam**:

- Adjunctive therapy in the treatment of partial onset seizures in adults and children ≥ 1 month of age with epilepsy (age ≥ 4 years and weighing > 20 kg for the tablets for oral suspension [Spritam])
- Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years with JME
- Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
- The extended-release tablets are only indicated for adjunctive therapy in the treatment of partial-onset seizures in patients ≥ 12 years of age with epilepsy

- **Methsuximide**:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- **Oxcarbazepine immediate-release formulations**:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- **Oxcarbazepine extended-release tablets**:
  - Adjunctive therapy in the treatment of partial seizures in adults and children 6 to 17 years of age
- **Pentobarbital**:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- **Perampanel**:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 12 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- **Phenobarbital (not FDA-approved)**:
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- **Phenytoin oral formulations**:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- **Phenytoin injection**:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- **Pregabalin**:
  - Adjunctive therapy for treatment of partial onset seizures in patients ≥ 4 years of age
- **Primidone**:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- **Rufinamide**:
  - Adults and pediatric patients ≥ 1 year of age
- **Stiripentol**
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- **Tiagabine**:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- **Topiramate**:
  - Initial monotherapy in patients with partial onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)

- Adjunctive therapy for adults and pediatric patients with partial onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Prophylaxis of migraine headache in patients ≥ 12 years of age

- **Valproic acid**:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures (in adults and pediatric patients down 10 years) that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
  - Migraine prophylaxis and bipolar disorder indications are for the delayed-release capsule formulation only (Stavzor, which is not currently marketed). For bipolar disorder:
    - Acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features; safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials
- **Vigabatrin**:
  - Refractory complex partial seizures as adjunctive therapy in patients ≥ 10 years of age who have responded inadequately to several alternative treatments; not indicated as a first-line agent
  - Infantile spasms as monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- **Zonisamide**:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- 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

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, mephobarbital, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2017*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2018*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.

- As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
  - Gabapentin and lamotrigine are established as efficacious/effective.
  - Carbamazepine is possibly efficacious/effective.
  - Topiramate and valproate are potentially efficacious/effective.
- As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Oxcarbazepine is potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- As initial monotherapy for children with newly diagnosed or untreated absence seizures:
  - Ethosuximide and valproate are established as efficacious/effective.
  - Lamotrigine is possibly efficacious/effective.
  - Gabapentin is established as inefficacious/ineffective.
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
- As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
  - Carbamazepine and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
- For patients with newly diagnosed JME:
  - Topiramate and valproate are potentially efficacious/effective.
  - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
- There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.

- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
  - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
    - For individuals with partial seizures:
      (i) Levetiracetam performed better than carbamazepine and lamotrigine.
      (ii) Lamotrigine performed better than all other treatments (aside from levetiracetam).
      (iii) Carbamazepine performed better than gabapentin and phenobarbital.
    - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
    - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
  - For the secondary outcome, time to first seizure:
    - For individuals with partial seizures, phenobarbital and phenytoin seem to perform better than most other drugs; and carbamazepine performed better than valproate, gabapentin, and lamotrigine.
    - For individuals with generalized seizures, phenytoin seems to work better than most other drugs.
    - There were few notable differences between the newer drugs (oxcarbazepine, topiramate, gabapentin, levetiracetam, and zonisamide) for either partial seizures or generalized seizures.
  - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
  - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.

- Data for individuals with generalized seizures are still limited and additional randomized trials are needed.

- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (OR 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.
- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2017*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine, oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannibidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments.

Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo. To date, no comparative trials have been published.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A*, *Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following :
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam use and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine, lacosamide, perampanel, pregabalin, and rufunamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
  - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine,

topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
  - Recommendations from the 2004 guideline include the following:
    - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
    - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
    - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
    - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
    - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
  - Recommendations from the 2018 guideline include the following:
    - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
      - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
      - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
      - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
      - Ezogabine use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
      - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
    - As monotherapy in patients with TRAFE:
      - Eslicarbazepine use may be considered to decrease seizure frequency.
      - Data are insufficient to recommend use of second- and the other third-generation AEDs.
    - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
    - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
    - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
      - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
      - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
      - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
      - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.

        - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
    - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
    - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
    - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
    - For treatment in the adult population, conclusions included the following:
        - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
        - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
        - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
        - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
        - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
        - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
    - For treatment in the pediatric population, conclusions included the following:
        - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
        - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
        - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
        - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is

better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*). (Reaffirmed July 18, 2015)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spams.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*). (Reaffirmed January 23, 2016)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
    - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
    - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
    - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
    - Recommendations/findings include the following:
        - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
        - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
        - Treatment options with established or probable efficacy include the following:
            - Focal seizures: levetiracetam
            - Epileptic spasms: High-dose or low-dose ACTH

- Dravet syndrome: stiripentol (not available in the United States)
  - Treatment options with possible efficacy include the following:
- Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
- Epileptic spasms: prednisone, vigabatrin
- Benign infantile convulsions: carbamazepine, phenobarbital, valproate
- Dravet syndrome: topiramate, zonisamide, valproate
- Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
- Provoked or situational seizures: carbamazepine
  - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.

- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
    - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
    - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
    - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
    - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
    - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
    - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
    - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
    - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
    - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
    - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
  - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.

- Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.

- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*). (Reaffirmed July 13, 2013)
  - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
    - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
    - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
    - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
    - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
  - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*).
  - The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2018*).
- Common AEs among AEDs include the following (*Schachter 2018*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, abdominal pain, anorexia
    - rash, pruritus
    - hyponatremia (carbamazepine, oxcarbazepine)
    - weight gain (ezogabine, pregabalin, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, behavioral changes, hyperactivity
    - attention disturbance, inattention
    - depression, mood alteration
    - confusion, memory impairment
    - ataxia, abnormal coordination, falls
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2018*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, stiripentol, valproate, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, levetiracetam, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, phenobarbital, rufinamide, tiagabine, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, primidone, phenobarbital, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (eslicarbazepine, ezogabine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, primidone, phenobarbital, valproate)
  - multiorgan hypersensitivity (gabapentin, lacosamide, lamotrigine, oxcarbazepine)
  - severe neuropsychiatric effects/hostility/aggression (perampanel)
  - vision loss (ezogabine)
  - hyponatremia (eslicarbazepine)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, and diazepam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Ezogabine:
  - Ezogabine can cause retinal and macular abnormalities and may be associated with vision loss. Ezogabine should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Ezogabine should be discontinued in patients who fail to show substantial clinical benefit after adequate titration. All patients taking ezogabine should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. If retinal pigmentary abnormalities or vision changes are detected, ezogabine should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.
- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either AST or ALT become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment is recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.

- Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*Vigabatrin REMS 2017*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Mephobarbital* (Mebaral)‡	tablets	oral	Once daily or divided 3 to 4 times per day	
Pentobarbital (Nembutal†)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfotyn†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi)	tablets, oral suspension	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Diazepam (Diastat, Valium)	tablets, oral solution, oral concentrate, rectal gel, injection	oral, rectal, IV, IM	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection is also for short-term acute use.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol	Oral solution	Oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Ezogabine (Potiga)‡	tablets	oral	3 times per day	Tablets should be swallowed whole.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	1 to 4 times per day (*Lexicomp 2017*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid (Depakene, Stavzor DR‡, Depacon)	capsules, delayed-release capsules, oral solution/ syrup, injection	oral, IV	2 to 4 times per day (*Lexicomp 2017*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available
‡ No brand or generic currently marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and it is often treated by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

REFERENCES

- Afinitor Disperz [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Inc.; April 2018.
- Aptiom [package insert], Marlborough, MA: Sunovion Pharmaceuticals Inc.; October 2017.
- Banzel [package insert], Woodcliff Lake, NJ: Eisai Inc.; June 2015.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758-1765.
- Briviact [package insert], Smyrna, GA: UCB Inc.; May 2018.
- Campos MSA, Ayres LR, Morelo MRS, Carizio FAM, Pereira LRL. Comparative efficacy of antiepileptic drugs for patients with generalized epileptic seizures: systematic review and network meta-analyses. *Int J Clin Pharm.* 2018 May 9. doi: 10.1007/s11096-018-0641-9.
- Carbatrol [package insert], Wayne, PA: Shire US Inc.; February 2018.
- Celontin [package insert], New York, NY: Pfizer Inc.; November 2013.
- Centers for Disease Control and Prevention (CDC). Epilepsy: Types of Seizures. CDC Web Site. https://www.cdc.gov/epilepsy/basics/types-of-seizures.htm. Updated April 25, 2018. Accessed August 16, 2018.
- Cerebyx [package insert], New York, NY: Pfizer Inc.; April 2018.
- Depacon [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakene [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote (tablets) [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote ER [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Depakote Sprinkle Capsules [package insert], North Chicago, IL: AbbVie Inc.; October 2017.
- Diacomit [package insert]. Beauvais, France: Biocodex; August 2018.
- Diastat & Diastat AcuDial [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; December 2016.
- Diazepam (injection) [package insert], Lake Forest, IL: Hospira Inc.; September 2016.
- Diazepam (oral solution) and Diazepam Intensol (oral concentrate) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; May 2016.
- Dilantin-125 (oral suspension) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Dilantin (capsules) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Dilantin Infatabs (chewable tablets) [package insert], New York, NY: Pfizer Inc.; October 2017.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Website. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 16, 2018.
- Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice Parameter: treatment of postherpetic neuralgia: an evidence-based report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2004; 63:959-965 (guideline reaffirmed February 8, 2008).
- Epidiolex [package insert]. Carslbad, CA: Greenwich Biosciences, Inc.; June 2018.
- Epilepsy Foundation. Lennox-Gastaut Syndrome. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes/lennox-gastaut-syndrome-lgs. Reviewed March 2014. Accessed August 16, 2018.
- Epilepsy Foundation. Seizure Types. Epilepsy Foundation Web site. https://epilepsychicago.org/epilepsy/seizure-types/generalized-seizures/. 2016. Accessed August 16, 2018.
- Epilepsy Foundation. Types of Epilepsy Syndromes. Epilepsy Foundation Web site. http://www.epilepsy.com/learn/types-epilepsy-syndromes. September 2013. Accessed August 16, 2018.
- Equetro [package insert], Parsippany, NJ: Validus Pharmaceuticals LLC; October 2016.
- FDA News Release. FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Food and Drug Administration website: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm611046.htm, Accessed August 21, 2018.
- Felbatol [package insert], Somerset, NJ: Meda Pharmaceuticals Inc.; August 2012.
- Fisher RS, Acevedo C, Arzimanoglou A, et al. A practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482.
- Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*. 2017(A);58(4):531-542.
- Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017(B);58(4):522-530.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(A);62:1252-1260.
- French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2004(B);62:1261-1273.
- French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomized, double-blind, placebo-controlled study. *Lancet.* 2016;388(10056):2153-2163. doi: 10.1016/S0140-6736(16)31419-2.
- Fycompa [package insert], Woodcliff Lake, NJ: Eisai Inc.; July 2017.
- Gabitril [package insert], North Wales, PA: Teva Pharmaceuticals USA Inc.; August 2016.
- Glauser T, Ben-Menachem E, Bourgeois B, et al; for the ILAE subcommission of AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia*. 2013;54(3):551-563.
- Glauser T, Shinnar S, Gloss D, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016;16(1):48-61.

- Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2012;78:1974-1980 (guideline reaffirmed July 18, 2015).
- Gralise [package insert], Newark, CA: Depomed Inc.; September 2015.
- GW Pharmaceuticals News Release. Biosciences announce FDA approval of Epidiolex (cannabidiol) oral solution- the first plant-derived cannabinoid prescription medicine. GW Pharmaceuticals Website. http://ir.gwpharm.com/news-releases/news-release-details/gw-pharmaceuticals-plc-and-its-us-subsidiary-greenwich. Accessed August 21, 2018.
- Harden CL, Meador KJ, Pennell PB, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(A);73:133-141 (guideline reaffirmed July 13, 2013).
- Harden CL, Pennell PB, Koppel BS, et al. Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding. Report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. *Neurology*. 2009(B);73:142-149 (guideline reaffirmed July 13, 2013).
- Hirschfeld RM, Bowden CL, Gitlin MJ, et al. Practice guideline for the treatment of patients with bipolar disorder; second edition. http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/bipolar.pdf. Originally published April 2002. Accessed August 20, 2018.
- Hirtz D, Berg A, Bettis D, et al. Practice Parameter: treatment of the child with a first unprovoked seizure. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2003;60:166-175 (guideline reaffirmed January 23, 2016).
- Horizant [package insert], Atlanta, GA: Arbor Pharmaceuticals LLC; October 2016.
- Hu Q, Zhang F, Teng W, et al. Efficacy and safety of antiepileptic drugs for refractory partial-onset epilepsy: a network meta-analysis. *J Neurol.* 2018;265(1):1-11. doi: 10.1007/s00415-017-8621-x.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2018(A);91(2):82-90. doi: 10.1212/WNL.0000000000005756.
- Kanner AM, Ashman E, Gloss D, et al. Practice guideline update summary: efficacy and tolerability of the new antiepileptic drugs II: treatment-resistant epilepsy. Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology.* 2018(B);91(2):74-81. doi: 10.1212/WNL.0000000000005755.
- Karceski S. Initial treatment of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated December 20, 2017. Accessed August 16, 2018.
- Keppra (injection) [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Keppra (tablets & oral solution) [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Keppra XR [package insert], Smyrna, GA: UCB Inc.; October 2017.
- Klonopin [package insert], South San Francisco, CA: Genentech Inc.; October 2017.
- Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. *Neurology*. 2015;84:1705-1713.
- Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. *N Engl J Med*. 2011;365:919-926.
- Lamictal (tablets, chewable dispersible tablets & orally disintegrating tablets) [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2018.
- Lamictal XR [package insert], Research Triangle Park, NC: GlaxoSmithKline; July 2018.
- LexiComp Web site. http://online.lexi.com/lco/action/home/switch. Accessed August 20, 2018.
- Lyrica [package insert], New York, NY: Pfizer Inc.; May 2018.
- Lyrica CR [package insert], New York, NY: Pfizer Inc.; October 2017.
- Mebaral [package insert], Deerfield, IL: Lundbeck Inc.; May 2009 (archived label available at https://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=76283. Accessed August 20, 2018.
- Mysoline [package insert], Bridgewater, NJ: Valeant Pharmaceuticals; January 2018.
- Nembutal [package insert], Lake Forest, IL: Akorn, Inc.; December 2016.
- Neurontin [package insert], New York, NY: Pfizer Inc.; October 2017.
- Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database of Systematic Reviews 2017, Issue 6. Art. No.: CD011412. DOI: 10.1002/14651858.CD011412.pub2.
- Onfi [package insert], Deerfield, IL: Lundbeck Inc.; June 2018.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 16, 2018.
- Oxtellar XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; December 2015.
- Peganone [package insert], Lebanon, NJ: Recordati Rare Diseases; July 2016.
- Phenobarbital (elixir) [package insert], Huntsville, AL: Qualitest Pharmaceuticals; February 2015.
- Phenobarbital (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; June 2011.
- Phenobarbital (tablet) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; May 2018.
- Phenytoin (injection) [package insert], Eatontown, NJ: West-Ward Pharmaceuticals; December 2017.
- Post RM. Bipolar disorder in adults: choosing maintenance treatment. UpToDate Web site. www.uptodate.com. Updated November 2, 2017. Accessed August 16, 2018.
- Potiga [package insert], Research Triangle Park, NC: GlaxoSmithKline; May 2016.
- Qudexy XR [package insert], Maple Grove, MN: Upsher-Smith Laboratories Inc.; March 2017.

- Rosati A, Ilvento L, Lucenteforte E, et al. Comparative efficacy of antiepileptic drugs in children and adolescents: a network meta-analysis. *Epilepsia.* 2018;59(2):297-314. doi: 10.1111/epi.13981.
- Sabril [package insert], Deerfield, IL: Lundbeck Inc.; April 2017.
- Schachter SC. Overview of the management of epilepsy in adults. UpToDate Web site. www.uptodate.com. Updated July 9, 2018. Accessed August 16, 2018.
- Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337-1345 (guideline reaffirmed July 18, 2015).
- Sirven JI. Evaluation and management of drug-resistant epilepsy. UpToDate Web site. www.uptodate.com. Updated March 2, 2018. Accessed August 16, 2018.
- Spritam [package insert], East Windsor, NJ: Aprecia Pharmaceuticals Company; February 2018.
- Stavzor [package insert], Miami, FL: Noven Therapeutics LLC; August 2014.
- Stovall J. Bipolar disorder in adults: Choosing pharmacotherapy for acute mania and hypomania. UpToDate Web site. www.uptodate.com. Updated February 06, 2018. Accessed August 20, 2018.
- Tegretol and Tegretol-XR [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corp.; March 2018.
- Topamax [package insert], Titusville, NJ: Janssen Pharmaceuticals Inc.; June 2018.
- Tranxene T-TAB [package insert], Lebanon, NJ: Recordati Rare Diseases Inc.; May 2018.
- Trileptal [package insert], East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2018.
- Trokendi XR [package insert], Rockville, MD: Supernus Pharmaceuticals Inc.; January 2018.
- Valium [package insert], South San Francisco, CA: Genentech Inc.; June 2017.
- Vigabatrin risk evaluation and mitigation strategy (REMS) document. Food and Drug Administration Web site. https://www.accessdata.fda.gov/drugsatfda_docs/rems/Vigabatrin_SSS_2017-10-23_Full.pdf. Updated October 2017. Accessed August 20, 2018.
- Vimpat [package insert], Smyrna, GA: UCB Inc.; November 2017.
- Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. *Epilepsia*. 2015;56(8):1185-1197.
- World Health Organization. Guidelines on neonatal seizures. World Health Organization Web site. http://www.who.int/mental_health/publications/guidelines_neonatal_seizures/en/. 2011. Accessed August 20, 2018.
- Zarontin (capsules) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zarontin (oral solution) [package insert], New York, NY: Pfizer Inc.; May 2016.
- Zhu LN, Chen D, Xu D, Tan G, Wang HJ, Liu L. Newer antiepileptic drugs compared to levetiracetam as adjunctive treatments for uncontrolled focal epilepsy: an indirect comparison. *Seizure*. 2017 Aug 16;51:121-132 (Epub).
- Zhao T, Feng X, Liu J, et al. Evaluate the efficacy and safety of anti-epileptic medications for partial seizures of epilepsy: A network meta-analysis. *J Cell Biochem*. 2017;118(9):2850-2864. doi: 10.1002/jcb.25936.
- Zonegran [package insert], St. Michael, Barbados: Concordia Pharmaceuticals Inc.; April 2016.

Publication Date: September 4, 2018

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Onfi® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)

Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Intractable treatment-resistant seizure disorder
❑ Seizures associated with Lennox-Gastaut syndrome (LGS)
❑ Other diagnosis: _____ ICD-10 Code(s): _____

Prescriber specialty:

Is Onfi prescribed by or in consultation with a neurologist? ❑ **Yes** ❑ **No**

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing (*National Heart, Lung, and Blood Institute [NHLBI] 2014*).
- The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development (*NHLBI 2014*).
- The goal of asthma management – asthma control – can be described in the following domains (*NHLBI 2007*):
  - Reduction of impairment
    - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the daytime, at night, or after exertion)
    - Require infrequent use (≤2 days a week) of short-acting beta-agonist (SABA) for quick relief of symptoms
    - Maintain (near) normal pulmonary function
    - Maintain normal activity levels (including exercise and other physical activity and attendance at work or school)
    - Meet patients' and families' expectations of and satisfaction with asthma care.
  - Reduction of risk
    - Prevent recurrent exacerbations of asthma and minimize the need for emergency department (ED) visits or hospitalizations
    - Prevent progressive loss of lung function; for children, prevent reduced lung growth
    - Provide optimal pharmacotherapy with minimal or no adverse effects.
- Current pharmacologic options for asthma management are categorized as: (1) long-term control medications to achieve and maintain control of persistent asthma, and (2) quick-relief medications used to treat acute symptoms and exacerbations.
  - Long-term control medications include:
    - Corticosteroids (inhaled corticosteroids [ICS] for long-term control; short courses of oral corticosteroids to gain prompt control of disease, long-term oral corticosteroids for severe persistent asthma)
    - Cromolyn sodium and nedocromil
    - Immunomodulators (e.g., omalizumab)
    - Leukotriene modulators
    - Long-acting β-agonists (LABAs)
    - Methylxanthines (i.e., theophylline)
  - Quick-relief medications include:
    - Anticholinergics (i.e., ipratropium bromide), as an alternative bronchodilator for those not tolerating a SABA
    - SABAs (therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm)
    - Systemic corticosteroids (not short-acting, but used for moderate and severe exacerbations) (*NHLBI 2007*)
- Approximately 5 to 10% of asthma patients have severe disease. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*).
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for a period of 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor, and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2017, Saini 2017*).
- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life.

CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 1 to 5 years (*Saini 2017*).

- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, sulfasalazine, and dapsone (*Khan 2017, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Schwartz et al 2016).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux 2016*).
- This monograph describes the use of Cinqair (reslizumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists, each approved as an add-on maintenance treatment for patients with severe asthma with an eosinophilic phenotype. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
  - Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2017, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2017*)

INDICATIONS

- Xolair is indicated for:
  - Patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - The treatment of adults and adolescents 12 years of age and older with CIU who remain symptomatic despite H_1-antihistamine treatment.

Limitations of use include the following:
  - Xolair is not indicated for the relief of acute bronchospasm or status asthmaticus.
  - Xolair is not indicated for treatment of other allergic conditions or other forms of urticaria.

- Fasenra is indicated for the add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.

Limitations of use include the following:
- Fasenra is not indicated for treatment of other eosinophilic conditions.
- Fasenra is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Nucala is indicated for:
  - The add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype.
  - The treatment of adult patients with EGPA.

Limitations of use include the following:
- Nucala is not indicated for the relief of acute bronchospasm or status asthmaticus.

- Cinqair is indicated for the add-on maintenance treatment of patients with severe asthma aged 18 years and older with an eosinophilic phenotype.

Limitations of use include the following:
- Cinqair is not indicated for treatment of other eosinophilic conditions.
- Cinqair is not indicated for the relief of acute bronchospasm or status asthmaticus.

- 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

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients at least 12 years of age with moderate to severe asthma for at least 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a step-wise manner.
  - In the 28-week study by Busse et al (N=525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; P=0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; P<0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; P=0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; P=0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N=546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; P<0.001) and steroid reduction phases (0.36 vs 0.75; P<0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N=246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; P=0.003). The percentages of patients with at least 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (P value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Solèr et al 2001, Holgate et al 2004*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (i.e., all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (P=0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies, 3,261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies, 1,889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies, 1,824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N=3,429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; P=0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; P=0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; P=0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients ages 6 to <12 years with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; rate ratio, 0.69; P=0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (P<0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors

concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who were established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients was found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0% to 33.6%). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit *(Ledford et al 2017)*.

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo (P≤0.001) (*Saini et al 2014*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1,312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group (P<0.00001) and dose dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%, P<0.0001). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2017)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n=80), benralizumab 2 mg (n=81), benralizumab 20 mg (n=81), or benralizumab 100 mg (n=82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n=142) or placebo (n=143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60, P=0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of at least 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; P=0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; P=0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N=1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n=407), benralizumab 30 mg every 4 weeks (n=400), or benralizumab 30 mg every 8 weeks (n=398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (rate ratio, 0.55; 95% CI, 0.42 to 0.71; P<0.0001) or every 8 weeks (rate ratio, 0.49; 95% CI, 0.37 to 0.64; P<0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n=425), benralizumab 30 mg every 8 weeks (n=441) or placebo (n=440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (rate ratio, 0.64; 95% CI, 0.49 to 0.85; P=0.0018) and every 8 weeks (rate ratio, 0.72; 95% CI, 0.54 to 0.95; P=0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N=211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n=106) or placebo (n=105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150, P=0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n=72), benralizumab 30 mg every 8 weeks (n=73), or placebo (n=75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo (P<0.001 for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; P=0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; P<0.001).
- FitzGerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n=2295 patients) of the results from the SIROCCO and CALIMA phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of at least 0 cells/µL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo versus 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; P<0.0001). In patients who

received benralizumab every 4 weeks who had eosinophil counts of at least 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; P<0.0001). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every 4 week and every 8 week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*

- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n=2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; P<0.00001) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration resulted no increasing incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; P=0.96) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥150 cells/μL in the peripheral blood at screening or ≥300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication *(Pavord et al 2012, Ortega et al 2014, Bel et al 2014)*.
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N=621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group (P<0.0001), 1.46 in the 250 mg mepolizumab group (P=0.0005), and 1.15 in the 750 mg mepolizumab group (P<0.0001). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N=576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group (P<0.001), and 0.83 per patient per year in the SC mepolizumab group (P<0.001). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo (P<0.001) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N=135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; P=0.008). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group (P=0.007) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1,192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; rate ratio, 0.53; 95% CI, 0.44 to 0.62; P<0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (rate ratio, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥150 cells/μL to 70% (rate ratio, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥500 cells/μL. At a baseline count <150 cells/μL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive

appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).

- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for at least 24 weeks. Four studies (N=1,388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; P=0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; P<0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n=68) or placebo (n=68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; P<0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; P<0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (rate ratio, 0.50; 95% CI, 0.36 to 0.70; P<0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; P<0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N=953) in patients with asthma who were required to have a blood eosinophil count ≥400 cells/µL, and at least 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: rate ratio, 0.50; 95% CI, 0.37 to 0.67; Study 3083: rate ratio, 0.41; 95% CI, 0.28 to 0.59; both P<0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N=315) in patients who were required to have a blood eosinophil count ≥400 cells/µL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; P=0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count <400 cells/µL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils

<400 cells/µL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥400 cells/µL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).

- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N=1,366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; P<0.00001). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; P<0.00001). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; P<0.00001). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).

COMPARATIVE REVIEWS

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated rate ratios of 0.66 (95% credible interval [CrI], 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CrI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median rate ratio of 0.63 (95% CrI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median rate ratio of 0.58 (95% CrI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function, and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with a duration of ≥12 weeks. A total of 18 omalizumab studies (N=4854) and 4 mepolizumab studies (N=1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2017)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N=6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2018, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. For patients with severe asthma uncontrolled on Step 4 treatment (e.g., 2 or more controllers plus as-needed reliever medication), phenotyping into categories such as severe allergic, aspirin-exacerbated or eosinophilic asthma is suggested. Anti-IgE treatment with omalizumab is recommended as the preferred option for the management of patients at Step 5 of treatment. Similarly, add-on anti-IL-5 therapy (i.e., benralizumab, mepolizumab, reslizumab) is recommended for patients aged ≥12 years with severe eosinophilic asthma that is uncontrolled on Step 4 treatment (*GINA 2018*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Updated joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab, cyclosporine, or a leukotriene receptor antagonist in patients with symptoms despite treatment with a 4-fold dose of modern second generation antihistamines (*Zuberbier et al 2013*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Schwartz et al 2016*).
  - These guidelines have not been updated to include the place in therapy for mepolizumab; however, the EGPA Consensus Task Force recommendations notes that mepolizumab hold promise for this condition based on the pilot studies available at the time of guideline development (*Groh et al 2015*).

SAFETY SUMMARY

Cinqair:

- Contraindication: History of hypersensitivity to Cinqair or excipients in the formulation.
- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warning and precaution:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
- The most common adverse reaction (≥2%) includes oropharyngeal pain.

Fasenra:

- Contraindication: History of hypersensitivity to Fasenra or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Systemic or inhaled corticosteroids should not be discontinued abruptly upon initiation of therapy with Fasenra. Corticosteroids should be decreased gradually, if appropriate.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥5%) include headache and pharyngitis.

Nucala:

- Contraindication: History of hypersensitivity to Nucala or excipients in the formulation.
- Key warnings and precautions:
  - Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.

- Herpes zoster infections have occurred in patients receiving Nucala. In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with Nucala compared with none in patients treated with placebo.
- The most common adverse reactions (≥5%) include headache, injection site reaction, back pain, and fatigue.

Xolair:

- Contraindication: Severe hypersensitivity reaction to Xolair or any ingredient of Xolair.
- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Observe patients closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥12 years of age, the most commonly observed adverse reactions in clinical studies (≥1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to <12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients (aged 17 years and younger) have not been established.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients younger than 12 years have not been established.

Drug	Route	Usual Recommended Frequency	Comments
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients younger than 12 years with asthma have not been established. • Safety and efficacy in pediatric patients other than those with asthma have not been established.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). • Safety and efficacy in pediatric patients with asthma below 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU below 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.
- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2018, NHLBI 2007*). Based on the limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA-approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU generally recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second

generation antihistamines and, in some cases, a leukotriene receptor antagonist (*Bernstein et al 2014, Zuberbier et al 2013, Powell et al 2015*).

- Cinqair, Fasenra , and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, with demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy (*GINA 2018*).
- Nucala is the only IL-5 antagonist approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients aged 18 years and older (12 years and older for Nucala and Fasenra), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis.

REFERENCES

- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189-1197.
- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
- Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789-798.
- Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
- Buhl R, Solèr M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J*. 2002;20(1):73-78.
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-90.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med*. 2014;2(11):879-890.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
- Cinqair prescribing information. Teva Pharmaceutical Industries Ltd. Frazer, PA. June 2016.
- Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343-373.
- Cockle SM, Stynes G, Gunsoy NB, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. *Respir Med*. 2017;123:140-148.
- Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810.
- Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
- DRUGS@FDA.com (database on the internet). Rockville (MD): U.S. Food and Drug Administration. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed November 20, 2017.
- Eisner MD, Zazzali JL, Miller MK, et al. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS study. *J Asthma*. 2012;49:642-648.
- Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017 Sep 21;9:CD010834.
- Fasenra prescribing information. AstraZeneca Pharmaceuticals. Wilmington, DE. November 2017.
- Ferguson GT, Fitzgerald JM, Beecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):568-576.
- FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6(1):51-64.
- Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.

- Food and Drug Administration press release. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair, including describing slightly higher risk of heart and brain adverse events. Published online September 26, 2014. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm414911.htm. Accessed November 20, 2017.
- Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015;26(7):545-553.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention (2018 update). 2018; www.ginasthma.org. Accessed June 26, 2018.
- Holgate S, Bousquet J, Wenzel S, et al. Efficacy of omalizumab, an antiimmunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin*. 2001;17(4):233-40.
- Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632-8.
- Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma. *J Allergy Clin Immunol*. 2017;139(5):1489-1495.e5.
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101-9.
- Khan DA. Chronic urticaria: treatment of refractory symptoms. UpToDate Web site. https://www.uptodate.com. Updated August 28, 2017. Accessed November 20, 2017.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-6.
- Lanier BQ, Corren J, Lumry W, et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91(2):154-9.
- Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.e2.
- Li J, Wang F, Lin C, et al. The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis. *J Asthma.* 2017;54(3):300-307.
- Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560-567.
- Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38(9):2058-2070.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
- Maurer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2018;141(3):1138-1139.e7.
- Nachef Z, Krishnan A, Mashtare T, Zhuang T, Mador MJ. Omalizumab versus mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: a network meta-analysis. *J Asthma*. 2018;55(1):89-100.
- Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). NHLBI 2007. Available from http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed November 20, 2017.
- National Heart, Lung, and Blood Institute. What is Asthma? 2014. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/asthma. Accessed November 20, 2017.
- Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev. 2014 Jan 13;(1):CD003559.
- Nucala prescribing information. GlaxoSmithKline LLC. Philadelphia, PA. December 2017.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-1207.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
- Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Expert Rev Clin Immunol;*2016;12(10):1059-1067.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651-659.
- Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2015;45(3):547-565.
- Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. Available from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. Accessed November 20, 2017.
- Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28-35.
- Saini S. Chronic urticarial: clinical manifestations, diagnosis, pathogenesis, and natural history. UpToDate Web site. https://www.uptodate.com. Updated June 29, 2017. Accessed December 12, 2017.
- Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Derm*. 2015;135:67-75.
- Schwartz J, Padmanabhan A, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice-evidence-based approach from the Writing Committee of the American Society for Apheresis: The seventh special issue. *J Clin Apher*. 2016;31(3):149-162.
- Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254-61.
- Tian BP, Zhang GS, Lou J, Zhou HB, Cui W. Efficacy and safety of benralizumab for eosinophilic asthma: A systematic review and meta-analysis of randomized controlled trials. *J Asthma.* 2017. [Epub ahead of print]

- Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma and Allergy. 2014;7:53-65.
- Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017;376(20):1921-1932.
- Xolair prescribing information. Genentech, Inc. South San Francisco, CA and Novartis Pharmaceuticals. East Hanover, NJ. May 2018.
- Yancey SW, Ortega HG, Keene ON, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;139(4):1167-1175.
- Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA/LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy*. 2014;69:868-887.

Publication Date: July 2, 2018

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Nucala® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
❑ Severe asthma with an eosinophilic phenotype
❑ Other diagnosis: _____ ICD-10 Code(s): _____

For severe asthma with an eosinophilic phenotype, answer the following:

Has the patient experienced inadequate control of asthmatic symptoms after a minimum of three months use of a high dose corticosteroid and controller medication? ❑ **Yes** ❑ **No**

Has the patient had at least two asthma exacerbations requiring medical intervention within the past 12 months? ❑ **Yes** ❑ **No**

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Nucala_SouthDakotaMedicaid_2018Oct-P

DSS
Strong Families - South Dakota's Foundation and Our Future

Please note: All information below is required to process this request.
Fax to 1-800-527-0531
Mon-Sat: 7am to 7pm Central

Xolair® Prior Authorization Request Form

DO NOT COPY FOR FUTURE USE. FORMS ARE UPDATED FREQUENTLY AND MAY BE BARCODED

Member Information (required)			Provider Information (required)		
Member Name:			Provider Name:		
Insurance ID#:			NPI#:	Specialty:	
Date of Birth:			Office Phone:		
Street Address:			Office Fax:		
City:	State:	Zip:	Office Street Address:		
Phone:			City:	State:	Zip:

Medication Information (required)		
Medication Name:	Strength:	Dosage Form:
❑ Check if requesting **brand**	Directions for Use:	
❑ Check if request is for **continuation of therapy**		

Clinical Information (required)

Select the diagnosis below:

❑ Asthma
❑ Chronic idiopathic urticaria (CIU)
❑ Other diagnosis: _____ ICD-10 Code(s): _____

For asthma, answer the following:

Does the patient have an elevated serum IgE level? ❑ **Yes** ❑ **No**
Are the patient's symptoms inadequately controlled with inhaled corticosteroids? ❑ **Yes** ❑ **No**
Does the patient have a positive skin test or in vitro reactivity to a perennial aeroallergen? ❑ **Yes** ❑ **No**

For chronic idiopathic urticarial, answer the following:

Does the patient remain symptomatic despite H1 antihistamine treatment? ❑ **Yes** ❑ **No**

Quantity limit requests:

What is the quantity requested per DAY? _____

What is the reason for exceeding the plan limitations?

❑ Titration or loading dose purposes
❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)
❑ Requested strength/dose is not commercially available
❑ Patient requires a greater quantity for the treatment of a larger surface area **[Topical applications only]**
❑ Other: _____

Are there any other comments, diagnoses, symptoms, medications tried or failed, and/or any other information the physician feels is important to this review?

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-800-527-0531.

Office use only: Xolair_SouthDakotaMedicaid_2017May-P