South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

June 21, 2019

DSS

Strong Families - South Dakota's Foundation and Our Future

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Strong Families - South Dakota's Foundation and Our Future

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

June 21, 2019
1:00 – 3:00 PM

Meeting Location:

Ramada Sioux Falls Airport Hotel
1301 West Russell
Sioux Falls, SD

Meeting Room – Galley 1

Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **PA reviews**
- **CGRP utilization**
- **Orilissa utilization**
- **CiproDex utilization**
- **ADD/ADHD utilization**
- **Dupixent**
- **Immunomodulator – Actemra**

New business
- **Hepatitis C**
- **Triptan utilization**
- **Opioid update**

Public comment accepted after individual topic discussion

Next meeting date 9/27/2019 & adjournment

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

Friday, March 8, 2019
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Ladwig called the meeting to order at 1:10 PM. The minutes of the December meeting were presented. Engelbrecht questioned if PPI criteria changes from the previous meeting had been disseminated to providers. Changes were implemented, but Jockheck commented that he would add notice regarding the criteria changes to the DSS website for the providers. Oehlke made a motion to approve. Van Gilder seconded the motion. Motion was approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from October 1, 2018 to December 31, 2018. A total of 1,506 PAs were reviewed of which 327 requests (22%) were received via telephone and 1,177 requests (78%) were received via fax. Engelbrecht questioned the need for PA if approval rate is 99%. An in-depth review of PAs with over 95% approval to be provided at the next meeting to determine PA necessity.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from October 1, 2018 to December 31, 2018. The top five therapeutic classes were atypical antipsychotics, selective beta-2 adrenergic agonists, anticonvulsants, and amphetamines. The top 15 therapeutic classes make up 31.69% 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 28.81% of total claims. Van Gilder commented generics' paid/Rx amount seemed higher than the previous quarter. Jockheck confirmed Indian Health Services (IHS) claims were included which are processed on an encounter fee schedule. IHS utilization data will be excluded henceforth. Committee also reviewed Fiscal Year PMPM figures. Ladwig commented on the corrections for years 2017 and 2018. Jockheck explained that moving to the new system with OptumRx resulted in the correction.

Old Business

Committee reviewed CGRP utilization comparing 3Q18 vs 4Q18. Committee requested to review utilization again at the next meeting.

Committee reviewed CiproDex utilization for 4Q18. Van Gilder commented on prescribers such as dentist, chiropractors, LPN, and students prescribing out of scope; in addition to prescribers from outside South Dakota. Jockheck commented that prescribers for IHS could be from other states.

Engelbrecht requested to review 1Q19 CiproDex utilization data at the next meeting. IHS data will be removed.

Engelbrecht commented on Dupixent's fax form and requested asthma diagnosis to be included. Updated fax form and clinical information to be brought back to the next meeting.

Ladwig requested an outcomes report for opioid edits that went into effect in 2018.

New business
After reviewing the ADD/ADHD utilization, committee requested utilization to be brought back to the next meeting. Utilization will be separated out by child vs adults.

The committee reviewed Consensi clinical information. There was no public comment. The committee requested to monitor utilization for this drug.

The committee reviewed Orilissa clinical information. Michael Gonzalez from AbbVie spoke regarding Orilissa. The committee requested to monitor utilization for this drug. Ladwig inquired what other Medicaid states are doing with this drug.

The committee reviewed clinical information on new immunomodulators. PAs will be added to new immunmodulators; including new and expanded indications for others. If a new indication is not straight forward, committee would like to review those.

The next meeting is scheduled for June 21, 2019. Tentative meeting date for September is September 27, 2019. Van Gilder made a motion to adjourn the P&T committee meeting. Oehlke seconded the motion. The motion passed unanimously and the meeting adjourned at 2:15 PM.

PA Report

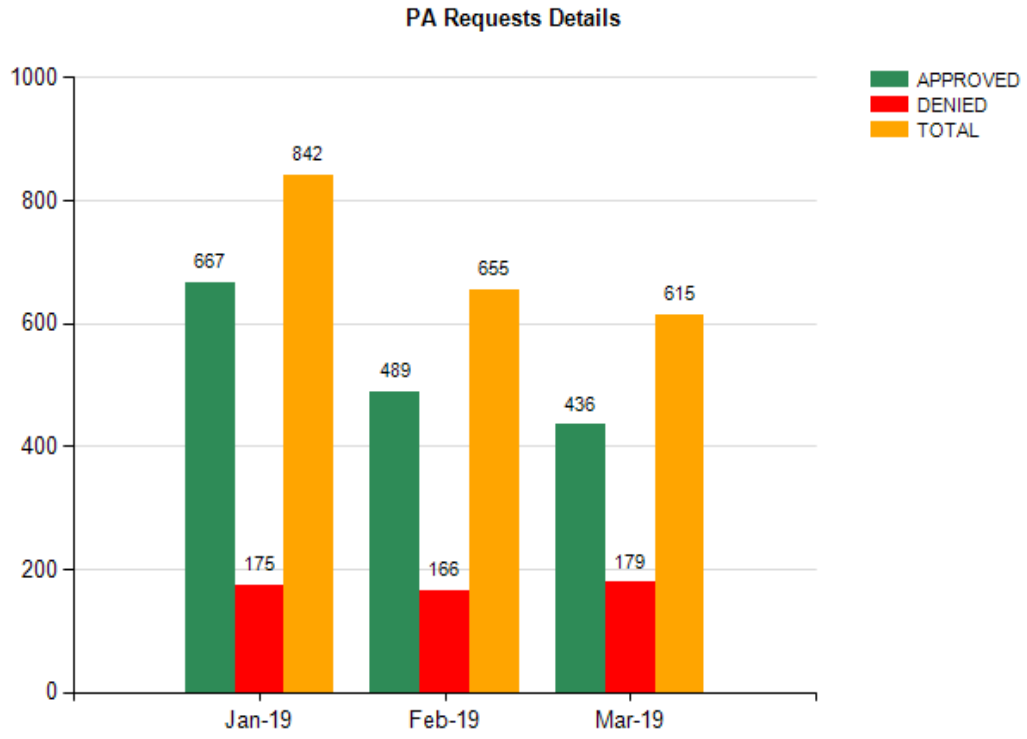
1/1/2019 to 3/31/2019

Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
URGENT	51	51	0	100.0%	0.0%
STANDARD	2061	2061	0	100.0%	0.0%
GRAND TOTAL	**2112**	**2112**	**0**	100.0%	0.0%

PA Initial Requests Summary

Month	Approved	Denied	Total
Jan-19	667	175	842
Feb-19	489	166	655
Mar-19	436	179	615
1Q19	1592	520	2112
Percent of Total	75.38%	24.62%	



Top 5 Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
65 - ANALGESICS - OPIOID*	263	106	369	71.27%	17.47%	TRAMADOL, HYDROCODONE/APAP
59 - ANTIPSYCHOTICS/ ANTIMANIC AGENTS*	251	19	270	92.96%	12.78%	RISPERIDONE, ETC
49 - ULCER DRUGS/ ANTISPASMODICS/ANTICHOLINERG	177	47	224	79.02%	10.61%	ESOMEPRAZOLE MAGNESIUM, ETC
58 - ANTIDEPRESSANTS*	191	24	215	88.84%	10.18%	DULOXETINE HCL, ETC
90 - DERMATOLOGICALS*	76	90	166	45.78%	7.86%	LIDOCAINE, SKLICE
Others -	634	234	868	73.04%	41.10%	
1Q19	1592	520	2112	75.38%		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
65 - ANALGESICS - OPIOID*	263	106	369	71.27%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	251	19	270	92.96%
58 - ANTIDEPRESSANTS*	191	24	215	88.84%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	177	47	224	79.02%
83 - ANTICOAGULANTS*	101	11	112	90.18%
72 - ANTICONVULSANTS*	100	59	159	62.89%
90 - DERMATOLOGICALS*	76	90	166	45.78%
27 - ANTIDIABETICS*	72	3	75	96.00%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	49	18	67	73.13%
66 - ANALGESICS - ANTI-INFLAMMATORY*	39	4	43	90.70%
52 - GASTROINTESTINAL AGENTS - MISC.*	37	17	54	68.52%
54 - URINARY ANTISPASMODICS	30	10	40	75.00%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	29	6	35	82.86%
67 - MIGRAINE PRODUCTS*	24	46	70	34.29%
16 - ANTI-INFECTIVE AGENTS - MISC.*	22	0	22	100.00%
12 - ANTIVIRALS*	20	13	33	60.61%
50 - ANTIEMETICS*	19	2	21	90.48%
41 - ANTIHISTAMINES*	14	3	17	82.35%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	13	4	17	76.47%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	11	0	11	100.00%
75 - MUSCULOSKELETAL THERAPY AGENTS*	10	5	15	66.67%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	7	0	7	100.00%
34 - CALCIUM CHANNEL BLOCKERS*	4	2	6	66.67%
36 - ANTIHYPERTENSIVES*	4	0	4	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	4	0	4	100.00%

86 - OPHTHALMIC AGENTS*	3	21	24	12.50%
39 - ANTIHYPERLIPIDEMICS*	3	1	4	75.00%
79 - MINERALS & ELECTROLYTES*	3	0	3	100.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	2	2	4	50.00%
02 - CEPHALOSPORINS*	2	1	3	66.67%
25 - CONTRACEPTIVES*	2	0	2	100.00%
82 - HEMATOPOIETIC AGENTS*	2	0	2	100.00%
94 - DIAGNOSTIC PRODUCTS*	2	0	2	100.00%
45 - RESPIRATORY AGENTS - MISC.*	1	1	2	50.00%
01 - PENICILLINS*	1	0	1	100.00%
11 - ANTIFUNGALS*	1	0	1	100.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	1	0	1	100.00%
68 - GOUT AGENTS*	1	0	1	100.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	1	0	1	100.00%
04 - TETRACYCLINES*	0	1	1	0.00%
33 - BETA BLOCKERS*	0	1	1	0.00%
38 - VASOPRESSORS*	0	1	1	0.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	0	1	1	0.00%
77 - VITAMINS*	0	1	1	0.00%
1Q19	1592	520	2112	
Percent of Total	75.38%	24.62%		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
Jan-19	18	90.00%	2	10.00%	20
Feb-19	15	78.95%	4	21.05%	19
Mar-19	13	86.67%	2	13.33%	15
1Q19	46	85.19%	8	14.81%	54

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
AIMOVIG	3	0	3	100.00%
AJOVY	1	0	1	100.00%
AMITIZA	4	0	4	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	0	1	1	0.00%
BUPRENORPHINE HCL	0	1	1	0.00%
CIMZIA STARTER KIT	1	0	1	100.00%
CLOBAZAM	1	0	1	100.00%
DARIFENACIN HYDROBROMIDE ER	1	1	2	50.00%
DEXILANT	1	0	1	100.00%
ELETRIPTAN HYDROBROMIDE	1	0	1	100.00%
EMGALITY	2	0	2	100.00%
ENBREL SURECLICK	0	1	1	0.00%
ESCITALOPRAM OXALATE	1	0	1	100.00%
FENTANYL	1	0	1	100.00%
HYDROCODONE/ACETAMINOPHEN	3	0	3	100.00%
INGREZZA	2	0	2	100.00%
LEDIPASVIR/SOFOSBUVIR	1	0	1	100.00%
LIDOCAINE	2	1	3	66.67%
LINZESS	1	0	1	100.00%
LYRICA	4	0	4	100.00%
MAVYRET	2	0	2	100.00%
METHADONE HCL	1	0	1	100.00%
METHYLPHENIDATE HYDROCHLORIDE ER	1	1	2	50.00%
MORPHINE SULFATE ER	1	0	1	100.00%
ORENCIA	1	0	1	100.00%
OXYCODONE HCL	1	0	1	100.00%
SABRIL	0	1	1	0.00%
STELARA	1	0	1	100.00%
TOLTERODINE TARTRATE	0	1	1	0.00%
TRAMADOL HCL	5	0	5	100.00%
TRETINOIN MICROSPHERE	1	0	1	100.00%
VIGABATRIN	1	0	1	100.00%
VYVANSE	1	0	1	100.00%
1Q19	46	8	54	

PA Approval Reviews

Approvals: 100%

Drug Class	Approved	Denied	Total	Approval Rate
16 - ANTI-INFECTIVE AGENTS - MISC.*	22	0	22	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	11	0	11	100.00%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	7	0	7	100.00%
36 - ANTIHYPERTENSIVES*	4	0	4	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	4	0	4	100.00%
79 - MINERALS & ELECTROLYTES*	3	0	3	100.00%
25 - CONTRACEPTIVES*	2	0	2	100.00%
82 - HEMATOPOIETIC AGENTS*	2	0	2	100.00%
94 - DIAGNOSTIC PRODUCTS*	2	0	2	100.00%
01 - PENICILLINS*	1	0	1	100.00%
11 - ANTIFUNGALS*	1	0	1	100.00%
20 - ALLERGENIC EXTRACTS/BIOLOGICALS MISC*	1	0	1	100.00%
68 - GOUT AGENTS*	1	0	1	100.00%
99 - MISCELLANEOUS THERAPEUTIC CLASSES*	1	0	1	100.00%

PA rejects for claims dollar exception, quantity level limit (QLL), DAW

Approvals: 96% – 79%

Drug Class	Approved	Denied	Total	Approval Rate
27 - ANTIDIABETICS* (GLP1- Agonists)	72	3	75	96.00%
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	251	19	270	92.96%
66 - ANALGESICS - ANTI-INFLAMMATORY*	39	4	43	90.70%
50 - ANTIEMETICS*	19	2	21	90.48%
83 - ANTICOAGULANTS*	101	11	112	90.18%
58 - ANTIDEPRESSANTS*	191	24	215	88.84%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	29	6	35	82.86%
41 - ANTIHISTAMINES*	14	3	17	82.35%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	177	47	224	79.02%

59: Aristada inj, Abilify inj, aripiprazole or olanzapine or risperidone tab QLL, risperidone ODT
41: Chew or ODT

South Dakota Medicaid

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 1/1/2019 - 3/31/2019				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/ Rx**	**%Total Claims**
SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	11,781	$147,959.99	$12.56	5.67%
MISCELLANEOUS ANTICONVULS	10,498	$1,101,151.72	$104.89	5.05%
AMINOPENICILLIN ANTIBIOTICS	9,795	$143,667.65	$14.67	4.72%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,431	$661,221.38	$78.43	4.06%
ATYPICAL ANTIPSYCHOTICS	7,641	$1,782,053.72	$233.22	3.68%
RESPIRATORY AND CNS STIMULANTS	6,923	$1,022,393.60	$147.68	3.33%
AMPHETAMINES	6,624	$1,114,679.40	$168.28	3.19%
SECOND GENERATION ANTIHIS	6,609	$76,361.06	$11.55	3.18%
OPIATE AGONISTS	6,444	$223,194.54	$34.64	3.10%
ADRENALS	5,988	$556,913.65	$93.00	2.88%
PROTON-PUMP INHIBITORS	5,957	$231,085.57	$38.79	2.87%
NEURAMINIDASE INHIBITORS	4,041	$395,167.92	$97.79	1.95%
THYROID AGENTS	3,777	$73,104.81	$19.36	1.82%
MISC. CENTRAL NERVOUS SYS	3,329	$176,650.32	$53.06	1.60%
MISC. ANXIOLYTICS, SEDATI	3,276	$122,568.72	$37.41	1.58%
TOTAL TOP 15 THERAPEUTIC CLASSES	101,114	$7,828,174.05	$77.42	48.68%

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 1/1/2019 - 3/31/2019				
AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/ Rx**	**%Total Claims**
ATYPICAL ANTIPSYCHOTICS	7,641	$1,782,053.72	$233.22	3.68%
AMPHETAMINES	6,624	$1,114,679.40	$168.28	3.19%
MISCELLANEOUS ANTICONVULS	10,498	$1,101,151.72	$104.89	5.05%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	229	$1,068,466.53	$4,665.79	0.11%
RESPIRATORY AND CNS STIMULANTS	6,923	$1,022,393.60	$147.68	3.33%
ANTINEOPLASTIC AGENTS	344	$747,977.65	$2,174.35	0.17%
SELECTIVE BETA-2-ADRENERGIC AGONISTS	8,431	$661,221.38	$78.43	4.06%
RAPID-ACTING INSULINS	1,233	$619,286.40	$502.26	0.59%
LONG-ACTING INSULINS	1,407	$611,233.10	$434.42	0.68%
ADRENALS	5,988	$556,913.65	$93.00	2.88%
SKIN AND MUCOUS MEMBRANE	420	$488,365.17	$1,162.77	0.20%
NEURAMINIDASE INHIBITORS	4,041	$395,167.92	$97.79	1.95%
CYSTIC FIBROSIS (CFTR) CORRECTORS	19	$391,040.02	$20,581.05	0.01%
HEMOSTATICS	28	$369,306.97	$13,189.53	0.01%
SOMATOTROPIN AGONISTS	93	$341,383.61	$3,670.79	0.04%
TOTAL TOP 15 THERAPEUTIC CLASSES	53,919	$11,270,640.84	$209.03	25.96%

Total Rx Claims from 1/1/2019 - 3/31/2019	207,720

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 1/1/2019 - 3/31/2019					
Drug Brand Name	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/ Rx	%Total Claims
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	7,847	$102,766.76	$13.10	3.78%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	5,100	$779,404.37	$152.82	2.46%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	3,907	$380,646.20	$97.43	1.88%
FLUOXETINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,861	$34,775.93	$9.01	1.86%
SERTRALINE HCL	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	3,704	$43,405.73	$11.72	1.78%
VYVANSE	AMPHETAMINES	3,470	$938,768.78	$270.54	1.67%
LEVOTHYROXINE SODIUM	THYROID AGENTS	3,333	$56,063.22	$16.82	1.60%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	3,195	$45,514.72	$14.25	1.54%
GABAPENTIN	MISCELLANEOUS ANTICONVULS	3,181	$54,980.55	$17.28	1.53%
AZITHROMYCIN	OTHER MACROLIDE ANTIBIOTICS	2,997	$54,874.17	$18.31	1.44%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,980	$155,733.86	$52.26	1.43%
TRAZODONE HYDROCHLORIDE	SEROTONIN MODULATORS	2,979	$29,937.19	$10.05	1.43%
ALBUTEROL SULFATE	SELECTIVE BETA-2-ADRENERGIC AGONISTS	2,931	$59,671.48	$20.36	1.41%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	2,657	$29,912.98	$11.26	1.28%
CETIRIZINE HCL	SECOND GENERATION ANTIHIS	2,393	$25,096.70	$10.49	1.15%
HYDROCODONE/ACETAMINOPHEN	OPIATE AGONISTS	2,247	$33,790.95	$15.04	1.08%
LISINOPRIL	ANGIOTENSIN-CONVERTING EN	2,204	$19,620.66	$8.90	1.06%
ESCITALOPRAM OXALATE	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	2,029	$23,407.00	$11.54	0.98%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	1,993	$21,190.96	$10.63	0.96%
AMOXICILLIN/CLAVULANATE P	AMINOPENICILLIN ANTIBIOTICS	1,945	$39,885.29	$20.51	0.94%
CEFDINIR	3RD GENERATION CEPHALOSPORIN ANTIBIOTICS	1,896	$40,073.27	$21.14	0.91%
GUANFACINE ER	MISC. CENTRAL NERVOUS SYS	1,857	$40,375.77	$21.74	0.89%
LORATADINE	SECOND GENERATION ANTIHIS	1,773	$20,318.14	$11.46	0.85%
ARIPIPRAZOLE	ATYPICAL ANTIPSYCHOTICS	1,739	$38,125.42	$21.92	0.84%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBIT	1,722	$19,501.68	$11.33	0.83%
FLUTICASONE PROPIONATE	CORTICOSTEROIDS	1,633	$25,353.56	$15.53	0.79%
PREDNISONE	ADRENALS	1,631	$16,829.87	$10.32	0.79%
RISPERIDONE	ATYPICAL ANTIPSYCHOTICS	1,569	$19,463.21	$12.40	0.76%
CLONAZEPAM	BENZODIAZEPINES (ANTICONV	1,561	$16,771.94	$10.74	0.75%
CEPHALEXIN	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	1,553	$27,090.67	$17.44	0.75%
COMPOUND	-	1,488	$58,073.67	$39.03	0.72%
CETIRIZINE HYDROCHLORIDE	SECOND GENERATION ANTIHIS	1,437	$15,064.65	$10.48	0.69%
LAMOTRIGINE	MISCELLANEOUS ANTICONVULS	1,372	$17,865.10	$13.02	0.66%
QUETIAPINE FUMARATE	ATYPICAL ANTIPSYCHOTICS	1,368	$18,852.07	$13.78	0.66%
ONDANSETRON ODT	5-HT3 RECEPTOR ANTAGONIST	1,363	$19,881.21	$14.59	0.66%
TRAMADOL HCL	OPIATE AGONISTS	1,339	$14,493.29	$10.82	0.64%
TRIAMCINOLONE ACETONIDE	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRANE)	1,328	$19,605.53	$14.76	0.64%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,265	$89,749.84	$70.95	0.61%
IBUPROFEN	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	1,230	$14,978.80	$12.18	0.59%
MIRTAZAPINE	ANTIDEPRESSANTS, MISCELLANEOUS	1,208	$16,391.38	$13.57	0.58%
CYCLOBENZAPRINE HYDROCHLO	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	1,190	$10,946.70	$9.20	0.57%
TOPIRAMATE	MISCELLANEOUS ANTICONVULS	1,162	$15,202.27	$13.08	0.56%
LEVETIRACETAM	MISCELLANEOUS ANTICONVULS	1,149	$23,255.55	$20.24	0.55%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,137	$130,289.82	$114.59	0.55%
VITAMIN D	VITAMIN D	1,135	$11,255.14	$9.92	0.55%
METFORMIN HYDROCHLORIDE	BIGUANIDES	1,135	$9,790.82	$8.63	0.55%
ALBUTEROL SULFATE HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,112	$49,931.59	$44.90	0.54%
VENTOLIN HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,112	$69,224.61	$62.25	0.54%
OMEPRAZOLE DR	PROTON-PUMP INHIBITORS	1,072	$12,294.28	$11.47	0.52%
PREDNISOLONE SODIUM PHOSP	ADRENALS	1,070	$15,685.80	$14.66	0.52%
TOTAL TOP 50 DRUGS		106,559	$3,826,183.15	$35.91	51.30%

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 1/1/2019 - 3/31/2019					
Drug Brand Name	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/ Rx	%Total Claims
VYVANSE	AMPHETAMINES	3,470	$938,768.78	$270.54	1.67%
METHYLPHENIDATE HYDROCHLO	RESPIRATORY AND CNS STIMULANTS	5,100	$779,404.37	$152.82	2.46%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	68	$447,489.06	$6,580.72	0.03%
INVEGA SUSTENNA	ATYPICAL ANTIPSYCHOTICS	210	$445,887.51	$2,123.27	0.10%
LATUDA	ATYPICAL ANTIPSYCHOTICS	397	$428,533.54	$1,079.43	0.19%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	3,907	$380,646.20	$97.43	1.88%
NOVOLOG FLEXPEN	RAPID-ACTING INSULINS	560	$304,403.70	$543.58	0.27%
ORKAMBI	CYSTIC FIBROSIS (CFTR) CORRECTORS	13	$272,086.49	$20,929.73	0.01%
AFINITOR DISPERZ	ANTINEOPLASTIC AGENTS	8	$254,086.78	$31,760.85	0.00%
LYRICA	MISCELLANEOUS ANTICONVULS	460	$231,963.26	$504.27	0.22%
KALYDECO	CYSTIC FIBROSIS (CFTR) POTENTIATORS	9	$215,117.70	$23,901.97	0.00%
LANTUS SOLOSTAR	LONG-ACTING INSULINS	592	$212,009.22	$358.12	0.28%
STELARA	SKIN AND MUCOUS MEMBRANE	12	$211,737.36	$17,644.78	0.01%
FLOVENT HFA	ADRENALS	872	$198,520.42	$227.66	0.42%
PULMOZYME	MUCOLYTIC AGENTS	55	$195,025.22	$3,545.91	0.03%
ENBREL SURECLICK	DISEASE-MODIFYING ANTIRHEUMATIC	38	$188,048.98	$4,948.66	0.02%
NORDITROPIN FLEXPRO	SOMATOTROPIN AGONISTS	54	$185,641.01	$3,437.80	0.03%
ARISTADA	ATYPICAL ANTIPSYCHOTICS	80	$183,616.38	$2,295.20	0.04%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC	27	$178,091.90	$6,596.00	0.01%
VIMPAT	MISCELLANEOUS ANTICONVULS	205	$168,244.78	$820.71	0.10%
AMPHETAMINE/DEXTROAMPHETA	AMPHETAMINES	2,980	$155,733.86	$52.26	1.43%
VRAYLAR	ATYPICAL ANTIPSYCHOTICS	142	$147,190.27	$1,036.55	0.07%
INGREZZA	-	25	$144,997.63	$5,799.91	0.01%
BANZEL	MISCELLANEOUS ANTICONVULS	73	$134,861.72	$1,847.42	0.04%
LEVEMIR FLEXTOUCH	LONG-ACTING INSULINS	283	$134,400.56	$474.91	0.14%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,137	$130,289.82	$114.59	0.55%
RECOMBINATE	HEMOSTATICS	3	$120,118.80	$40,039.60	0.00%
SYMDEKO	CYSTIC FIBROSIS (CFTR) CORRECTORS	6	$118,953.53	$19,825.59	0.00%
ADVAIR DISKUS	SELECTIVE BETA-2-ADRENERGIC AGONISTS	293	$118,344.58	$403.91	0.14%
TRACLEER	VASODILATING AGENTS (RESPIRATORY TRACT)	12	$117,688.30	$9,807.36	0.01%
INVEGA TRINZA	ATYPICAL ANTIPSYCHOTICS	17	$117,139.88	$6,890.58	0.01%
H.P. ACTHAR	PITUITARY	1	$116,686.50	$116,686.50	0.00%
TRESIBA FLEXTOUCH	LONG-ACTING INSULINS	208	$116,575.99	$560.46	0.10%
JANUVIA	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	278	$116,328.26	$418.45	0.13%
REXULTI	ATYPICAL ANTIPSYCHOTICS	117	$109,742.34	$937.97	0.06%
NOVOLOG	RAPID-ACTING INSULINS	222	$107,983.08	$486.41	0.11%
AMOXICILLIN	AMINOPENICILLIN ANTIBIOTICS	7,847	$102,766.76	$13.10	3.78%
ADVAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	290	$102,497.78	$353.44	0.14%
COSENTYX SENSOREADY PEN	SKIN AND MUCOUS MEMBRANE	18	$102,395.35	$5,688.63	0.01%
XOLAIR	RESPIRATORY TRACT AGENTS, MISC	30	$102,230.14	$3,407.67	0.01%
ADVATE	HEMOSTATICS	7	$101,450.10	$14,492.87	0.00%
IMBRUVICA	ANTINEOPLASTIC AGENTS	8	$99,226.35	$12,403.29	0.00%
CREON	DIGESTANTS	77	$98,437.49	$1,278.41	0.04%
ABILIFY MAINTENA	ATYPICAL ANTIPSYCHOTICS	49	$94,749.83	$1,933.67	0.02%
SYMBICORT	ADRENALS	296	$94,224.29	$318.33	0.14%
NOVOLOG PENFILL	RAPID-ACTING INSULINS	217	$90,180.20	$415.58	0.10%
VICTOZA	INCRETIN MIMETICS	122	$89,838.59	$736.38	0.06%
PROAIR HFA	SELECTIVE BETA-2-ADRENERGIC AGONISTS	1,265	$89,749.84	$70.95	0.61%
SABRIL	MISCELLANEOUS ANTICONVULS	4	$87,712.43	$21,928.11	0.00%
XYNTHA SOLOFUSE	HEMOSTATICS	5	$80,277.00	$16,055.40	0.00%
TOTAL TOP 50 DRUGS		32,169	$9,762,093.93	$303.46	15.49%

Utilization and PA Information

Time frame: 1/1/2019 – 3/31/2019
Red font denotes drug is on Prior Authorization

CGRP Inhibitors (PA)

	4Q 2018				1Q 20109			
Drug Name	**Tota l Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizing Members**
Aimovig	32	$17,502.21	$546.94	18	48	$27,102.51	$564.64	22
Ajovy	4	$2,332.1	$583.03	3	10	$5630.40	$565.35	6
Emgality	0				4	3,350.46	$837.62	3

Orilissa

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Orilissa	3	$2,511.49	$837.16	2	29, 33

*Some states are watching utilization; other states added to PA

Time frame: 1/1/2019 – 3/31/2019

CiproDex

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
CiproDex	329	$72,522.22	$220.43	309	0 – 60

Provider Specialty	Prescriber Count	Utilization	Paid Amount	Member Count	Age Range	Prescriber State	Pharmacy State
Emergency Medicine	2	2	$471.46	2	5, 25	SD	SD
Family Practice	31	25	$6,928.35	31	5-30	Hettinger ND, SD	SD
Family Practice, Adult Med	1	1	$237.38	1	2	SD	SD
Internal Medicine	2	3	$712.14	3	2, 9	SD	SD
Nurse Practitioner	4	7	$1,414.86	6	1-40	SD	SD
Nurse Practitioner, Adult Health	1	2	$454.65	2	17, 39	SD	SD
Nurse Practitioner, Family Health	25	32	$6,916.96	32	0-33	SD	SD
Nurse Practitioner, Pediatric Care	2	5	$1,153.28	5	2-19	SD	SD
Nurse Practitioner, Primary Care	1	2	$474.76	2	2	SD	SD
Orthopedic Surgery	1	1	$237.38	1	1	SD	SD
Otolaryngology	17	71	$14,926.19	69	0-60	Pipestone MN, Omaha NE, SD	Sioux City IA, Ashely ND, SD
Otolaryngology, Otolaryngology/Facial Plastic Surgery	1	23	$4,717.91	23	1-17	SD	SD
Otology & Neurotology	1	1	$237.38	1	14	Omaha, NE	SD
Pediatrics	21	51	$11,084.09	49	1-20	Columbus NE, Raton NM, SD	SD
Physician Assistant	19	34	$7,261.14	29	0-22	SD	SD
Physician Assistant, Medical	5	24	$5,465.09		0-15	SD	SD
Plastic Surgery, Facial	1	2	$457.95	2	1, 15	SD	SD
Pulmonology, Pediatric	1	1	$220.57	1	9	SD	SD
Specialist	1	1	$237.38	1	3	Omaha NE	SD
Student in an Organized Health Care Education/ Training Program/ Student, Health Care	20	35	$8,234.46	35	0-29	Luverne MN, Durham NC, SD	SD

ADD/ADHD Drugs

Summary

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 0-20 years
Amphetamines	5,304	$946,863.89	$178.52	2,003	3-20
Respiratory & CNS Stimulants	6,530	$959,470.53	$146.93	2,384	3-20
Central Alpha-Agonists	111	$13,358.10	$120.34	45	5-20
Misc Central Nervous System	3,079	$120,103.40	$39.01	1,185	4-20
Wakefulness-Promoting Agents	9	$221.32	$24.59	4	15-19

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 21-85 years
Amphetamines	1,320	$167,815.51	$127.13	453	21-64
Respiratory & CNS Stimulants	375	$51,014.42	$136.04	144	21-62
Central Alpha-Agonists	4	$280.52	$70.13	2	28, 32
Misc Central Nervous System	204	$14,567.51	$71.41	78	21-85
Wakefulness-Promoting Agents	65	$13,615.57	$209.47	25	22-64

Amphetamine

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 0-20 years
Amphetamine • Adzenys XR tab/ER susp • Dyanavel XR suspension	10	$2,288.90	$228.89	5	6-11
Amphetamine-dextroamphetamine • Adderall XR cap • amphet/dextr tab • amphet/dextr cap ER • Mydavis	2,160	$119,839.23	$55.48	832	3-20
Dextroamphetamine sulfate • dextroamphetamine tab • dextroamphetamine cap ER	101	$7,118.78	$70.48	42	3-20
Lisdexamfetamine dimesylate • Vyvanse cap • Vyvanse chew	3,033	$817,616.98	$269.57	1,229	4-20

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age 0-20 years
Amphetamine • amphetamine 10mg tab	2	$326.98	$163.49	1	40
Amphetamine-dextroamphetamine • Adderall XR cap • Amphet/dextr tab • Amphet/dextr cap ER • Mydavis	857	$44,081.50	$51.44	288	21-64
Dextroamphetamine sulfate • dextroamphetamine tab • dextroamphetamine cap ER	24	$2,255.23	$93.96	11	26-58
Lisdexamfetamine dimesylate • Vyvanse cap • Vyvanse chew	437	$121,151.80	$227.24	169	21-60

Respiratory & CNS Stimulants

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Caffeine citrate	18	$11,908.65	$661.59	14	0
• Caffeine citrate solution					
Dexmethylphenidate	**1,545**	**$161,018.75**	**$104.22**	**542**	4-20
• dexmethylphenidate tab	274	$11,838.55	$43.21	123	
• dexmethylphenidate cap ER	1,266	$147,231.79	$116.30	494	
• Focalin cap XR	5	$1,948.41	$389.68	3	
Methylphenidate	**58**	**$19,023.25**	**$327.99**	**28**	
• Cotempla tab	22	$8,254.86	$375.22	9	5-12
• Daytrana patch	36	$10,768.39	$299.12	19	6-19
Methylphenidate hcl					
• Aptensio cap XR	10	$2,258.01	$225.80	4	6-8
• Concerta tab	27	$4,035.51	$149.46	12	8-17
• Metadate tab ER 20mg	1	$61.88	$61.88	1	16
• methylphenidate chew	64	$13,334.52		29	3-10
• methylphenidate solution	18	$1,493.55		9	6-14
• methylphenidate cap	453	$43,785.67	$96.66	198	5-20
• methylphenidate cap ER	157	$23,553.91	$150.02	71	5-15
• methylphenidate tab	638	$12,596.94	$19.74	298	3-18
• methylphenidate tab ER	3,427	$636,673.88	$185.78	1,393	3-20
• Quillichew chew ER & susp	129	$40,799.93	$316.28	55	4-13
• Ritalin LA cap	3	$834.73	$278.24	3	8-13

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Caffeine citrate	0				
• Caffeine citrate solution					
Dexmethylphenidate	**31**	**$3,048.52**	**$98.33**	**13**	21-59
• dexmethylphenidate tab	9	$406.80	$45.20	5	
• dexmethylphenidate cap ER	22	$2,641.72	$120.08	8	
Methylphenidate hcl					
• Metadate tab ER 20mg	1	-	-	1	41
• methylphenidate cap	4	$416.46	$104.12	2	21
• methylphenidate cap ER	27	$2,605.70	$96.50	14	21-56
• methylphenidate tab	118	$3,211.95	$27.22	48	21-62
• methylphenidate tab ER	194	$41,731.79	$215.11	75	21-43

Misc Central Nervous System

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Atomoxetine • atomoxetine cap	759	$68,797.62	$90.64	330	5-20
Guanfacine (ADHD) • guanfacine tab ER	2,320	$51,305.42	$22.11	902	4-20

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Atomoxetine • atomoxetine cap • Strattera cap	143	$13,146.27	$91.93	54	21-54
Guanfacine (ADHD) • guanfacine tab ER	59	$1,226.89	$20.79	24	21-85

Central Alpha-Agonists

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Clonidine tab ER (ADHD) • clonidine tab ER	111	$13,358.10	$120.34	45	5-20

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Clonidine hcl (ADHD) • clonidine tab ER	4	$280.52	$70.13	2	28, 32

Wakefulness-Promoting Agents

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Modafinil • modafinil tab	9	$221.32	$36.89	4	15-19

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Modafinil • modafinil tab • Provigil tab	44	$12,678.56	$288.15	17	22-64
Armodafinil • armodafinil tab	21	$937.01	$44.62	8	28-62

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2018*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2019b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2018*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2018*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2019c*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2019d*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- In August of 2018, an extended-release methylphenidate capsule (Jornay PM) was approved by the FDA. In addition, an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) was also approved in late January 2019. Launch dates have not yet been announced for either product.
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	✔
Evekeo ODT (amphetamine sulfate)†	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Adzenys ER (amphetamine ER)	-
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	-
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Aptensio XR (methylphenidate HCl ER)	-
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Jornay PM (methylphenidate HCl ER)†	-
methylphenidate HCl ER (CD)	✔
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

†An extended-release methylphenidate capsule (Jornay PM) and an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) have both been recently approved by the FDA; however, launch dates have not yet been announced for either product.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019, Facts & Comparisons 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Evekeo ODT (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER)
ADHD*		✓	✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.*	✓								✓			✓	✓	
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications							✓			✓				
Narcolepsy**	✓			✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy	✓											✓		

(eg, repeated diets, group programs, and other drugs).†														
Moderate to severe BED in adults											✓			

(*Prescribing Information*: *Adderall 2017*, *Adderall XR 2018*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2017*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2017, Desoxyn 2017, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2016*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2018, Jornay PM 2018, Kapvay 2018, Mydayis 2017, Methylin Oral Solution 2017, methylphenidate chewable tablets 2018, methylphenidate ER 2017, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2017*, *Vyvanse 2018, Zenzedi 2017*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), Methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Evekeo ODT are approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- 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

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, an amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (amphetamine sulfate).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [LS] mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
    - The first study was a 6-week open-label (OL) dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Jornay PM Prescribing Information 2018*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (difference in least squares [LS] mean -5.9; 95% CI, -9.1 to -2.7).

- A randomized, DB, MC, PC, parallel group, forced-dose titration trial conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.

- Mydayis, a new mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (*Mydayis Prescribing Information 2017, Weisler et al 2017*) (see results below in Table 3 below).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared

to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
  - A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
  - A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
    - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
  - A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.
- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2019d*, *AAP 2011).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
  - A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
  - A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.

- A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.

- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2018*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to -0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD-0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD-0.29; 95% CI, -0.54 to -0.05).

- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with

lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).

- A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led CBT, lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.
- A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of cognitive behavioral therapy (CBT) and CBT-guided self-help (moderate quality of evidence), and low quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors, and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2011), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2015) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
  - The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment

- CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
- Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.

o Medications
- Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
- Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.

o Combination psychotherapy and pharmacotherapy
- For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
- Although limited evidence is available, combined treatment is frequently used in clinical practice.

- The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines for medical care of patients with obesity (*Garvey et al 2016*) recommend the following for patients with overweight or obesity who have BED:
  - o Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - o Treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, CBT, and/or psychological interventions
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - ○ Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - ○ Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - ○ Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - ○ Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Evekeo ODT (amphetamine)	4 to 6 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.
Adderall XR	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
(mixed amphetamine salts ER)					capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
				Narcolepsy Daily	
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	*ADHD*: Daily to twice daily *Obesity*: 30 min before each meal	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The liquid should be given 30 to 45 minutes before meals. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products.
Methylphenidate ER	3 to 8 h	Tablets			

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					The ER tablets must be swallowed whole and never crushed or chewed.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	Peak concentration occurs 14 hours after dose with gradual decline thereafter.	Capsules	Oral	Daily in the evening	The capsules may be swallowed whole or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
				hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2015, Pharmacist's Letter 2016, Krull 2019d*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2011*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2019d*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2019*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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Publication Date: March 1, 2019

Criteria Review

Dupixent – diagnosis for moderate to severe asthma – criteria consideration

1. No trial of first line drug(s)

2. Trial and failure of inhaled corticosteroid (ICS) within the last 120 days

3. Trial and failure of ICS AND one of the following controller within the last 120 days
    a. long-acting beta2 agonist (LABA) OR
    b. LABA/ICS combination OR
    c. long-acting muscarinic antagonists (LAMA) OR
    d. leukotriene modifiers (montelukast) OR
    e. theophylline

4. Concurrent use of inhaled corticosteroid and with Dupixent therapy

5. Concurrent use of ICS AND one of the following controller with Dupixent
    a. LABA OR
    b. LABA/ICS combination OR
    c. LAMA OR
    d. leukotriene modifiers OR
    e. theophylline

Actemra – diagnosis of Giant Cell Arteritis

1. Require biopsy or proof of CGA or accept clinical diagnosis?

2. Trial of oral or parenteral corticosteroid within the last 120 days?

3. Rheumatologist consultation

Hepatitis C Utilization

Red font denotes drug is on Prior Authorization

Year 2014

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Olysio	11	$255,698.30	$23,245.30		
Harvoni	2	$65,744.20	$32,872.10		
Sovaldi	56	$1,636,418.26	$26,221.76		
TOTAL	**69**	**$1,957,860.76**	**$28,374.79**		

Year 2015

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Harvoni	22	$721,284.80	$32,785.67		
Sovaldi	18	$555,430.00	$30,857.22		
TOTAL	**40**	**$1,276,714.80**	**$31,917.87**		

Recipients Year 2014-2015: 33

Year 2016

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Epclusa	10	$260,175.80	$26,017.58	4	34-62
Harvoni	7	$168,279.90	$24,039.99	3	55-59
Sovaldi	5	$146,165.50	$29,233.10	2	54, 55
TOTAL	**22**	**$574,621.20**	**$26,119.15**	**9**	

Recipients: 9

Year 2017

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Epclusa	22	$572,409.86	$26,018.63	8	35-62
Harvoni	5	$164,435.50	$32,887.10	2	29, 54
Mavyret	3	$41,345.70	$13,781.90	2	37, 52
TOTAL	**30**	**$788,191.06**	**$26,273.06**	**12**	

Recipients: 12

Year 2018

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Epclusa	20	$500,383.96	$25,019.20	6	45-62
Harvoni	5	$153,890.55	$30,778.11	3	32-58
Mavyret	28	$382,366.14	$13,655.94	12	31-62
Vosevi	3	$74,781.60	$24,927.20	1	38
Total	**56**	**$1,111,422.55**	**$19,846.83**	**22**	

Recipients: 22

January – May 2019

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Epclusa	9	$218,958.15	$24,331.68	5	42-64
sofosbuvir-velpatasvir	5	$40,039.30	$8,007.86	4	30-57
ledipasvir-sofosbuvir	2	$24,021.00	$12,010.50	1	55
Mavyret	8	$103,111.98	$12,888.99	5	27-39
Total	**24**	**$386,130.43**	**$57,239.03**	**15**	

Recipients: 15

Summary

Drug Name	Total Rx	Paid Amount	Paid/Rx	Recipients treated from year 2016 to May 2019
Epclusa	61	$1,551,927.77	$25,441.44	23
sofosbuvir-velpatasvir	5	$40,039.30	$8,007.86	4
Harvoni	41	$1,273,634.95	$31,064.26	8
ledipasvir-sofosbuvir	2	$24,021.00	$12,010.50	1
Mavyret	39	$526,823.82	$13,508.30	19
Olysio	11	$255,698.30	$23,245.30	
Sovaldi	79	$2,338,013.76	$29,595.11	2
Vosevi	3	$74,781.60	$24,927.20	1
TOTAL	**241**	**$6,084,940.50**		**58**

Recipients Year 2014-2015: 33 (drug specific data not available from year 2014 to 2015)

Recipient Year 2016-May 2019: 58

Total Recipients January 2014 to May 2019: 91

Hep C Criteria

PA Requirements for initial treatment:

HEPATITIS C DIRECT-ACTING ANTIVIRAL AGENTS will be considered for coverage under the pharmacy benefit program when the following criteria are met:

1. Patient is 18 years of age or older **AND**

2. One of the following:
2.1 Liver biopsy confirming a Metavir score of F3 or F4, unless medically contraindicated; **OR**
2.2 Fibroscan score of 10 or greater; **OR**
2.3 Serum aspartate aminotransferase (AST)-to-platelet ratio index (APRI) score of 2 or greater; **OR**
2.4 Documentation of severe extrahepatic manifestations of hepatitis C infection
AND

3. Prescribed by or in consultation with one of the following:
- Hepatologist
- Gastroenterologist
- Infectious disease specialist

AND

4. Attestation that patient is drug and alcohol free for the past 6 months **AND**

5. Female patients prescribed ribavirin must have a negative pregnancy test within 30 days prior to initiation of therapy and monthly during treatment

INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is primarily transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2018*).
  - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
  - The CDC estimates that 2.4 million persons in the United States (U.S.) have chronic hepatitis C (CHC).
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant (*CDC 2018*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2015, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
  - Rapid virologic response (RVR): undetectable viral load at week 4
  - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
  - End-of-treatment response (ETR): undetectable viral load at the end of treatment
  - Sustained virologic response (SVR): continued undetectable viral load 12 weeks after the completion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2018*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first DAA-containing regimens were single-ingredient DAAs that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the DAAs, including: Daklinza, Epclusa, Harvoni, Mavyret, Sovaldi, Viekira Pak, Vosevi, and Zepatier.
  - In May 2018, AbbVie announced the discontinuation of Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir). These discontinuations were voluntary, and not due to any safety, efficacy, or quality issues. These products will no longer be available, effective January 1, 2019 (*FDA Drug Shortages 2019*).
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daklinza (daclatasvir)*	--
Epclusa (sofosbuvir/velpatasvir)	✔
Harvoni (ledipasvir/sofosbuvir)	✔
Mavyret (glecaprevir/pibrentasvir)	--
Sovaldi (sofosbuvir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

*As of December 2018, the manufacturer has ceased distribution of 90 mg tablets of Daklinza; distribution of 30 and 60 mg tablets is expected to end as of June 2019 (*FDA Drug Shortages 2019*).

(*Drugs@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Daklinza (daclatasvir)	Epclusa (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/ sofosbuvir)	Mavyret (glecaprevir-pibrentasvir)	Sovaldi* (sofosbuvir)	Viekira Pak (ombitasvir/ paritaprevir/ ritonavir/ dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/ grazoprevir)
Genotype 1	✔	✔	✔	✔	✔	✔	✔	✔
Genotype 2		✔		✔	✔		✔	
Genotype 3	✔	✔		✔	✔		✔	
Genotype 4		✔	✔	✔	✔		✔	✔
Genotype 5		✔	✔	✔			✔	
Genotype 6		✔	✔	✔			✔	

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

† Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

(*Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2018, Sovaldi 2018, Viekira Pak 2018, Vosevi 2017, Zepatier 2018*)

- 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

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in 3 pivotal phase 3 trials.
  - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (*Poordad et al 2016*).

- ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
- ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).

- ALLY-3C was a phase 3, OL, MC, single-arm study that examined the efficacy of daclatasvir plus sofosbuvir plus RBV for 24 weeks in patients (n = 78) with HCV genotype 3 and compensated cirrhosis. SVR12 was achieved in 87% of patients; SVR12 rates were 93% and 79% for treatment-naïve and treatment-experienced patients, respectively (*Poordad et al 2018*).
- ALLY-3+ was a phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa

- The clinical safety and efficacy of Epclusa was evaluated in 4 pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled (PC), MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
  - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
  - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, $p < 0.001$) (*Foster et al 2015*).
  - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).
- A randomized, OL trial conducted in Spain compared 12 weeks of Epclusa to 12 weeks of Epclusa plus RBV in patients (n = 204) with HCV genotype 3 and compensated cirrhosis. SVR12 rates were 91% and 96% in the Epclusa and Epclusa plus RBV groups, respectively (*Esteban et al 2018*).
- A meta-analysis of 6 randomized controlled trials (n = 1427) found that 12 weeks of Epclusa treatment resulted in SVR12 rates of 98.2%, 99.4%, 94.7%, 99.6%, 97.1%, and 98.8% in HCV genotypes 1, 2, 3, 4, 5, and 6, respectively (*Ahmed H et al 2018[a]*).

Harvoni

Adults

- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 3 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 HCV with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).
  - ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
  - ION-4 was an OL, MC trial in 335 patients evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
  - SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
  - Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
  - In an OL, randomized study, Harvoni for 12 weeks was compared to sofosbuvir plus RBV for 24 weeks in a cohort of Egyptian patients (n = 200) with treatment-naïve genotype 4 HCV. SVR12 was higher with Harvoni (99% vs 80% with sofosbuvir plus RBV) (*Ahmed OA et al 2018*). Another OL randomized study in Egyptian patients (n = 255) compared Harvoni and Harvoni plus RBV for 8 or 12 weeks. SVR12 rates were 95% and 90% among patients receiving 8 weeks of Harvoni and Harvoni plus RBV, respectively. The SVR12 rate for patients receiving 12 weeks of Harvoni (with or without RBV) was 98% (*Shiha et al 2018*).
  - ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gane et al 2015*).
  - SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric

- A phase 2, OL, MC study (n = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).
- A phase 2, OL, MC study evaluated the efficacy of Harvoni for 12 weeks (n = 89) in patients aged 6 to 11 years with chronic HCV, primarily genotype 1, infection. Treatment was given for 24 weeks for IFN-experienced patients with HCV genotype 1 and cirrhosis (n = 1); or IFN-experienced with HCV genotype 3 with or without cirrhosis (n = 2). Among patients treated for 12 weeks, SVR12 was achieved in 99% of patients (88/89); the SVR12 rate was 100% (3/3) for patients given Harvoni for 24 weeks. One patient with genotype 1a and cirrhosis who was treatment-naïve experienced virologic relapse 4 weeks after a 12-week course of treatment (*Murray et al 2018*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 5 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7% (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017, Asselah et al 2018[a], Mavyret prescribing information 2018*).
  - ENDURANCE-2 was a randomized, DB, placebo-controlled, MC study assessing the efficacy of Mavyret for 12 weeks in non-cirrhotic patients with genotype 2 HCV (n = 196). The SVR12 rate in the treatment group was 99% (*Asselah et al 2018[a]*).
- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146). (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of Sovaldi plus Daklinza was -1.2% (95% CI, -5.6% to 3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2018, Wyles et al 2017*).
  - A pooled analysis of 5 trials in patients (n = 693) with HCV genotype 3 found that treatment with Mavyret for 8 or 12 weeks achieved SVR12 in 95% of treatment-naïve patients without cirrhosis; treatment-naïve patients with cirrhosis who were treated for 12 weeks had an SVR12 rate of 97%. Treatment-experienced patients without cirrhosis achieved SVR12 rates of 90% and 96% with 12 and 16 weeks of Mavyret treatment, respectively. Treatment-experienced patients with cirrhosis achieved SVR12 rates of 94% with 16 weeks of Mavyret treatment (*Flamm et al 2018*).
- ENDURANCE-5,6 was a single-arm, OL, MC trial examining the efficacy of Mavyret in patients (n = 84) with HCV genotypes 5 and 6. Patients without cirrhosis or with compensated cirrhosis were treated with 8 or 12 weeks of Mavyret, respectively. The overall SVR12 rate was 97.6%, with 95.7% and 98.4% of patients with HCV genotype 5 and 6 infections, respectively, achieving SVR12 (*Asselah et al 2018[b]*).
- EXPEDITION-2 was an OL study in HCV/HIV-1 co-infected patients (n = 153) evaluating Mavyret in HCV genotypes 1 through 6 with or without compensated cirrhosis for 8 or 12 weeks, respectively. Treatment-naïve and treatment-experienced patients were both included. The overall SVR12 rate was 98% (*Rockstroh et al 2018*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up *(Gane et al 2017, Mavyret prescribing information 2018).*

- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2018, Poordad et al 2017*).
  - In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).
- MAGELLAN-2 was an OL trial that included treatment-naïve or treatment-experienced patients (n = 100) with chronic HCV genotype 1 through 6 who had received a liver or kidney transplant. The overall SVR12 was 98% after 12 weeks of therapy (*Reau et al 2018*). In 2018, Mavyret received approval for use in liver and kidney transplant recipients (*Mavyret prescribing information 2018*).
- In a pooled analysis of 9 trials in patients (n = 2041) with HCV genotypes 1 through 6 without cirrhosis, treatment with Mavyret for 8 or 12 weeks resulted in SVR12 rates of 98% and 99%, respectively (*Puoti et al 2018*).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in 6 pivotal phase 3 trials.
  - NEUTRINO was a single-arm, OL study of Sovaldi in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
  - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with Sovaldi plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz et al 2013*).
  - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with Sovaldi and RBV or matching placebos. Rates of SVR at 12 weeks were significantly higher in the Sovaldi treatment group compared to placebo (78 vs 0%, respectively; $p < 0.001$) (*Jacobson et al 2013*).
  - In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with Sovaldi and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
  - The VALENCE trial evaluated Sovaldi in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
  - PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of Sovaldi in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

Pediatric

- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).

Vosevi

- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with

other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 8 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-IV)
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
  - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, DB, PC trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.

- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- The OL TURQUOISE-IV trial (n = 36) enrolled genotype 1b patients in Russia and Belarus with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients received Viekira Pak plus RBV for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Isakov et al 2018*).
- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Zepatier

- The safety and efficacy of Zepatier were evaluated in 7 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a DB, PC, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2015, Brown et al 2018*).
  - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
  - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).
  - C-CORAL was a randomized, DB, PC study evaluating Zepatier for 12 weeks in treatment-naïve patients (n = 489) with genotype 1, 4, or 6 HCV infection. SVR12 was achieved in 94.4% of patients receiving Zepatier. SVR12 rates of 98.2%, 91.9%, and 66.7% were seen in patients with genotype 1b, 1a, and 6 infections, respectively (*Wei et al 2018*).
- A meta-analysis of 8 trials (n = 1297) found an overall SVR rate of 96.6% with Zepatier treatment in patients with genotype 1 HCV (*Ahmed H et al 2018[b]*).
- In a pooled analysis of clinical trial data, treatment-naïve and treatment-experienced patients with genotype 4 HCV infection (n = 155) had SVR12 rates of 96.4% (treatment-naïve) and 88.6% (treatment-experienced) after 12 or 16 weeks of Zepatier with or without RBV (*Asselah et al 2018[c]*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2018*).
  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Viekira Pak is contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:

- Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
- Viekira Pak carries a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.

- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Daklinza in combination with Sovaldi: headache and fatigue
    - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea
    - Epclusa: headache and fatigue
    - Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
    - Harvoni: fatigue, headache, and asthenia
    - Mavyret: headache and fatigue
    - Sovaldi in combination with RBV: fatigue and headache
    - Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
    - Viekira Pak with RBV: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
    - Viekira Pak without RBV: nausea, pruritus, and insomnia
    - Vosevi: headache, fatigue, diarrhea, and nausea
    - Zepatier: fatigue, headache, and nausea.
    - Zepatier with RBV: anemia and headache

- In October 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. This *Boxed Warning* was based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with DAAs. In a few cases, HBV reactivation in patients treated with DAAs resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Daklinza (daclatasvir)	Oral	One tablet once daily (60 mg dose); must be used in combination with Sovaldi	*Recommended dosage modification with CYP3A inhibitors and inducers*: • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily *Duration of therapy:* • 12 to 24 weeks (when used in combination with Sovaldi)
Epclusa (sofosbuvir/velpatasvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD).

Drug	Route	Usual Recommended Frequency	Comments
			Duration of therapy: • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. *Duration of therapy:* • 12 to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Oral	Three tablets daily	• Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B). *Duration of therapy:* • 8 to 16 weeks
Sovaldi (sofosbuvir)	Oral	One tablet once daily; must be used in combination with RBV ± PegIFN or Daklinza	• Safety and efficacy have not been established in patients with severe renal impairment. *Duration of therapy:* • 12 to 24 weeks (when used in combination with Daklinza)
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. • Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). *Duration of therapy:* • 12 weeks
Zepatier (elbasvir/grazoprevir)	Oral	One tablet once daily	• Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. • Contraindicated in patients with moderate hepatic impairment

Drug	Route	Usual Recommended Frequency	Comments
			(Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure. *Duration of therapy:* • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2018*).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2018*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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Publication Date: April 30, 2019

Triptan Utilization

Red font denotes drug is on Prior Authorization

Time frame 10/1/2018 – 3/31/2019

Drug Name	Total Rx	Paid Amount	Paid/Rx	Price per tab or inj	Utilizing Members	Age Range
almotriptan 6.25mg (Axert)	2	$415.00	$207.50	$34	1	32
almotriptan 12.5mg	1	$281.13	$281.13	$23	1	48
*eletriptan 20mg (Relpax)	4	$243.49	~$79.00	$9	2	33-36
*eletriptan 40mg	28	$1,891.60	$67.56	$9	7	29-55
*Relpax 40mg	8	$388.18	$48.52	$9	2	39-43
frovatriptan 2.5mg (Frova)	6	$1,296.71	$216.12	$25	3	28-37
naratriptan 1mg (Amerge)	5	$175.61	$35.12	$4	2	18, 31
naratriptan 2mg	20	$521.77	~$27.46	$3	10	17-62
rizatriptan 10mg (Maxalt)	167	$2,968.13	$17.77	$2	73	12-60
rizatriptan 5mg	17	$305.31	$17.96	$2	13	10-60
**rizatriptan 5mg ODT	17	$302.70	$17.81	$2	14	8-15
**rizatriptan 10mg ODT	23	$457.21	$19.88	$2	11	10-48
sumatriptan 6mg/0.5 inj (Imitrex)	55	$,6825.53	$126.40	$52	10	14-55
sumatriptan 5mg spray	12	$2,891.60	$241.05	$40	7	6-37
sumatriptan 20mg spray	10	$2,329.80	$233.08	$39	5	10-50
sumatriptan 25mg tab	134	$2,119.12	$15.81	$2	78	8-62
sumatriptan 50mg tab	350	$5,662.32	$16.18	$2	173	5-63
sumatriptan 100mg tab	453	$7,006.11	$15.47	$3	182	12-64
*Imitrex 100mg	2	$1,128.58	$564.29	$63	1	57
zolmitriptan 2.5 mg tab (Zomig)	6	$191.77	$31.96	$5	4	15-52
zolmitriptan 5 mg tab	22	$1,229.59	$55.89	$6	9	18-58
**zolmitriptan 5 mg ODT	2	$51.68	~$32.00	$6	1	41
Zomig 2.5mg spray	3	$1,375.65	$458.55	$78	2	27, 31
Zomig 5mg spray	8	$3,749.73	$468.72	$78	6	13-35

*Step Therapy – try generics first

** Silent Auth – difficulty in swallowing

Therapeutic Class Overview
Anti-migraine Agents (triptans)

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype and is associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (Cutrer et al, 2017; Snow et al, 2002; IHS, 2018[a], IHS, 2018[b]).
- The migraine 1-year prevalence rate in Americans is approximately 12% (17% of women and 6% of men) (Cutrer et al, 2017; Lipton et al, 2001).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (FDA Industry Guidance [migraine], 2018; Tfelt-Hansen et al, 2012).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (Clinical Pharmacology, 2018). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2018).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (Bajwa et al, 2018). Some treatment guidelines do not differentiate among various formulations (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the American Academy of Neurology [AAN] and the American Headache Society [AHS], 2013; Snow et al, 2002). Additional key therapies for the treatment of migraines include nonsteroidal anti-inflammatory drugs (NSAIDs), dihydroergotamine (DHE nasal spray or inhaler), and opioid medications; however, some medications are not recommended for regular use (Marmura et al, 2015; Silberstein et al, 2012 [guideline reaffirmed in 2015]; Erratum in Subcommittee of the AAN and the AHS, 2013). For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (Robbins et al, 2016). In pediatric patients, the Child Neurological Society recommends ibuprofen, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (DRUGS@FDA, 2018). Branded products are outlined in Table 1.
- According to DRUGS@FDA, the marketing status of ALSUMA and SUMAVEL DOSEPRO is discontinued; therefore, these products have been removed from the therapeutic class overview (DRUGS@FDA, 2018).
- In October 2017, the FDA announced Teva's voluntary discontinuation of ZECUITY (sumatriptan iontophoretic transdermal system) due to post-marketing reports of application site reactions, including severe redness, cracked skin, blistering/welts, and burns/scars associated with the product (FDA Drug Shortages and Discontinuations, 2017). Therefore, this product has been removed from the therapeutic class overview.

- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMERGE (naratriptan hydrochloride tablet)	various	02/10/1998	✔
AXERT (almotriptan malate tablet)	various	05/07/2001	✔
FROVA (frovatriptan succinate tablet)	various	11/08/2001	✔
IMITREX (sumatriptan tablet, nasal spray, injection)	various	12/28/1992	✔
IMITREX STATDOSE (sumatriptan cartridges for injection)	various	12/23/1996	✔
MAXALT (rizatriptan benzoate tablet)	various	06/29/1998	✔
MAXALT MLT (rizatriptan benzoate orally disintegrating tablet)	various	06/29/1998	✔
ONZETRA XSAIL (sumatriptan nasal powder)	Merck & Co., Inc.	01/27/2016	-
RELPAX (eletriptan hydrobromide tablet)	Pfizer	12/26/2002	✔
TREXIMET (sumatriptan/naproxen sodium tablet)	GlaxoSmithKline	04/15/2008	✔
ZEMBRACE SYMTOUCH (sumatriptan injection)	Nupathe Inc.	01/28/2016	-
ZOMIG (zolmitriptan nasal spray, tablet)	various	09/30/2003	✔ (tablets only)
ZOMIG-ZMT (zolmitriptan orally disintegrating tablet)	various	02/13/2001	✔

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	AMERGE (naratriptan tablet)	AXERT (almotriptan tablet)	FROVA (frovatriptan tablet)	IMITREX (sumatriptan tablets, nasal spray, injection)	IMITREX STATDOSE (sumatriptan cartridges for injection)	MAXALT (rizatriptan tablet)	MAXALT MLT (rizatriptan ODT)	ONZETRA XSAIL (sumatriptan nasal powder)	RELPAX (eletriptan tablet)	ZEMBRACE SYMTOUCH (sumatriptan injection)	ZOMIG (zolmitriptan nasal spray, tablet)	ZOMIG ZMT (zolmitriptan ODT)	TREXIMET (sumatriptan/naproxen tablet)
Acute treatment of migraine with or without aura	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔ ‡	✔	✔
Acute treatment of cluster headache				✔ *	✔								
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔						
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)		✔ §											
Acute treatment of migraine with or without aura (aged ≥ 12 years)											✔ †‡		✔

Abbrv: ODT = orally disintegrating tablet
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
Class Limitations of Use: All agents in class are not intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established.

(Prescribing information: AMERGE, 2016; AXERT, 2017; FROVA, 2018; IMITREX injection, 2018; IMITREX nasal spray, 2017; IMITREX tablets, 2017; MAXALT, 2015; MAXALT MLT, 2015; ONZETRA XSAIL, 2016; RELPAX, 2013; TREXIMET, 2016; ZEMBRACE SYMTOUCH, 2017; ZOMIG nasal spray, 2016; ZOMIG tablets, 2018; ZOMIG ZMT, 2018)

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

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours and sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (Bird et al, 2014; Brandes et al, 2007; Cady et al, 2015; Derry et al, 2012 [a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Law et al, 2016; Oldman et al, 2002; Pascual et al, 2007; Poolsup et al, 2005; Prescribing information: IMITREX, 2018; ZEMBRACE SYMTOUCH, 2017; Richer et al, 2016).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. 5-HT_1 receptor agonists have been evaluated in numerous meta-analyses and comparative trials with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All 5-HT_1 receptor agonists are effective at treating migraines and are well-tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (Derry et al, 2012[a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Oldman et al, 2002; Pascual et al, 2007):
  - o Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-free and headache relief at 2 hours post-dose for oral agents (Oldman et al, 2002); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (Ferrari et al, 2002; Pascual et al, 2007). Naratriptan 2.5 mg has lower efficacy rates of pain-free and headache relief at 2 hours (Pascual et al, 2007) while eletriptan has a lower rate of recurrence (Ferrari et al, 2002).
  - o Subcutaneous sumatriptan is the most effective for migraine treatment but is associated with more adverse events (AEs) relative to the other 5-HT_1 receptor agonist formulations (Oldman et al, 2002; Derry et al, 2012[c]).
  - o Frovatriptan has the least number of head-to-head trials with active comparators. A recent pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group (P<0.001) (Cortelli et al, 2011).
  - o Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (Brandes et al, 2007).
  - o Most 5-HT_1 receptor agonists are well-tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (Ferrari et al, 2002).
- Recent evidence is summarized below:
  - o The newest intranasal sumatriptan formulation, ONZETRA XSAIL, was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines through the TARGET and COMPASS studies. The TARGET study (n=230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs. 45%, respectively; P=0.002). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs. 27%; P=0.03) (Cady et al, 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n=275; 1,531 migraines assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores (P<0.001). At 2 hours, the rates of pain relief (freedom) were comparable (Tepper et al, 2015).
  - o Data to support the approval of ZEMBRACE SYMTOUCH were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (Prescribing Information: ZEMBRACE SYMTOUCH, 2017; IMITREX, 2018).
  - o In a randomized, double-blind, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (ZEMBRACE SYMTOUCH) and 6 mg subcutaneous sumatriptan (SUMAVEL DOSEPRO – now discontinued) were compared in 20 patients with rapidly-escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs

52.6%, respectively; P=0.87). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the the 6-mg dose (1 patient vs 4 patients) (Cady et al, 2017).
  - A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-free after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs. sumatriptan 25 mg), rizatriptan 10 mg (vs. sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs. sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence AEs were found (Derry et al, 2014).
  - A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (Bird et al, 2014).
  - The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. The DB, 4-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours of administration (29.7% vs. 16.6%, respectively; P<0.001). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% more of patients) (Winner et al, 2016).
  - In pediatric patients, 1 Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing pain freedom in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be with higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (Richer et al, 2016).

SAFETY SUMMARY

- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT_1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in asthma, rhinitis, and in those patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID-use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.
- The following warnings and precautions are associated with medications in class:
  - Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vaso-spasm-

related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides. Almotriptan, rizatriptan, and zolmitriptan, have had reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures reported following administration. Sumatriptan/naproxen also has warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema may worsen heart failure or cause hyperkalemia and renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); the potential to mask inflammation and fever; and elevated liver enzymes have been reported with use.
  - Injectable sumatriptan (IMITREX and IMITREX STATDOSE) has a warning for hypersensitivity reactions, including anaphylaxis and angioedema. In addition, the needle shield of the prefilled syringe contains a latex derivative that has the potential to cause allergic reactions in patients sensitive to latex.
  - Zolmitriptan ODTs contain phenylalanine, in which the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - Generally, the most common AEs associated with 5-HT_1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT_1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Oral agents			
AMERGE (naratriptan)	Tablet: 1 mg 2.5 mg	Adult: 1 mg or 2.5 mg orally as a single dose; may repeat administration in 4 hours. Max daily dose: 5 mg.	Safety of treating > 4 migraines in 1 month has not been established.
AXERT (almotriptan)	Tablet: 6.25 mg 12.5 mg	Adult and adolescent (≥12 years): 6.25 mg or 12.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose for adults: 25 mg.	Safety of treating >4 migraines in 1 month has not been established. In adults, 12.5 mg dose is more effective.
FROVA (frovatriptan)	Tablet: 2.5 mg	Adult: 2.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 7.5 mg.	Safety of treating >4 migraines in 1 month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
IMITREX (sumatriptan)	Tablet: 25 mg 50 mg 100 mg	Adult: 25, 50, or 100 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 200 mg.	Safety of treating >4 migraines in 1 month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose.
MAXALT, MAXALT MLT (rizatriptan)	Tablet; Orally disintegrating tablet: 5 mg 10 mg	Adult: 5 mg or 10 mg orally as a single dose. Max daily dose: 30 mg. Pediatric (≥6 years): Weight based dosing of 5 mg for <40 kg and 10 mg for ≥40 kg. May repeat administration in 2 hours in adults and 24 hours in pediatric patients. Dose adjustments are needed for patients taking propranolol concomitantly.	Safety of treating >4 migraines/month in adults or children, and >1 dose within 24 hours in patients 6 to 12 years of age have not been established.
RELPAX (eletriptan)	Tablet: 20 mg 40 mg	Adult: 20 or 40 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 80 mg. Max single dose: 40 mg.	Safety of treating >3 migraines in 1 month has not been established.
TREXIMET (sumatriptan/ naproxen)	Tablet: 10/60 mg 85/500 mg	Adult and adolescent (≥12 years): 1 tablet (85/500 mg for adults and 10/60 mg for adolescents) orally as a single dose. Max daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet in a 24 hour period for adolescents.	Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Orally disintegrating tablet; Tablet: 2.5 mg 5 mg	Adult: starting dose is 1.25 or 2.5 mg dose; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >3 migraines in 1 month has not been established.
Intranasal agents			
IMITREX nasal spray (sumatriptan)	Nasal spray: 5 or 20 mg/actuator unit-of-use inhaler	Adult: 5, 10, or 20 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 40 mg. Max single dose: 20 mg.	Safety of treating >4 migraines in 1 month has not been established.
ONZETRA XSAIL (sumatriptan)	Nasal powder: 2 breath-powered delivery systems containing 11 mg sumatriptan per each nosepiece	Adult: 22 mg (2 nosepieces) administered using the breath-powered delivery device; may repeat administration in 2 hours. Max daily dose: 2 doses (44 mg/4 nosepieces).	Safety of treating >4 migraines in 1 month has not been established. Breath-powered powder delivery requiring a forceful blow into each nostril.
ZOMIG (zolmitriptan)	Nasal spray: 2.5 or 5 mg/spray single-use nasal spray units	Adult and adolescent (≥12 years): 2.5 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >4 migraines in 1 month has not been established.
Subcutaneous agents			
IMITREX (sumatriptan)	Subcutaneous injection: 6 mg single dose vial	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg,	Administer the needle only to the skin; intramuscular

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
		particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	(IM) or intravascular (IV) delivery should be avoided.
IMITREX STATDOSE (sumatriptan)	Subcutaneous injection: 4 and 6 mg single dose, prefilled cartridges for pen use	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided.
ZEMBRACE SYMTOUCH (sumatriptan)	Subcutaneous injection: 3 mg single dose, prefilled autoinjector	Adult: 3 mg injected subcutaneously; each dose should be separated by at least 1 hour. May administer up to 4 times per day. Max daily dose: 12 mg. Max single dose: 3 mg.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided. Administer dose to the upper arm or thigh. May be administered at least 1 hour following a dose of another sumatriptan agent.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
AXERT (almotriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	For CrCL ≤30 mL/minute, an initial dose of 6.25 mg and a max dose of 12.5 mg/day are recommended.	Dosage adjustment required for moderate to severe impairment, reduce dose to 6.25 mg and a max dose of 12.5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
RELPAX (eletriptan)	No overall difference in safety or efficacy between elderly and younger patients. BP was increased to a greater extent in elderly patients. Additionally, a statistically	Safety and efficacy have not been established.	No significant change in clearance for patients with mild, moderate, or severe impairment; although, BP elevations were observed in this population. No	Use in severe impairment is not recommended.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Drug would not be expected to cause any adverse effects in breastfed infants,

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	significant increased half-life (from 4.4 hours to 5.7 hours) was observed between elderly and younger patients. No dose adjustments are recommended.		dosage adjustment required.		especially if the infant is >2 months; use with caution.
FROVA (frovatriptan)	Mean blood concentrations were 1.5 to 2 times higher in elderly patients versus younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No dosage adjustment is required.	An estimated 2-fold increase in AUC is predicted with severe impairment; use with caution. No dosage adjustment is required for mild to moderate impairment.	†Unclassified There are no adequate data on the developmental risk associated with the use of frovatriptan in pregnant women. Several studies have suggested women with migraine may be at increased risk of preeclampsia. Use with caution. Unknown whether excreted in breast milk; use with caution.
AMERGE (naratriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (CrCL ≤15 mL/min) is contraindicated.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (Child-Pugh C) is contraindicated.	†Unclassified Several studies have suggested women with migraine may be at increased risk of preeclampsia. Post-marketing reports of naratriptan included mainly first trimester exposures. The incidence of major birth defects with naratriptan was similar to the incidence of the general US population (2.2% vs. 2.2 to 2.9%, respectively). Use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown whether excreted in breast milk; use with caution.
MAXALT, MAXALT MLT (rizatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <6 years of age.	No dosage adjustment is required.	Drug plasma concentrations are 30% greater with moderate impairment. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, ZEMBRACE SYMTOUCH (sumatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	Not studied.	The maximum single oral dose should not exceed 50 mg. Use of IMITREX, IMITREX STATDOSE, ONZETRA XSAIL, and ZEMBRACE SYMTOUCH in severe impairment is contraindicated.	Pregnancy Category C* (ONZENTRA XSAIL, ZEMBRACE SYMTOUCH) †Unclassified (IMITREX, IMITREX STATDOSE) Overall, data from a pregnancy exposure registry have not detected an increased frequency of birth defects or a consistent pattern of birth defects associated with sumatriptan exposure during pregnancy. Several studies have suggested women with migraine may be at increased risk of preeclampsia. A registry study reported a 4.2% occurrence of major birth defects during first-trimester exposure and during any trimester of exposure which is numerically higher than the 2.2% to 2.9% rate of major birth defects among deliveries to women with migraine. ALL FORMULATIONS: Excreted in breast milk after subcutaneous administration. Unknown excretion after oral administration. Withhold breastfeeding for 12 hours after oral, nasal, or subcutaneous administration to

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					minimize infant exposure.
TREXIMET (sumatriptan/ naproxen)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	No renal dosage adjustment required for mild to moderate impairment. Not recommended for severe impairment (CrCL ≤30 mL/min). Renal effects of the drug may hasten progression of renal dysfunction in pre-existing renal disease.	Administer 1 10/60 mg tablet in a 24 hour period for mild to moderate impairment. Use in severe impairment is contraindicated.	Pregnancy Category C during the first 2 trimesters; Pregnancy Category X during the third trimester* Both agents are excreted in breast milk. Limited information indicates that levels are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant; use with caution.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established for the nasal spray in children <12 years of age and <18 years of age for oral formulations.	Clearance was reduced by 25% in patients with severe impairment (CrCL ≤25 mL/min); no significant change in clearance was observed in moderate impairment (CrCL 26 to 50 mL/min). No dosage adjustment required.	Dosage adjustment required for moderate to severe impairment, reduce dose to 1.25 mg and a max dose of 5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Abbrv: AAP = American Academy of Pediatrics; AUC = area under the curve; BP = blood pressure; CrCL = creatinine clearance; CV = cardiovascular; ODT = orally disintegrating tablet

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

(American Academy of Pediatrics, 2001; LactMed, 2018)

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2018; Clinical Pharmacology, 2018).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/nonsteroidal anti-inflammatory combination product (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet) and zolmitriptan (nasal spray, orally disintegrating tablet, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (Francis et al, 2010). Almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen and zolmitriptan are available generically in at least 1 dosage form or strength (DRUGS@FDA, 2018).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of ZEMBRACE SYMTOUCH) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and –dynamic data, subcutaneous and intranasal formulations generally have a quicker onset of action and subcutaneous formulations generally have a lower NNT but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of placebo-controlled trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- According to the AAN, American College of Physicians-American Society of Internal Medicine, and U.S. Headache Consortium, 5-HT_1 receptor agonists are clinically interchangeable for the treatment of migraines. These guidelines do not provide a recommendation for the use of 1 agent over another. In addition, non-oral formulations provide relief for patients unable to swallow due to symptoms of nausea and vomiting (Evers et al, 2009; Francis et al, 2010; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 (guideline reaffirmed in 2015); Erratum in Subcommittee of the AAN and the AHS, 2013; Snow et al, 2002). According to the 2015 AHS evidence

assessment, triptans (regardless of formulation) and DHE (nasal spray or inhaler) have been established to be effective treatments for acute migraines in adults. Reaffirming the AAN migraine guidelines, the recommendation remains that clinicians should consider medication efficacy and potential AEs when prescribing acute medications for migraine. Opioid medications are probably effective; however, they are not recommended for regular use (Marmura et al, 2015). For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (Francis et al, 2010; Robbins et al, 2016). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (Robbins et al, 2016). In pediatric patients, older guidelines published by the Child Neurological Society recommend ibuprofen as first-line therapy for the treatment of migraines, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.

- All 5-HT_1 receptor agonists are generally effective for the acute treatment of migraine attacks and are well-tolerated with a similar safety profile. Although some 5-HT_1 receptor agonists have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, the clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injection treatments have been associated with the fastest onset of action; therefore, are amenable to quick relief. However, injectable triptans are associated with more AE compared to oral or topical dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient needs, response, and preference, migraine severity, and tolerability.

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Publication date: January 4, 2019

Opioid Update

	Number of Unique Utilizing Members	Total # Opioid Rxs	Avg Days Supply (Total Days Supply/ Total Rxs)	Avg fill quantity (Total Quantity/ Total Rxs)	Total # Rxs	% of Opioid Rxs (Total Opioid Rxs/Total Rxs)	Clinical Edits
Jan-18	2,065	3,149	15.31	67.34	74,581	4.22%	
Feb-18	1,944	2,745	15.45	68.64	67,030	4.10%	
Mar-18	2,075	3,060	15.28	67.36	71,322	4.29%	
Apr-18	1,960	2,837	15.09	67.25	67,217	4.22%	
May-18	1,987	2,943	15.19	68.84	69,310	4.25%	
Jun-18	1,916	2,740	14.17	62.48	62,761	4.37%	Decrease refill threshold
Jul-18	1,878	2,732	15.09	64.52	63,910	4.27%	
Aug-18	1,882	2,536	15.19	64.94	68,156	3.72%	Opioid Naïve & LAO-SAO
Sep-18	1,719	2,282	15.24	63.38	64,471	3.54%	
Oct-18	1,754	2,405	14.98	62.45	71,559	3.36%	MED 300
Nov-18	1,684	2,277	15.60	65.35	67,871	3.35%	MED 270
Dec-18	1,628	2,173	15.48	66.15	64,196	3.38%	MED 240
Jan-19	1,695	2,343	15.23	61.86	72,293	3.24%	MED 220
Feb-19	1,615	2,172	14.81	60.10	67,280	3.23%	MED 200
Mar-19	1,682	2,284	15.18	61.90	68,149	3.35%	MED 180

MME/Day	< 90	90–179	180-240	>240
January 2018	1,677	186	68	92
February 2018	1,592	195	58	64
March 2018	1,707	188	64	73
April 2018	1,606	196	52	62
May 2018	1,615	214	50	63
June 2018	1,592	163	48	62
July 2018	1,543	181	48	56
August 2018	1,598	138	34	55
September 2018	1,447	138	36	44
October 2018	1,483	137	32	50
November 2018	1,423	134	28	43
December 2018	1,375	125	30	44
January 2019	1,421	126	42	41
February 2019	1,355	122	28	39
March 2019	1,416	126	30	37

SDM_1Q18

Dec 17 to Mar 18

Opioid Utilization Snapshot

Opioid Claims

11,283

5.1% prescription claims filled for an opioid

0.3% higher than Med D benchmark

Utilizers

3,835

37.6% are high utilizers[1]

3.4% lower than high utilizers Med D benchmark

Short acting opioids **64.7%** of opioid Rxs

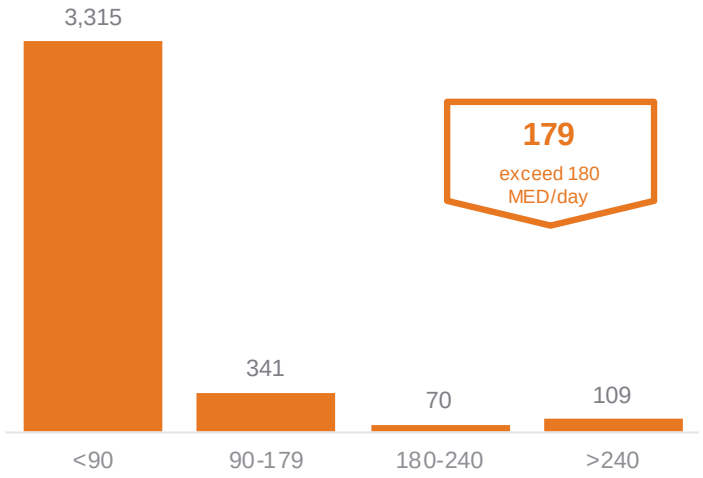
MAT[2] **223** of opioid Rxs

Rescue Therapy[3] 9 Rx(s)

CDC Guidelines advise prescribers to manage pain with lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day

Utilizers by Cumulative MED[4]

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



[1]Defined as 3+ opioid scripts within 120 days period; [2] **MAT** - Medication Assisted Therapy (e.g., buprenorphine, etc..); [3] **Overdose Rescue Therapy** – opioid overdose reversal with Narcan (naloxone), etc. [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

SDM_1Q18

Dec 17 to Mar 18

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy

137

opioid utilizing members with 3+ pharmacies

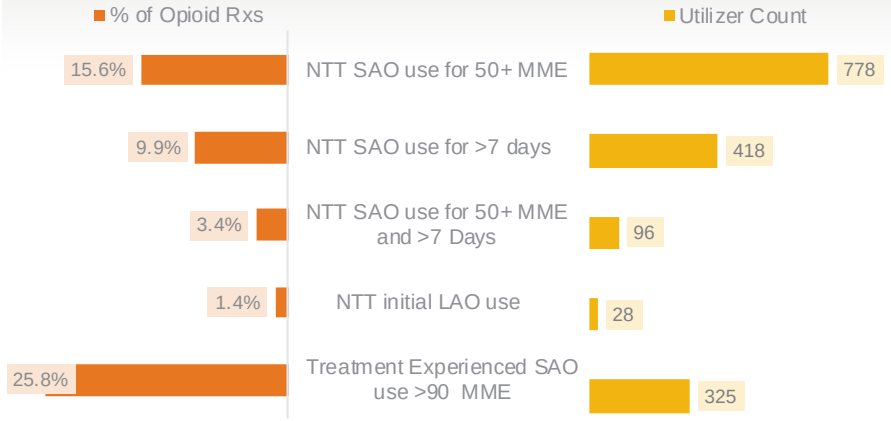
Shoppers: Poly Prescriber

399

opioid utilizing members with 3+ prescribers

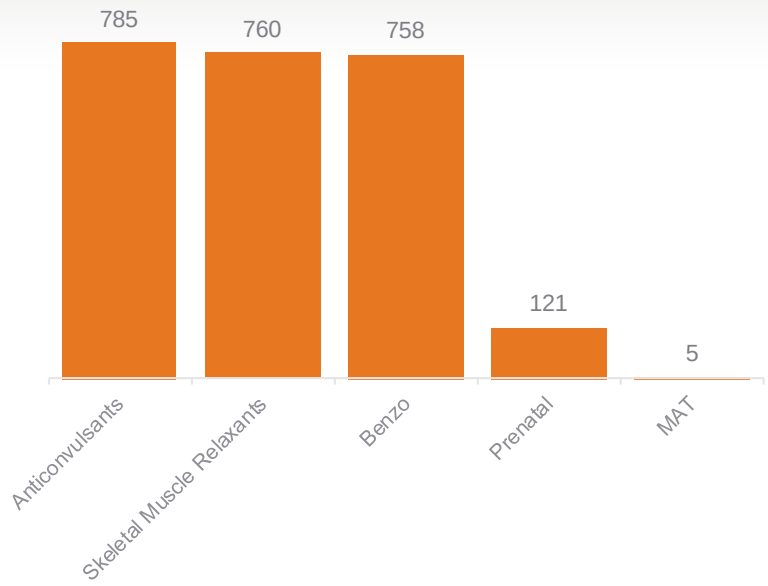
22.7%
of all Opioid Rxs

Non-Compliance to CDC Guidelines[7] for Opioid Prescriptions (NTT[8] and Chronic)



A retrospective review of claims indicates that **1,116 utilizing members** during this timeframe would have hit our opioid fill UM sif program was implemented.

Utilizers with Opioid Medication Combinations[9]



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[7]JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464; [8]NTT – New To Therapy SAO – Short Acting Opioid; LAO – Long Acting Opioid;
[9]Anticonvulsants - gabapentin, pregabalin, anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

SDM_1Q19

Dec 18 to Mar 19

Opioid Utilization Snapshot

Opioid Claims

8,447

3.9% prescription claims filled for an opioid

0.5% lower than Med D benchmark

Utilizers

3,253

33.6% are high utilizers[1]

10.3% lower than high utilizers Med D benchmark

Short acting opioids **63.4%** of opioid Rxs

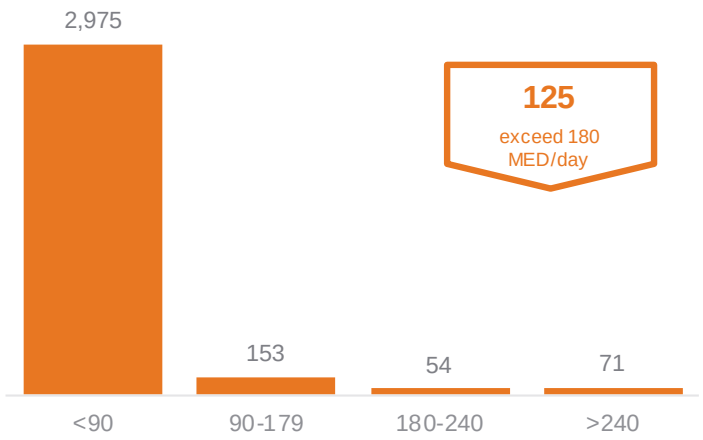
MAT[2] **436** of opioid Rxs

Rescue Therapy[3] 15 Rx(s)

CDC Guidelines advise prescribers to manage pain with lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day

Utilizers by Cumulative MED[4]

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



[1]Defined as 3+ opioid scripts within 120 days period; [2] **MAT** - Medication Assisted Therapy (e.g., buprenorphine, etc..); [3] **Overdose Rescue Therapy** – opioid overdose reversal with Narcan (naloxone), etc. [4]**MED** – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; [5]JAMA. 2016 Apr 19;315(15):1624-45. [6]MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

SDM_1Q19

Dec 18 to Mar 19

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy

56

opioid utilizing members with 3+ pharmacies

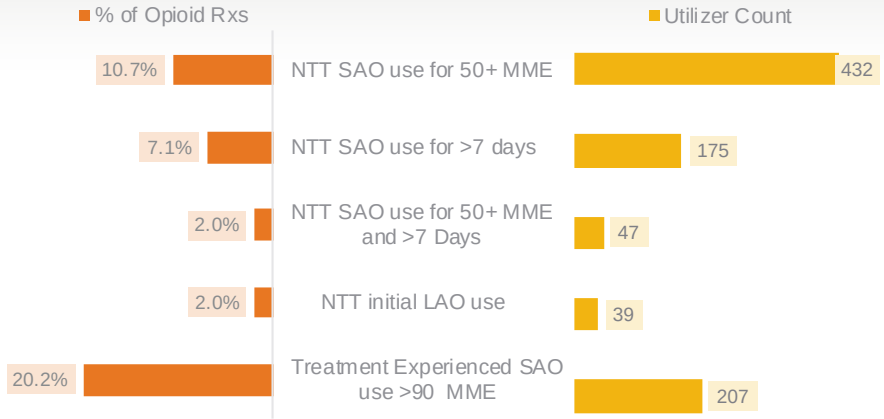
Shoppers: Poly Prescriber

169

opioid utilizing members with 3+ prescribers

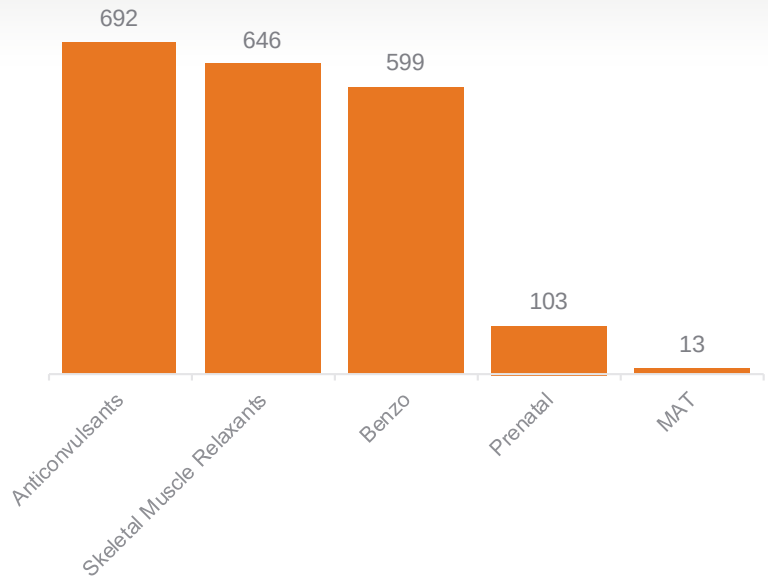
17.0%
of all Opioid Rxs

Non-Compliance to CDC Guidelines[7] for Opioid Prescriptions (NTT[8] and Chronic)



A retrospective review of claims indicates that **583 utilizing members** during this timeframe would have hit our opioid fill UM sif program was implemented.

Utilizers with Opioid Medication Combinations[9]



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[7] JAMA. 2016 Apr 19;315(15):1624-45. doi: 10.1001/jama.2016.1464; [8] NTT – New To Therapy SAO – Short Acting Opioid; LAO – Long Acting Opioid;
[9] Anticonvulsants - gabapentin, pregabalin, anticonvulsant benzodiazepines (clobazam, clonazepam, diazepam)

Field Definitions

Dashboard is based on the 120 days of most recent history claims.

Opioid Utilization Snapshot

Opioid claims – total number of opioid claims identified within most recent 120 days claims history
% of Opioid claims - % of opioid claims out of total claims with the period
Benchmark % (claims)- indicates percent difference of your prescription claims filled for an opioid in comparison to segment benchmark
% of Short Acting Opioids – percent of SAO scripts out of total opioid scripts
MAT Rxs – a number of Medication Assisted Therapy (e.g., buprenorphine, etc.) scripts out of total opioid scripts
Rescue Therapy – a number of Rxs for opioid overdose reversal with Narcan (naloxone), etc
Utilizer count – total number of utilizers with opioid Rxs within the period
% of high utilizers - % of utilizers with 3+ opioid scripts within 120 days period
Benchmark % (utilizers)- indicates percent difference of your opioid utilizers in comparison to segment benchmark
Utilizers by Cumulative MED (graph) - Morphine Equivalent Dose is relative potency of an opioid to standard of morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period; **[Total call out]** is a sum of utilizers with 180+ MED.
MME – Morphine Milligram Equivalent represents a relative potency of an opioid to a morphine dose.

Opioid Utilization Opportunity Assessment

Shoppers: Poly Pharmacy – a number of opioid utilizing members with 3 or more pharmacies
Shoppers: Poly Prescriber – a number of opioid utilizing members with 3 or more prescribers
Non-Compliance to CDC Guidelines for Opioid Prescriptions (NTT and Chronic) (graph) – depicts a number of members and % opioid Rxs for New To Therapy (NTT) and chronic opioid use for each of the defined categories; **%Total** – indicates total percent of opioid scripts for the categories.
Retrospective members (call out) - a retrospective review of claims indicating the number members that would have hit Orx opioid fill UMs if program was implemented during the reporting time period.
Opioid Medication Combinations of High-Risk (graph) – depicts a number of opioid utilizers for each opioid/drug type combination.