South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

December 11, 2020

South Dakota
Department of
Social Services

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South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

December 11, 2020
1:00 – 3:00 PM

Meeting Link: https://optum.webex.com
Meeting Number (access code): 178 866 0132
Meeting Password: HtNMy7Rp?45

Tap to join from a mobile device (attendees only)
+1-763-957-6300,,1788660132## US/Canada (Preferred)

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Join from a video system or application
Dial 1788660132@optum.webex.com
You can also dial 173.243.2.68 and enter your meeting number.

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Call to order

Approval of previous meeting minutes

PA update

Review of top 15 therapeutic categories/top 50 drugs

Old business
- **90-Day Fill update**
- **Nayzilam & Valtoco utilization**
- **Humira CF PA**
- **Atypical Antipsychotic utilization in children**
- **Reyvow, Ubrelvy, & Nurtec ODT fax form**
- **Opioid update**

New business
- **Antidiabetics PA approval review**
- **Ulcer drugs PA approval review**
- **Accumulation edit**
- **ADHD utilization**
- **Orkambi PA review**
- **Evrysdi**

Public input accepted after individual topic discussion
Next meeting date January 2020 & adjournment

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

Friday, September 18, 2020
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Darger called the meeting to order at 1:14 PM. The minutes of the June meeting were presented. Holland made a motion to approve. Oehlke seconded the motion. The motion was unanimously approved via roll call vote.

Synder updated the committee on DSS staff. Sarah Akers left DSS. Matthew Ballard is the new Deputy Division Director of Medical Services. In addition, the hepatitis C criteria will be expanding to F2 score effective 1/1/2021.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from April 1, 2020 to June 30, 2020. A total of 1,358 PAs were reviewed of which 147 requests (11%) were received via telephone and 807 requests (59%) were received via fax, and 404 (30%) were reviewed via electronically. This was a 23% decrease of PAs received from the previous quarter.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from April 1, 2020 to June 30, 2020. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, amphetamines, anticonvulsants, and cystic fibrosis correctors. The top 15 therapeutic classes make up 24.88% of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 10.8% of total claims. New utilization for Uptravi was noted on the top 50 drugs based on amount paid.

Old Business

CGRP & Orilissa utilization

The committee reviewed the calcitonin gene related peptide (CGRP) and triptan utilization comparing 1Q20 through 2Q20. The committee also reviewed utilization of Orilissa and Oriahnn comparing 1Q20 through 2Q20. Committee commented observing appropriate utilization. Committee decided to not monitor quarterly but if spikes in utilization occur to bring them back for further review. Ladwig was satisfied with number of members utilizing Epidiolex.

Atypical antipsychotic utilization in children
Committee reviewed atypical antipsychotic utilization in children 17 years old and under. As part of the review, Stanley had spoken to hospitalists in child and adolescent specialties as reference points since these physicians see many children with the majority being critical cases. They commented regarding the 17% of children taking multiple products. Stanley also provided insight on treatment for autistic spectrum disorder and dementia where there is not a standard approach that works every time. Jockheck suggested eliminating the two drug criteria and have the option of using two drugs through an appeal process in the PA criteria. Stanley inquired of the 17% utilizers how many were seen by psychiatrists? He requested diagnosis information for the next meeting. In addition, the use of ADHD medications was also briefly discussed. Darger and Stanley will review how other Medicaid states are handling criteria.

Review of Reyvow & Ubrelvy fax form
Ladwig made a motion to table this review until the next meeting. Stanley seconded the motion. Roll call vote was passed unanimously.

Opioid update
The committee reviewed 2Q20 opioid outcomes compared to previous quarters from the opioid initiatives. Utilization trends downward. Ladwig inquired for poly pharmacy information if pharmacy counted as each pharmacy or each chain. Jockheck confirmed for each pharmacy.

New Committee Member
Darger warmly welcomed new committee member, Dr. Heather Preuss, a provider in Hot Springs. Jockheck also expressed his thanks and welcomed Dr. Preuss. Preuss expressed her wish to observe and learn.

New Business
Humira CF utilization
Darger had requested to compare Humira and Humira citrate free (CF) at the last meeting. Jockheck confirmed favorable savings for Humira compared to the new formulation of Humira CF. Darger expressed there is no difference in therapy except Humira CF doesn't sting as bad as the citrate version. Committee discussed using Humira citrate version before allowing Humira CF. Jenna Gianninoto from AbbVie was available for any questions from the committee. Ladwig motioned to bring proposed PA criteria to the next meeting. Holland seconded the motion. The motion was unanimously approved via roll call vote.

Nurtec ODT
Nurtec ODT clinical information was presented for review. Chelsea Leroue from Biohaven provided public comment on Nurtec ODT. Committee discussed adding Nurtec ODT to the current PA for Reyvow and Ubrelvy. Oehlke made the motion and Van Gilder seconded the motion. The motion was unanimously approved via roll call vote.

Palforzia
Palforzia clinical information was presented for review. Shannon Payne from Aimmune provided public comment on Palforiza. Darger reiterated the stringent REMS on Palforzia. Holland recommended monitoring it.

Nayzilam & Valtoco
Clinical information on Nayzilam and Valtoco were presented for review. Cindy Hartford from Neuretis provided public comment on Valtoco. Preuss cited main concern would be abuse potential. Stanley inquired about the number of doses in each nasal spray. Hartford replied a single dose in each nasal spray. Ladwig suggested watching utilization. Utilization data will be provided for Nayzilam, Valtoco and the diazepam rectal gels.

Adjournment

Snyder inquired about using zoom or another video conference call application for the next meeting. Darger expressed his favor and committee agreed. The next meeting is scheduled for December 11, 2020. The March meeting is tentatively scheduled on March 5, 2021. Ladwig made a motion to adjourn the meeting and Preuss seconded the motion. The motion passed unanimously by everyone leaving, and the meeting adjourned 2:35 PM.

PA Report
7/1/2020 – 9/30/2020

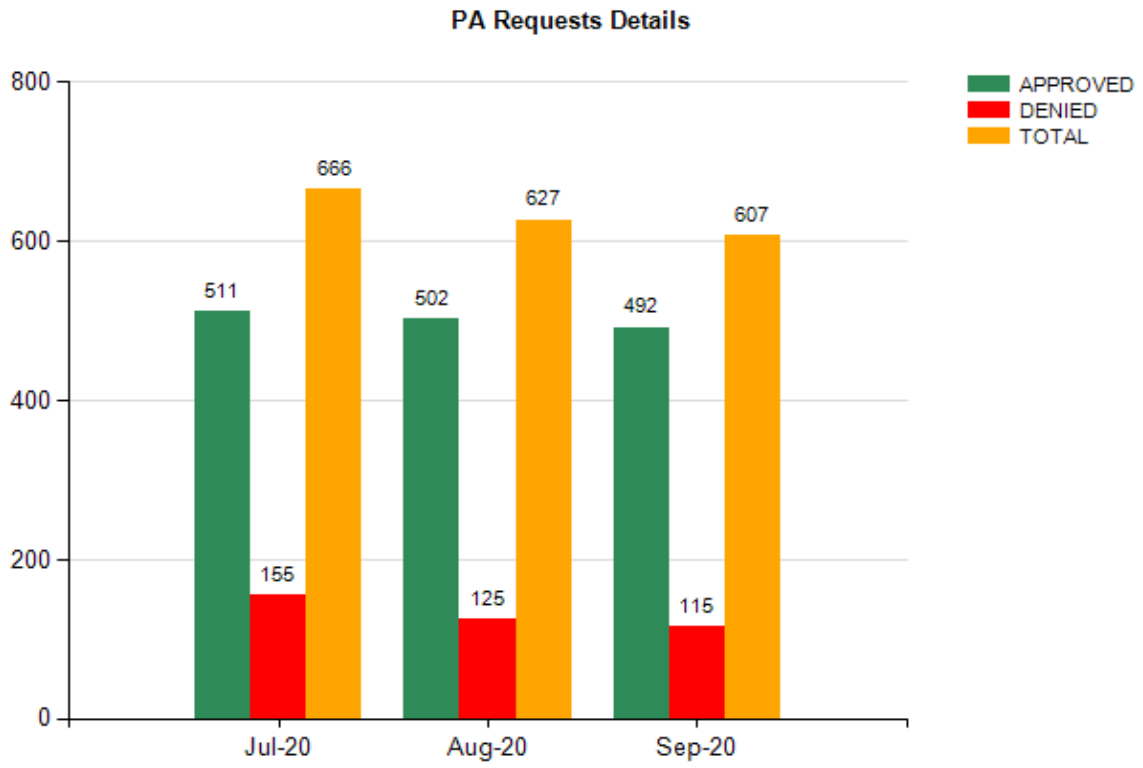
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 Hrs Urgent - 24 Hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
STANDARD	1,846	1,846	0	100.00%	0.00%
URGENT	54	54	0	100.00%	0.00%
GRAND TOTAL	**1,900**	**1,900**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
TOTAL	**1,900**	**178**	**9.4%**	**1,051**	**55.3%**	**671**	**35.3%**

PA Initial Requests Summary

Month	Approved	Denied	Total
July-20	511	155	666
August-20	502	125	627
September-20	492	115	607
3Q20	**1,505**	**395**	**1,900**
Percent of Total	**79.21%**	**20.79%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTICS/ANTIMANIC	279	21	300	93.00%	15.79%	, RISPERIDONE
58 - ANTIDEPRESSANTS	205	36	241	85.06%	12.68%	, DULOXETINE HYDROCHLORIDE
65 - ANALGESICS - OPIOID	128	74	202	63.37%	10.63%	HYDROCODONE/APAP, TRAMADOL HCL
90 - DERMATOLOGICALS	106	79	185	57.30%	9.74%	MALATHION, CLINDAMYCIN/BP
49 - ULCER/ANTISPASMODICS/ ANTICHOLINERGICS	136	26	162	83.95%	8.53%	ESOMEPRAZOLE MAGNESIUM,
Others -	651	159	810	80.37%	42.63%	
	279	21	300	93.00%	15.79%	
3Q20	**1,505**	**395**	**1,900**	**79.21%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	279	21	300	93.00%
58 - ANTIDEPRESSANTS*	205	36	241	85.06%
27 - ANTIDIABETICS*	141	5	146	96.58%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	136	26	162	83.95%
65 - ANALGESICS - OPIOID*	128	74	202	63.37%
90 - DERMATOLOGICALS*	106	79	185	57.30%
72 - ANTICONVULSANTS*	97	29	126	76.98%
52 - GASTROINTESTINAL AGENTS - MISC.*	63	7	70	90.00%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	61	14	75	81.33%
54 - URINARY ANTISPASMODICS*	43	10	53	81.13%
66 - ANALGESICS - ANTI-INFLAMMATORY*	38	4	42	90.48%
41 - ANTIHISTAMINES*	29	5	34	85.29%
16 - ANTI-INFECTIVE AGENTS - MISC.*	23	7	30	76.67%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	23	1	24	95.83%
67 - MIGRAINE PRODUCTS*	20	27	47	42.55%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	16	10	26	61.54%
50 - ANTIEMETICS*	15	2	17	88.24%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	11	4	15	73.33%
39 - ANTIHYPERLIPIDEMICS*	9	5	14	64.29%
75 - MUSCULOSKELETAL THERAPY AGENTS*	9	2	11	81.82%
83 - ANTICOAGULANTS*	9	1	10	90.00%
33 - BETA BLOCKERS*	7	1	8	87.50%
34 - CALCIUM CHANNEL BLOCKERS*	6	0	6	100.00%
45 - RESPIRATORY AGENTS - MISC.*	5	0	5	100.00%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	4	1	5	80.00%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	4	1	5	80.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	3	1	4	75.00%
02 - CEPHALOSPORINS*	2	1	3	66.67%
12 - ANTIVIRALS*	2	9	11	18.18%
00 - COMPOUND & MISCELLANEOUS	1	0	1	100.00%
07 - AMINOGLYCOSIDES*	1	0	1	100.00%
19 - PASSIVE IMMUNIZING AND TREATMENT AGENTS*	1	0	1	100.00%
22 - CORTICOSTEROIDS*	1	0	1	100.00%
32 - ANTIANGINAL AGENTS*	1	1	2	50.00%
3Q20	**1,505**	**395**	**1,900**	
Percent of Total	**79.2%**	**20.8%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
July-20	26	74.29%	9	25.71%	35
August-20	8	61.54%	5	38.46%	13
Seotember-20	12	92.31%	1	7.69%	13
3Q20	46	75.41%	15	24.59%	61

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
PREGABALIN	6	0	6	100.00%
AIMOVIG	4	0	4	100.00%
FLUOXETINE HYDROCHLORIDE	3	0	3	100.00%
NORDITROPIN FLEXPRO	2	0	2	100.00%
OXYCODONE/ACETAMINOPHEN	2	0	2	100.00%
STELARA	2	1	3	66.67%
XIFAXAN	2	1	3	66.67%
AJOVY	1	0	1	100.00%
AMITIZA	1	0	1	100.00%
AMPHETAMINE/DEXTROAMPHETAMINE	1	0	1	100.00%
ARIPIPRAZOLE	1	0	1	100.00%
BELBUCA	1	0	1	100.00%
CEPHALEXIN	1	0	1	100.00%
CLINDAMYCIN PHOSPHATE/BENZOYL PEROXIDE	1	0	1	100.00%
DESVENLAFAXINE ER	1	2	3	33.33%
DULOXETINE HYDROCHLORIDE	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
ENOXAPARIN SODIUM	1	0	1	100.00%
EPCLUSA	1	2	3	33.33%
EPIDIOLEX	1	0	1	100.00%
ESOMEPRAZOLE MAGNESIUM	1	0	1	100.00%
FENTANYL	1	0	1	100.00%
GATTEX	1	0	1	100.00%
GEODON	1	0	1	100.00%
INTUNIV	1	0	1	100.00%
KISQALI	1	0	1	100.00%
OXYCODONE HYDROCHLORIDE	1	0	1	100.00%
OXYCONTIN	1	0	1	100.00%
RISPERIDONE	1	0	1	100.00%
TAZORAC	1	0	1	100.00%
XOLAIR	1	0	1	100.00%
XOLEGEL	1	0	1	100.00%
COSENTYX SENSOREADY PEN	0	1	1	0.00%
HARVONI	0	1	1	0.00%
MAVYRET	0	5	5	0.00%
VYVANSE	0	1	1	0.00%
XTAMPZA ER	0	1	1	0.00%
3Q20	**46**	**15**	**61**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 7/1/2020 – 9/30/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	12,536	$171,679.42	$13.69	6.47%
2	ANTICONVULSANTS, MISCELLANEOUS	11,167	$951,260.88	$85.18	5.76%
3	ATYPICAL ANTIPSYCHOTICS	8,686	$2,371,163.32	$272.99	4.48%
4	SECOND GENERATION ANTIHISTAMINES	7,955	$91,382.98	$11.49	4.10%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	6,638	$474,573.52	$71.49	3.42%
6	RESPIRATORY AND CNS STIMULANTS	6,085	$617,394.80	$101.46	3.14%
7	PROTON-PUMP INHIBITORS	6,011	$202,390.76	$33.67	3.10%
8	AMPHETAMINES	5,945	$1,057,082.35	$177.81	3.07%
9	OPIATE AGONISTS	5,913	$185,143.27	$31.31	3.05%
10	ADRENALS	4,761	$565,632.92	$118.81	2.46%
11	AMINOPENICILLIN ANTIBIOTICS	4,046	$58,728.77	$14.52	2.09%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	3,893	$112,740.86	$28.96	2.01%
13	THYROID AGENTS	3,568	$70,437.84	$19.74	1.84%
14	LEUKOTRIENE MODIFIERS	3,476	$49,554.06	$14.26	1.79%
15	CONTRACEPTIVES	3,458	$112,814.15	$32.62	1.78%
Total		**94,138**	**$7,091,979.90**	**$75.34**	**45.56%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 7/1/2020 – 9/30/2020					
	AHFS Description	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	ATYPICAL ANTIPSYCHOTICS	8,686	$2,371,163.32	$272.99	4.48%
2	AMPHETAMINES	5,945	$1,057,082.35	$177.81	3.07%
3	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	198	$1,031,351.44	$5,208.85	0.10%
4	ANTICONVULSANTS, MISCELLANEOUS	11,167	$951,260.88	$85.18	5.76%
5	CYSTIC FIBROSIS (CFTR) CORRECTORS	44	$928,680.85	$21,106.38	0.02%
6	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	375	$912,590.83	$2,433.58	0.19%
7	HEMOSTATICS	44	$800,900.52	$18,202.28	0.02%
8	ANTINEOPLASTIC AGENTS	302	$680,666.32	$2,253.86	0.16%
9	RESPIRATORY AND CNS STIMULANTS	6,085	$617,394.80	$101.46	3.14%
10	LONG-ACTING INSULINS	1,393	$612,602.17	$439.77	0.72%
11	ADRENALS	4,761	$565,632.92	$118.81	2.46%
12	SELECTIVE BETA-2-ADRENERGIC AGONISTS	6,638	$474,573.52	$71.49	3.42%
13	RAPID-ACTING INSULINS	1,322	$467,173.34	$353.38	0.68%
14	INCRETIN MIMETICS	561	$433,094.25	$772.00	0.29%
15	ENZYMES	8	$411,897.60	$51,487.20	0.004%
Total		**47,529**	**$ 12,316,065.11**	**$259.13**	**24.52%**

Total Rx Claims from 7/1/2020 – 9/30/2020	**193,872**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 7/1/2020 – 9/30/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,431	$359,202.30	$81.07	2.29%
2	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE	4,338	$46,197.25	$10.65	2.24%
3	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,660	$154,103.19	$42.10	1.89%
4	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,632	$41,924.11	$11.54	1.87%
5	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,462	$48,077.66	$13.89	1.79%
6	ANTICONVULSANTS, MISCELLANEOUS	GABAPENTIN	3,402	$58,866.86	$17.30	1.75%
7	SEROTONIN MODULATORS	TRAZODONE	3,177	$32,771.87	$10.32	1.64%
8	AMPHETAMINES	VYVANSE	3,147	$912,987.21	$290.11	1.62%
9	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	2,988	$37,616.81	$12.59	1.54%
10	THYROID AGENTS	LEVOTHYROXINE SODIUM	2,893	$50,011.07	$17.29	1.49%
11	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE	2,757	$39,262.76	$14.24	1.42%
12	AMPHETAMINES	AMPHETAMINE/DEXTROAM	2,651	$122,037.20	$46.03	1.37%
13	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM OXALATE	2,449	$33,362.30	$13.62	1.26%
14	ANGIOTENSIN-CONVERTING ENZYME INHIBITOR	LISINOPRIL	2,268	$21,164.14	$9.33	1.17%
15	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE HCL	2,182	$26,487.49	$12.14	1.13%
16	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,125	$38,888.96	$18.30	1.10%
17	OPIATE AGONISTS	HYDROCODONE/APAP	2,091	$31,440.87	$15.04	1.08%
18	SECOND GENERATION ANTIHISTAMINES	LORATADINE	2,040	$22,477.55	$11.02	1.05%
19	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION	2,011	$41,427.53	$20.60	1.04%
20	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	1,963	$23,422.08	$11.93	1.01%
21	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,822	$21,352.16	$11.72	0.94%
22	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	1,806	$22,472.76	$12.44	0.93%
23	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONATE	1,789	$27,303.11	$15.26	0.92%
24	1ST GENERATION CEPHALOSPORIN ANTIBIO	CEPHALEXIN	1,675	$26,816.50	$16.01	0.86%
25	BIGUANIDES	METFORMIN	1,606	$14,607.07	$9.10	0.83%
26	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,605	$20,241.80	$12.61	0.83%
27	ANTICONVULSANTS, MISCELLANEOUS	LAMOTRIGINE	1,552	$22,859.93	$14.73	0.80%
28	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE FUMARATE	1,537	$20,064.64	$13.05	0.79%
29	COMPOUNDS	-	1,472	$177,497.27	$120.58	0.76%
30	SEL. SEROTONIN, NOREPI REUPTAKE INHIBITOR	DULOXETINE	1,440	$21,982.96	$15.27	0.74%
31	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,437	$15,772.81	$10.98	0.74%
32	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE	1,434	$27,830.84	$19.41	0.74%
33	CENTRAL ALPHA-AGONISTS	CLONIDINE	1,390	$13,790.30	$9.92	0.72%
34	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRAN)	TRIAMCINOLONE ACETON	1,334	$21,471.33	$16.10	0.69%
35	ANTICONVULSANTS, MISCELLANEOUS	LEVETIRACETAM	1,333	$28,238.12	$21.18	0.69%
36	ADRENALS	PREDNISONE	1,273	$13,498.83	$10.60	0.66%
37	OPIATE AGONISTS	TRAMADOL HCL	1,224	$13,061.45	$10.67	0.63%
38	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,223	$17,278.41	$14.13	0.63%
39	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPRINE	1,205	$12,075.69	$10.02	0.62%
40	DIHYDROPYRIDINES	AMLODIPINE BESYLATE	1,176	$11,460.71	$9.75	0.61%
41	ANTICONVULSANTS, MISCELLANEOUS	TOPIRAMATE	1,170	$17,240.64	$14.74	0.60%
42	ANTIBACTERIALS (SKIN, MUCOUS MEMBRANE)	MUPIROCIN	1,147	$24,929.68	$21.73	0.59%
43	SULFONAMIDE ANTIBIOTICS (SYSTEMIC)	SULFAMETHOXAZOLE/TRIM	1,138	$18,341.28	$16.12	0.59%
44	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	1,131	$22,498.19	$19.89	0.58%
45	VITAMIN D	VITAMIN D	1,094	$11,150.30	$10.19	0.56%
46	OTHER NONSTEROIDAL ANTI-INFLAM. AGENTS	IBUPROFEN	1,087	$13,496.73	$12.42	0.56%
47	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	1,082	$18,635.36	$17.22	0.56%
48	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	LORAZEPAM	1,080	$12,259.79	$11.35	0.56%
49	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANATE	1,051	$21,012.21	$19.99	0.54%
50	LOOP DIURETICS	FUROSEMIDE	1,048	$9,804.51	$9.36	0.54%
	TOTAL TOP 50 DRUGS		**98,028**	**$2,860,774.59**	**$29.18**	**50.56%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 7/1/2020 –9/30/2020						
	AHFS Description	**Drug Label Name**	**Total Rxs**	**Pharmacy Due Amount**	**Paid/Rx**	**%Total Claims**
1	AMPHETAMINES	VYVANSE	3,147	$912,987.21	$290.11	1.62%
2	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	262	$603,311.29	$2,302.71	0.14%
3	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	25	$551,304.01	$22,052.16	0.01%
4	ATYPICAL ANTIPSYCHOTICS	LATUDA	381	$461,515.82	$1,211.33	0.20%
5	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN	62	$455,347.30	$7,344.31	0.03%
6	ENZYMES	STRENSIQ	8	$411,897.60	$51,487.20	0.00%
7	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	18	$376,735.14	$20,929.73	0.01%
8	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,431	$359,202.30	$81.07	2.29%
9	ATYPICAL ANTIPSYCHOTICS	ARISTADA	135	$340,554.16	$2,522.62	0.07%
10	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	STELARA	17	$335,989.98	$19,764.12	0.01%
11	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	274	$280,100.87	$1,022.27	0.14%
12	MUCOLYTIC AGENTS	PULMOZYME	57	$244,385.13	$4,287.46	0.03%
13	VESICULAR MONOAMINE TRANSPORT2 INHIB	INGREZZA	43	$238,770.53	$5,552.80	0.02%
14	HEMOSTATICS	RECOMBINATE	4	$219,052.80	$54,763.20	0.00%
15	LONG-ACTING INSULINS	LANTUS SOLOSTAR	565	$209,585.62	$370.95	0.29%
16	ADRENALS	FLOVENT HFA	879	$203,601.27	$231.63	0.45%
17	ANTICONVULSANTS, MISCELLANEOUS	VIMPAT	221	$187,577.73	$848.77	0.11%
18	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	51	$182,360.93	$3,575.70	0.03%
19	HEMOSTATICS	HEMLIBRA	3	$180,371.52	$60,123.84	0.00%
20	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	COSENTYX SENSOREADY	30	$179,146.67	$5,971.56	0.02%
21	COMPOUNDS	-	1,472	$177,497.27	$120.58	0.76%
22	ATYPICAL ANTIPSYCHOTICS	REXULTI	166	$168,581.71	$1,015.55	0.09%
23	INCRETIN MIMETICS	TRULICITY	205	$155,737.32	$759.69	0.11%
24	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,660	$154,103.19	$42.10	1.89%
25	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SURECLICK	26	$141,095.22	$5,426.74	0.01%
26	ANTINEOPLASTIC AGENTS	IBRANCE	11	$137,048.67	$12,458.97	0.01%
27	ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	18	$133,889.13	$7,438.29	0.01%
28	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	252	$133,836.19	$531.10	0.13%
29	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	60	$127,043.64	$2,117.39	0.03%
30	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	40	$125,571.39	$3,139.28	0.02%
31	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	258	$125,418.84	$486.12	0.13%
32	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	279	$124,456.09	$446.08	0.14%
33	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	342	$122,360.62	$357.78	0.18%
34	INCRETIN MIMETICS	OZEMPIC	152	$122,083.26	$803.18	0.08%
35	AMPHETAMINES	AMPHETAMINE/DEXTROA	2,651	$122,037.20	$46.03	1.37%
36	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	263	$119,874.25	$455.80	0.14%
37	CYSTIC FIBROSIS (CFTR) POTENTIATORS	KALYDECO	5	$119,533.15	$23,906.63	0.00%
38	RAPID-ACTING INSULINS	INSULIN ASPART FLEXPEN	347	$117,896.38	$339.76	0.18%
39	HEMOSTATICS	XYNTHA SOLOFUSE	10	$117,462.66	$11,746.27	0.01%
40	ANTICONVULSANTS, MISCELLANEOUS	BANZEL	63	$115,592.25	$1,834.80	0.03%
41	ANTICONVULSANTS, MISCELLANEOUS	EPIDIOLEX	51	$113,979.47	$2,234.89	0.03%
42	ANTITOXINS AND IMMUNE GLOBULINS	HIZENTRA	19	$110,604.70	$5,821.30	0.01%
43	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	TALTZ	16	$108,238.40	$6,764.90	0.01%
44	HCV POLYMERASE INHIBITOR ANTIVIRALS	EPCLUSA	5	$104,668.68	$20,933.74	0.00%
45	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	33	$103,531.98	$3,137.33	0.02%
46	ALPHA- AND BETA-ADRENERGIC AGONISTS	EPINEPHRINE	341	$101,606.05	$297.96	0.18%
47	VASODILATING AGENTS (RESPIRATORY TRACT)	UPTRAVI	5	$100,960.54	$20,192.11	0.00%
48	RAPID-ACTING INSULINS	NOVOLOG FLEXPEN	266	$99,629.35	$374.55	0.14%
49	IMMUNOMODULATORY AGENTS	TECFIDERA	12	$95,718.48	$7,976.54	0.01%
50	DIRECT FACTOR XA INHIBITORS	ELIQUIS	226	$94,801.01	$419.47	0.12%
	TOTAL TOP 50 DRUGS		**21,867**	**$10,628,654.97**	**$486.06**	**11.28%**

Utilization

90 Day Fill Update – Implemented 10/1/2020

Anticonvulsants

	2Q 2020				3Q 2020				
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Age Range**
Nayzilam (midazolam)	2	$1,076.92	$538.46	2	10	$5,434.06	$543.41	8	13 - 35
Valtoco nasal spray	0				0				
Diastat Acudial Rectal Gel	4	$1,178.31	$294.58	2	0				
diazepam rectal gel	50	$13,432.88	$268.66	38	60	$16,023.71	$267.06	41	0 - 58

Humira CF PA

Proposed Criteria: Must try Humira citrate before CF allowed

- Electronic Review:
  - Look back – 90 days, 120 days, etc?
  - How long should the trial be before citrate is intolerable?
  - Grandfathering?
- Manual Review:
  - If only allowed for **intolerable injection site pain** and not for smaller needle, then PA review can only be accomplished via manual review
- Messaging examples – what would make the most sense to providers?
  - PA REQ: TRY HUMIRA CITRATE BEFORE CITRATE-FREE FOR XX DAYS FIRST
  - PA REQ: HUMIRA CF ONLY ALLOWED FOR INTOLERABLE INJECTION SITE PAIN
- Additional consideration – Pediatric dosages
  - Humira 10mg/0.2ml and Humira 20mg/0.4ml syringes discontinued eff 1/1/2020
  - Humira 10mg/0.1ml and Humira 20mg/0.2ml syringes **CF** only available

	2Q 2020				3Q 2020			
Drug Name	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**	**Total Rx**	**Paid Amount**	**Paid/Rx**	**Utilizer**
Humira Inj 40mg/0.4 ml	8	$54,217.50	$6,777.19	8	5	$32,529.96	$6,505.99	3
Humira Kit 40mg/0.8 ml	2	$16,252.70	$8,126.35	2	5	$43,341.43	$8,668.26	3
Humira Pen Inj 40mg/0.4 ml	37	$249,357.33	$6,739.39	37	39	$292,682.61	$7,504.68	17
Humira Pen Inj 40mg/0.8 ml	17	$119,298.60	$7,017.56	17	14	$103,023.60	$7,358.83	8
Humira Pen Inj CD/UC/HS	1	$16,214.99	$16,214.99	1	0			
Humira Pen Kit CD/UC/HS	1	$16,681.47	$16,681.47	1	1	$16,681.47	$16,681.47	1
Humira Pen Kit PS/UV	1	$11,124.46	$11,124.46	1	1	$11,121.16	$11,121.16	1

Red font denotes drug is on PA

Atypical Antipsychotic Utilization in Children (17 years old and younger)

	Year 2019		
Identifier	Unique Utilizers	% Per Utilizer	% Per Member <17
One Product Concurrent > 90 Days	793	59.8%	1.62%
One or More Products Concurrent < 90 Days	297	22.4%	0.61%
Two or More Products Concurrent > 90 Days	**235**	**17.7%**	**0.48%**
Grand Total	1,325	100.0%	
Members Age 17 or less - 4/2020	49,057		

Demographic Utilization Time Frame: 8/1/2019 to 7/31/2020 – Review of 235 Members

Member Demographics

Gender	Total Members
Female	83
Male	145
Total	**228**

*7 members – eligibility ended or no utilization after 7/31/2019

Age	Female	Male	Total Members	Misc Notes
4 years		1	**1**	Initial target age – 3 years old
5 years		2	**2**	
6 years	1	1	**2**	
7 years	2	10	**12**	
8 years	3	5	**8**	
9 years	1	13	**14**	
10 years	2	8	**10**	
11 years	1	8	**9**	
12 years	3	11	**14**	
13 years	11	8	**19**	
14 years	11	18	**29**	
15 years	17	16	**33**	
16 years	10	14	**24**	
17 years	12	17	**29**	
18 years	8	12	**20**	
19 years	1	1	**2**	
Total	**83**	**145**	**228**	

*195 members had birthdays during 8/1/2019 to 7/31/2020

*33 members did not have birthdays yet or already had one

Plan Types	Female	Male	Total Members
Foster	28	36	64
IHS	10	13	23
NoCopay	35	69	104
Standard	19	46	65
Total	**92**	**164**	**256**

*28 members switched plan types

Atypical Antipsychotic PA Criteria:

1. Diagnosis of one of the following:
    - Aphagia
    - Autistic disorder
    - Bipolar depression
    - Bipolar disorder
    - Bipolar II disorder
    - Conduct disorders
    - Cyclothymic disorder
    - Dementia in other diseases
    - Dementia, unspecified
    - Dysphagia, unspecified
    - Dysthymic disorder
    - Intermittent explosive disorder
    - Mania
    - Mood (affective) disorders, unspecified
    - Oppositional defiant disorder
    - Persistent mood (affective) disorders
    - Schizophrenia
    - Schizophreniform disorder
    - Tourette's syndrome
    - Unspecified psychosis
    - Vascular dementia

OR

2. Both of the following:
    a. Patient has a diagnosis of depression **AND**
    b. Patient has tried and failed 2 different antidepressants

AND

3. Children younger than 6 years of age must have a psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care

AND

4. For alternative dosage forms (e.g., rapid dissolve tablets, injectables, extended-release), one of the following criteria must be met:
    a. The patient is unable to swallow **OR**
    b. The patient failed a standard dosage form from this drug class in the last 30 days

Utilization Date Range: 1/1/2020 to 10/31/2020 – Review of 235 Members

All Diagnosis

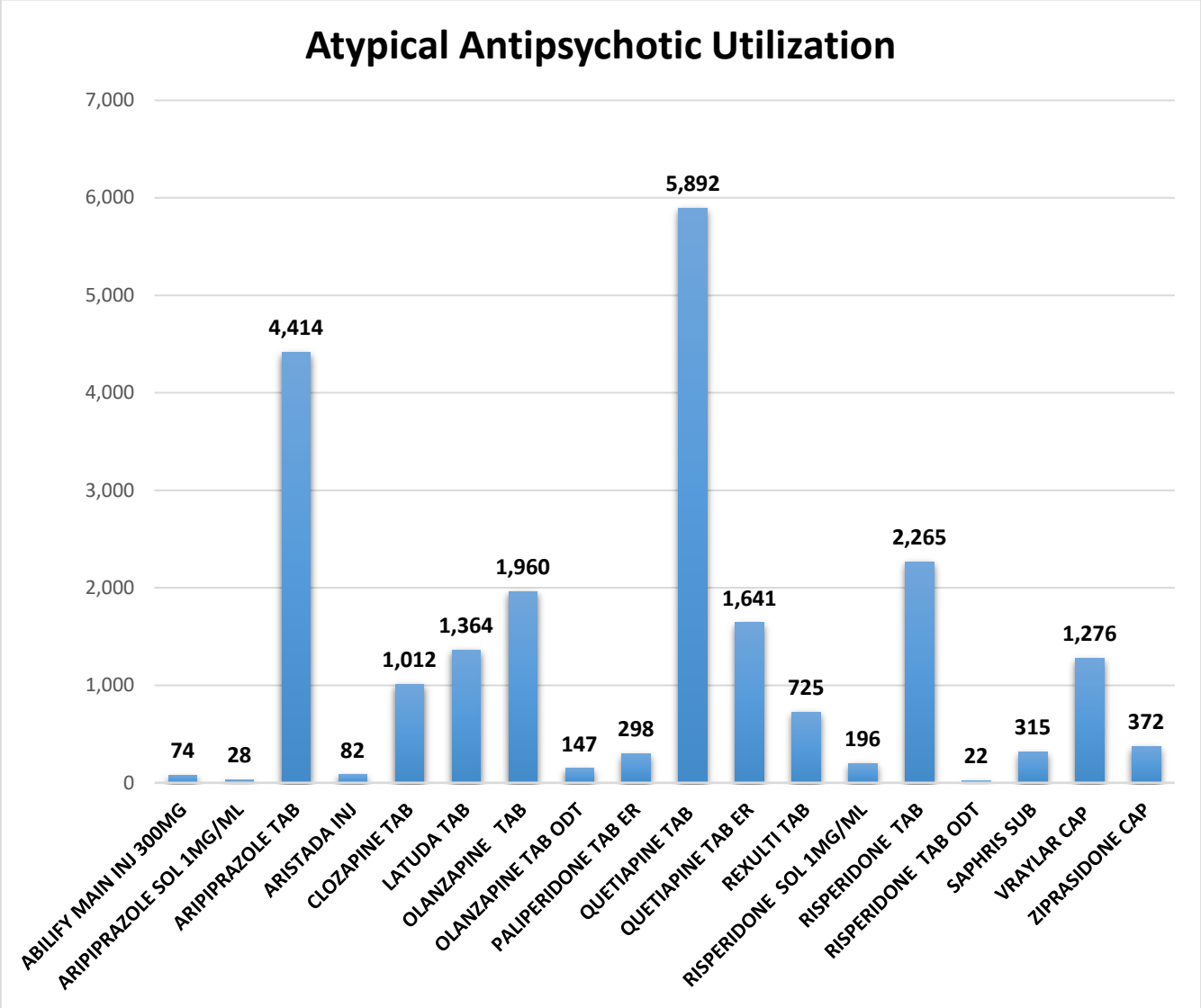
Assault	11
Certain conditions originating in the perinatal period	24
Certain infectious and parasitic diseases	203
Congenital malformations, deformations and chromosomal abnormalities	66
Diseases of the circulatory system	33
Diseases of the digestive system	319
Diseases of the ear and mastoid process	232
Diseases of the eye and adnexa	528
Diseases of the genitourinary system	190
Diseases of the musculoskeletal system and connective tissue	675
Diseases of the nervous system	234
Diseases of the respiratory system	676
Diseases of the skin and subcutaneous tissue	321
Endocrine, nutritional and metabolic diseases	115
Event of undetermined intent	2
External causes of morbidity	67
Factors influencing health status and contact with health services	1,495
Injury, poisoning and certain other consequences of external causes	983
Intentional self-harm	45
Mental, Behavioral and Neurodevelopmental disorders	**2,373**
Neoplasms	135
Other external causes of accidental injury	99
Pregnancy, childbirth and the puerperium	20
Supplementary factors related to causes of morbidity classified elsewhere	44
Surgical and other medical procedures as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure	1
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	1,804
Unknown	280

Mental, Behavioral and Neurodevelopmental disorders (F01-F99)

Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	424
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	697
Behavioral syndromes associated with physiological disturbances and physical factors	29
Disorders of adult personality and behavior	43
Intellectual disabilities	46
Mental and behavioral disorders due to psychoactive substance use	180
Mental disorders due to known physiological conditions	8
Mood [affective] disorders	673
Pervasive and specific developmental disorders	214
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	55
Unspecified mental disorder	4

Utilization Date Range: 1/1/2020 to 10/31/2020 – Review of 235 Members

- 193 members with atypical antipsychotic utilization
- 42 members without atypical antipsychotic utilization
- 123 males to 70 females
- Age range from 5 to 19 years old
- Not able to link diagnosis with specific medication given



Most Common Combinations

Members taking two different drugs or two different dosage forms

Aripiprazole combo	Risperidone combo	Olanzapine & other combo	Quetiapine & other combo
aripiprazole/olanzapine 1 member	risperidone/olanzapine 3 members		quetiapine/Abilify Main Inj 1 member
aripiprazole/quetiapine 7 members	risperidone/quetiapine 3 members	olanzapine/quetiapine 3 members	quetiapine/quetiapine ER 4 members
aripiprazole/risperidone 11 members	risperidone/risperidone ODT 1 member		quetiapine/Rexulti 3 members
aripiprazole/Latuda 1 member	risperidone/Latuda 3 member	olanzapine/Saphris 1 member	quetiapine/Latuda 1 member
aripiprazole/Vraylar 1 member	risperidone /Vraylar 1 member	olanzapine/Vraylar 1 member	Saphris/Vraylar 1 member
aripiprazole/ziprasidone 1 member		olanzapine ODT/paliperidone ER 1 member	Saphris/ziprasidone 1 member
aripiprazole/Aristada Inj 1 member		Latuda/ paliperidone ER 1 member	

Members taking 3 or more different drugs/dosage forms

aripiprazole/olanzapine/risperidone 2 members	quetiapine ER/quetiapine/ziprasidone 1 member
aripiprazole/olanzapine/quetiapine 3 members	quetiapine ER/quetiapine/Latuda 1 member
aripiprazole/quetiapine/risperidone 1 member	quetiapine/risperidone /olanzapine 1 member
aripiprazole/quetiapine/Latuda 1 member	quetiapine/Latuda/Rexulti 1 member
aripiprazole/olanzapine/quetiapine/risperidone 1 member	quetiapine/Latuda/Vraylar 1 member
aripiprazole /olanzapine/risperidone/Latuda 1 member	quetiapine ER/quetiapine/clozapine/olanzapine ODT/olanzapine 1 member
aripiprazole /olanzapine/quetiapine/Vraylar 1member	olanzapine/clozapine/Vraylar 1 member

South Dakota Department of Social Services

Please note: All information below is required to process this request.
Fax to 1-844-403-1029
Mon-Sat: 7am to 7pm Central

Nurtec ODT™, Reyvow®, Ubrelvy™ Prior Authorization Request Form

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

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

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

Clinical Information (required)

Select the diagnosis below:

❑ Acute treatment of migraine with or without aura

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

Clinical information:

Has the patient had a trial and failure of a triptan in the last 120 days? ❑ **Yes** ❑ **No**

Has the patient had an inadequate response, intolerance to, or contraindication to triptans? ❑ **Yes** ❑ **No**

Does the patient have cardiovascular disease? ❑ **Yes** ❑ **No**

Quantity limit requests:

What is the quantity requested per DAY? _____

What is the reason for exceeding the plan limitations?

❑ Titration or loading dose purposes

❑ Patient is on a dose-alternating schedule (e.g., one tablet in the morning and two tablets at night, one to two tablets at bedtime)

❑ Requested strength/dose is not commercially available

❑ Other: _____

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

_____

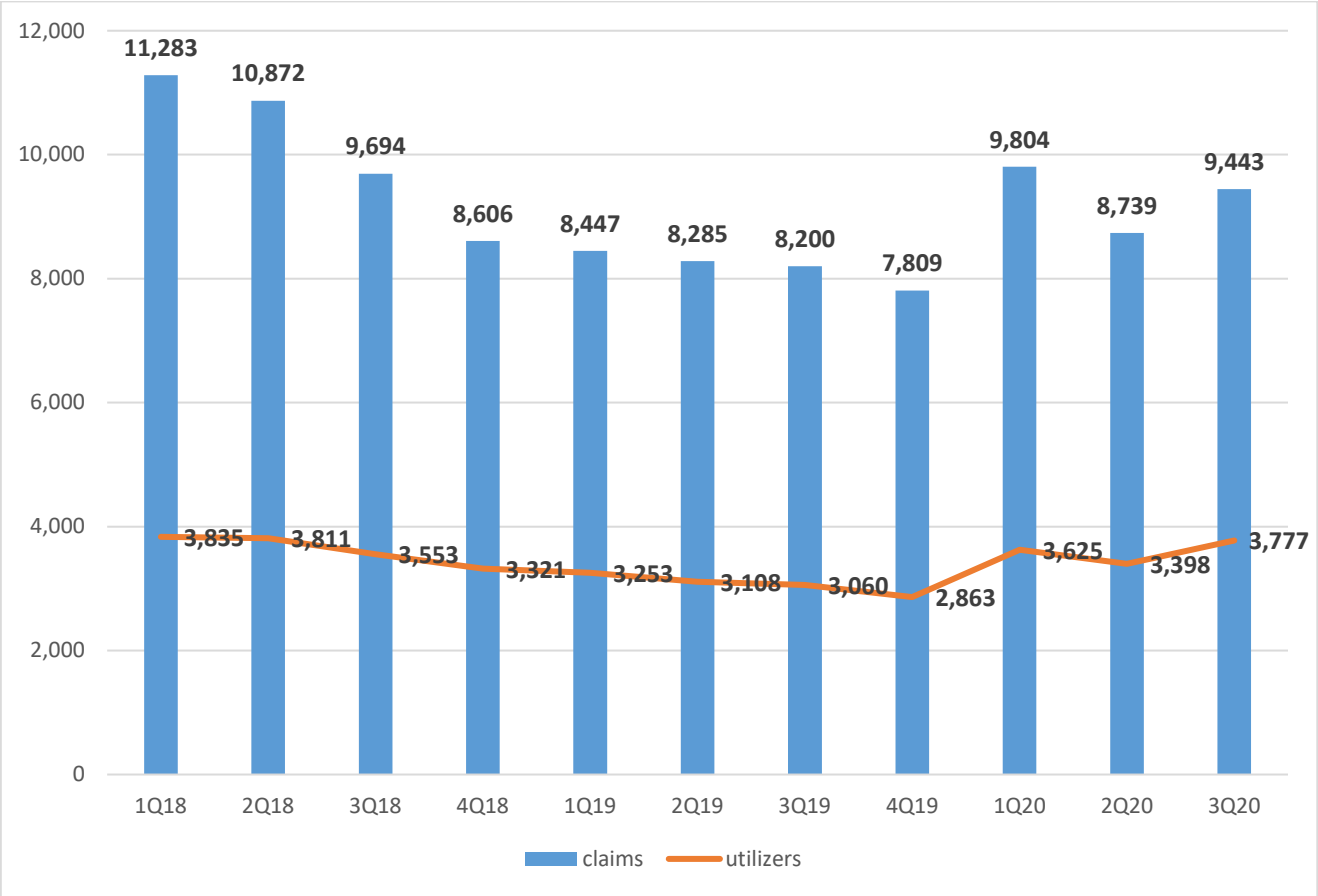
_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-844-403-1029.

Opioid Summary



-1Q2018 to 4Q2019 excludes IHS
-1Q2020 to current includes IHS

Eligibility

Date	Avg eligible members	Total utilizing members	% utilizing members
1Q2020	123,552	27,893	22.6%
2Q2020	126,777	20,747	16.4%
3Q2020	132,373	23,388	17.7%
1/2020	123,552	27,893	22.6%
2/2020	123,869	27,366	22.1%
3/2020	123,298	26,008	21.1%
4/2020	124,889	20,425	16.4%
5/2020	126,946	20,313	16.0%
6/2020	128,495	21,503	16.7%
7/2020	130,398	22,607	17.3%
8/2020	132,965	23,365	17.6%
9/2020	133,755	24,191	18.1%
10/2020	135,049	24,085	17.8%

Opioid Utilization Snapshot

SDM 2Q2020

Mar 20 to Jun 20

Opioid Claims **8,739**

3.0% prescription claims filled for an opioid

0.6% lower than Medicaid FFS benchmark

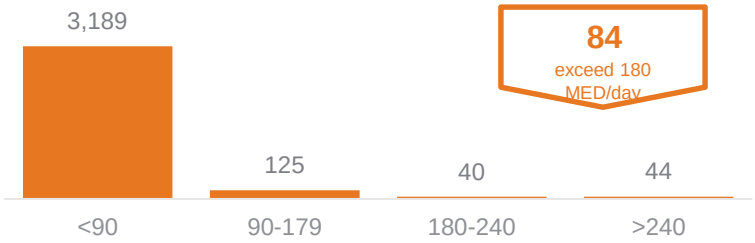
Utilizers **3,398**

32.7.0% are high utilizers[1]

-20% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

49 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

231 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

3Q2020

Jun 20 to Sep 20

Opioid Claims **9,443**

3.3% prescription claims filled for an opioid

0.4% lower than Medicaid FFS benchmark

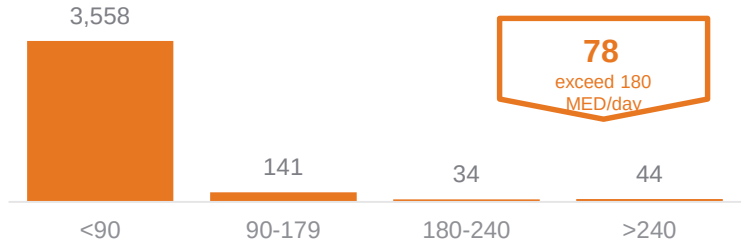
Utilizers **3,777**

31.1% are high utilizers[1]

-19.4% lower than high utilizers Medicaid FFS

Utilizers by Cumulative MED[4]

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



Shoppers: Poly Pharmacy

50 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

254 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUM Rx®

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

Opioid Utilization

SDM 3Q2020
Opportunities date range: Jun - Sep 2020
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 3,777

3.3% of all Rx claims are filled for an Opioid

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

- Opioid prescriptions account for 3.3% of all prescriptions this period, which is 0.4% lower than the benchmark
- 1,175 high opioid utilizers were identified this period, which is -19.4% lower than the benchmark

Opioid claims

PERCENT OPIOID CLAIMS
3.3%

0.4% under benchmark

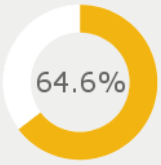
Opioid utilizers

HIGH UTILIZERS
31.1%
1,175 high utilizers

-19.4% under benchmark

High utilizers – 3+ opioid scripts withiin 120 days

Claim breakdown



short acting opioids

64.6% of all opioid Rxs were filled for short acting opioids. **868** Rxs were for medication assisted therapy (MAT) and **50** were for rescue therapy. CDC guidelines advise prescribers to manage pain with the lowest effective dose and to avoid or carefully justify doses for chronic users >90mg MME/day.

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

Utilizers by cumulative MED

78 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,558	141	34	44

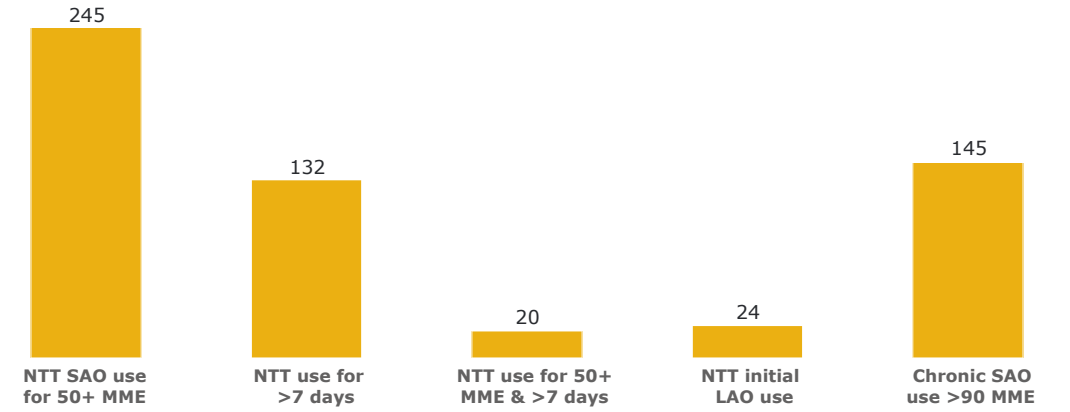
MED – Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period

Opioid Opportunity Assessment

SDM 3Q2020
Opportunities date range: Jun - Sep 2020
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers

new to therapy and chronic use



7.0% of opioid Rxs	5.3% of opioid Rxs	1.0% of opioid Rxs	1.4% of opioid Rxs	12.1% of opioid Rxs

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

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

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
735	546	779	N/A	113

Anticonvulsants –view definition

PA Reviews & Utilization

PA Drug Class Summary 3Q2020

Drug Class	Approved	Denied	Total	Approval Rate
ANTIPSYCHOTICS/ANTIMANIC AGENTS*	279	21	300	93.00%
ANTIDEPRESSANTS*	205	36	241	85.06%
ANTIDIABETICS*	141	5	146	96.58%
ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERGIC	136	26	162	83.95%

Antidiabetics PA Approval Review

Incretin Mimetics Criteria:

1. Does the patient have a diagnosis of type 2 diabetes mellitus?

Approvals

- 1 approval for Bydureon Pen
- 3 approvals for Ozempic
- 3 approvals for Trulicity
- 6 approvals for Victoza

Denials

- 2 denials for Ozempic
- 2 denials for Victoza

PCSK9 Inhibitors:

- 2 approvals for Praluent
- 6 approvals for Repatha

Insulins:

- 4 approvals for Novolog, Novolog Flexpen, Insulin Aspart – QLL limit
- 1 approval for Toujeo – QLL limit
- 1 approval for Lantus – QLL limit
- 1 approval for Humulin 70/30 Kwikpen – QL limit

Ulcer Drugs PA Approval Review

Drugs on PA: Aciphex sprinkles, Dexilant, Nexium, esomeprazole, Protonix PAK, PrevPac, Zegerid, Talicia, Prevacid Solutab, Prilosec DR suspension pack

Criteria

Aciphex sprinkles, Nexium oral packet, Protonix PAK, Zegerid oral packet, Prevacid Solutab, Prilosec DR suspension pack:

1. One of the following:
   a. Patient is less than 13 years of age **OR**
   b. Patient has a diagnosis which confirms a difficulty in swallowing

All other targets:

1. One of the following:
   a. Diagnosis of erosive esophagitis, Barrett's esophagitis, or Zollinger-Ellison Syndrome **OR**
   b. Trial and failure (after a minimum of 14 days) in the past year with at least one of the following generics or Patient has experienced an adverse reaction (must be documented on a MedWatch form), allergy or contraindication to ALL of the following:
      - omeprazole
      - pantoprazole
      - rabeprazole
      - lansoprazole

Approvals – 70%

- 16 approvals for Dexilant
- 36 approvals for esomeprazole
- 23 approvals for lansoprazole ODT
- 6 approvals for Nexium
- 2 approvals for pantoprazole QLL limit –2 per day
- 4 approvals for Prevacid Solutab

Denials – 30%

- 2 denials for pantoprazole QLL limit – 2 per day
- 1 denial for Dexilant
- 18 denials for esomeprazole – failure to try omeprazole, pantoprazole, rabeprazole, lansoprazole
- 3 denials for lansoprazole ODT – no difficulty swallowing
- 1 denial for Nexium – failure to try omeprazole, pantoprazole, rabeprazole, lansoprazole

Time frame: 7/1/2020 to 9/30/2020
Red font denotes drug is on Prior Authorization

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Dexilant	167	$49,879.85	$298.68	81	8 - 63
Nexium cap	12	$2,067.71	$172.31	5	29 - 61
esomeprazole cap	178	$3,063.29	$17.20	91	7 - 66
Nexium granules	17	$6,220.95	$365.94	9	0 - 39
esomeprazole granules	46	$10,168.08	$221.05	25	0 - 42
Prevacid cap	1	$402.16	$406.16	1	31
Prevacid tab	10	$3,781.00	$378.10	7	0 - 39
lansoprazole cap	378	$6,701.53	$17.73	197	0 - 87
lansoprazole susp	4	$282.00	$70.50	2	2, 4
lansoprazole tab	21	$5,264.59	$250.69	14	0 - 25
lansoprazole ODT	107	$26,432.45	$247.03	52	0 - 58
first-omeprazole susp	10	$963.00	$96.30	6	0 - 5
omeprazole cap	3,259	$37,866.78	$11.62	1,689	0 - 101
Prilosec POW	2	$1,389.52	$694.76	1	0
pantoprazole tab	844	$10,121.95	$11.99	431	10 – 89
Protonix PAK	1	$465.60	$465.60	1	9

Accumulation Edit

Edit that prevent members from filling refills early.
The refill threshold is 75% for non-controls and 85% for controls.

- Example: If member consistently refills 5 days early each month, by the 8th month (the 5-day supply is counted at the end of month) the system will calculate the member has 30 days supply and reject for refill to soon.

ADHD Utilization

Time frame: 7/1/2020 to 9/30/2020
History of utilization reviews:

- March 2019 P&T meeting – reviewed utilization of all members on ADD/ADHD medications
- June 2019 P&T meeting – reviewed utilization of members aged 1-20 years old vs 21 years old & older
- September 2019 P&T meeting – reviewed utilization of members aged 26 years old & older

ADD/ADHD Drugs (21 years old and older only)

Summary

Class	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Amphetamines	1,574	$206,686.60	$131.31	536	21-64
Respiratory & CNS Stimulants	474	$32,358.18	$68.27	148	21-64
Central Alpha-Agonists	12	$667.63	$55.64	5	34-61
Central Nervous System Agents	280	$14,594.05	$52.12	94	21-60
Wakefulness-Promoting Agents	69	$9,001.65	$130.46	29	21-64

Amphetamine

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Amphetamine-dextroamphetamine	**994**	**$49,014.31**		**342**	
• Adderall tab	2	$912.72	$456.36	1	39
• Adderall XR cap	8	$1,683.11	$210.39	4	22-48
• amphet/dextroamephtamine cap ER	446	$27,622.63	$61.93	163	21-64
• amphet/dextroamephtamine tab ER	528	$15,911.05	$30.13	197	21-64
• Mydavis	10	$2,884.80	$288.48	4	21-28
Dextroamphetamine sulfate					
• dextroamephtamine cap ER	6	$939.17	$156.53	2	34, 51
• dextroamephtamine tab	21	$1,086.39	$51.73	9	28-60
Lisdexamfetamine dimesylate					
• Vyvanse cap	553	$155,646.73	$281.46	212	21-63

Respiratory & CNS Stimulants

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Dexmethylphenidate	**32**	**$2,812.98**		**11**	
• dexmethylphenidate tab	9	$260.58	$28.95	4	21-52
• dexmethylphenidate cap ER	23	$2,552.40	$110.97	8	21-50
Methylphenidate hcl	**381**	**$29,545.20**		**138**	
• methylphenidate cap ER	36	$2,493.28	$69.56	15	22-42
• methylphenidate tab	109	$2,511.78	$23.04	49	21-64
• methylphenidate tab ER	236	$24,540.14	$103.98	85	21-61

Central Alpha-Agonists

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Clonidine hcl (ADHD)					
• clonidine tab ER	12	$667.63	$55.64	5	34-61

Central Nervous System Agents

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Age Range
Atomoxetine					
• atomoxetine cap	175	$11,209.27	$64.05	62	21-61
• Strattera	3	$1,234.38	$411.46	1	23
Guanfacine (ADHD)					
• guanfacine tab ER	102	$1,439.79	$19.99	33	21-59

Wakefulness-Promoting Agents

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizing Members	Member Age Range
Modafinil					
• modafinil tab	47	$1,242.00	$26.42	22	21-64
• Provigil tab	2	$3,446.08	$1,723.04	1	43
Armodafinil					
• armodafinil tab	14	$464.42	$33.17	5	34-59
Solriamfetol					
• Sunosi	6	$3,849.15	$641.53	3	29, 32, 43

Concomitant therapy with ADD/ADHD medication:

- Atypical antipsychotics – 201 members
- Benzodiazepines – 132 members
- Opioids – 122 members
- Benzodiazepines & Opioids – 45 members
- Antipsychotics & Benzodiazepines & Opioids – 14 members

ADHD Criteria of other States

State A

- PA for under 6 years old for long and short acting products
  1. Patient has a diagnosis of Attention Deficit Hyperactivity Disorder **AND**
  2. Patient's clinical team is currently addressing psychosocial issues and non-medical interventions **AND**
  3. Patient has received a psychosocial evaluation prior to this request **AND**
  4. Patient has had a prior trial and inadequate response to non-medication alternatives **AND**
  5. Patient will be monitored in accordance with the ADHS/DBHS Clinical Practice Protocol on Psychiatric Best Practice Guidelines for Children: Birth to Five Years of Age **AND**
  6. The medication will be prescribed at a dose that does not exceed the FDA recommended maximum daily dosage

State B

- PA for under age 6 years old for all long acting stimulants
- No PA required from 6 to 20 years old as long as they are not requesting therapy with duplicate stimulant
- PA for 21 years and older for listed diagnosis & duplicate therapy – must have valid diagnosis for use
- Same rules above follow for short acting stimulants except for PA for 3 years old and under for short acting stimulants
- FDA-labeled diagnoses or approved compendia diagnoses
  - ADHD
  - Narcolepsy
  - Binge eating disorder (lisdexamfetamine only)
  - Depression
  - Mania (dextroamphetamine only)
  - Cocaine dependence (dextroamphetamine only)
  - Personality disorder
  - Schizophrenia
  - Sleep deprivation

State C

Approval will be given if the following criteria is met and documented:

- General Criteria (Children and Adults)
  1. A diagnosis of ADD/ADHD or other FDA approved diagnosis.
  2. Only one long-acting stimulant (amphetamine and methylphenidate products) may be used at a time.
  3. A 30-day transitional overlap in therapy will be allowed.
  4. Other treatable causes of ADD/ADHD have been ruled out.
- ADD/ADHD Criteria (Children up to age 18 years)
  1. The recipient is at least three years of age (short-acting stimulants) or at least six years of age (long-acting stimulants, long-acting alpha agonists, atomoxetine).

An initial evaluation or regular examination has been done within the past 12 months with the treating prescriber.

Allows an exception if the prescriber is a psychiatrist and there is an ADHD diagnosis on the claim.

State D

- PA for all non-preferred products for all ages
- Preferred drugs – no PA for under 21 years old
- Preferred drugs – PA for 21 years old and over for indication

State E

PA required for members 21 years old and older (members 20 years old and younger subject to criteria if exceeding 80mg/day of total amphetamine):

- Preferred agent
  - Agent must **not** be prescribed by a pain clinic
  - Patient does **not** meet any of the following:
    1. Concurrently taking a sedative, hypnotic, opioid (including buprenorphine), MAOI agent, or meprobamate/carisoprodol
    2. No active alcohol or substance abuse for last 3 years
    3. Glaucoma
    4. Hyperthyroidism
    5. Symptomatic arteriosclerosis, cardiac disease and/or abnormalities
  - Patient has a diagnosis of ADD and/or ADHD; **AND**
  - Patient has a diagnosis of ADD and/or ADHD; **AND**
    1. Documentation that the symptoms affect the patient's ability to function in daily life tasks in at least 2 major settings or creates significant difficulties in at least 2 major settings **OR**
    2. Patient has a diagnosis of Narcolepsy supported with documentation of polysomnography; **OR**
    3. Diagnosis or organs brain disorder **OR**
    4. Diagnoses of treatment resistant MDD (major depressive disorder) **AND**
       - Adequate T/F of 3 agents at appropriate dose for 3 weeks minimum from at least 3 distinct drug classes
         - SSRI
         - SNRI
         - New generation antidepressants
         - TCA
- Non-Preferred agent
  - Requires T/F, contraindication or intolerance of 2 preferred agents

Orkambi clinical PA criteria review

1. Patient must have a diagnosis of cystic fibrosis **AND**
2. Patient must be 2 years of age or older **AND**
3. Patient must have a laboratory confirmation of homozygous F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene **AND**
4. Prescribed by or in consultation with a pulmonologist or specialist affiliated with a CF care center

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Mbrs	Age Range
Cystic Fibrosis Potentiators						
Kalydeco (ivacaftor)	4	$96,005.52	$24,001.38	#56/28 days	2	6 - 15
Cystic Fibrosis Correctors						
Symdeko (tezacaftor-ivacaftor)	1	$736.70 ($21,768.80)	$736.70 ($21,768.80)	#56/28 days	1	11
Orkambi (lumacaftor-ivacaftor)*	15	$315,313.95	$21,020.93	#59.73/28 days	7	2 - 6
Trikafta (elexacafor-tezacaftor-ivacaftor)	21	$458,519.79	$21,834.28	#84/28 days	8	12 - 57

All drugs will hit High Dollar PA
*Clinical PA

Evrysdi

Time frame: 10/1/2020 – 11/17/2020

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty/ Days Supply	Utilizing Mbrs	Age Range
Evrysdi (risdiplam)*	3	$67,043.58	$22,351.36	160/24 days	2	14, 25
Spinraza (nusinersen)						
Zolgensma (onasemnogene abeparvovec-xioi)						

*Hits High Dollar PA

South Dakota Department of Social Services

Please note: All information below is required to process this request.
Fax to 1-844-403-1029
Mon-Sat: 7am to 7pm Central

Orkambi® Prior Authorization Request Form

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

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

Medication Information (required)

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

Clinical Information (required)

Select the diagnosis below:

❑ Cystic fibrosis (CF)

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

Clinical information:

Does the patient have a laboratory confirmation of homozygous F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene? ❑ **Yes** ❑ **No**

Was the requested medication prescribed by or in consultation with a pulmonologist or specialist affiliated with a CF care center? ❑ **Yes** ❑ **No**

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

_____

_____

_____

_____

Please note: This request may be denied unless all required information is received.
For urgent or expedited requests please call 1-855-401-4262.
This form may be used for non-urgent requests and faxed to 1-844-403-1029.

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons in the spinal cord and brainstem, leading to progressive muscular atrophy and weakness (*Genetics Home Reference 2020, Mercuri et al 2018[a]*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant mortality (*Bodamer 2020*).
- SMA is an autosomal recessive inherited disorder. The overall incidence is between 4 and 10 per 100,000 live births, and 1 person in 50 to 90 is a carrier of a mutation that can cause SMA (*Bodamer 2020*).
- The *SMN1* gene is responsible for the production of SMN protein, which is ubiquitously expressed in all cells throughout fetal and post-natal development. Deletion or mutations in the *SMN1* gene lead to a shortage of the protein. Without this protein, motor neurons degenerate and nerve impulses are not carried between the brain and muscles, resulting in characteristic muscle weakness and impaired movement (*Bodamer 2020, Finkel et al 2018, Genetics Home Reference 2020*).
  - There is also a modifying (or "backup") gene called *SMN2*, which generates a smaller amount of functional SMN protein. The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have a less severe SMA type *(Bodamer 2020, Calucho et al 2018*).
- There are several forms of SMA with varying degrees of severity and ages of onset (*Bodamer 2020, Genetics Home Reference 2020, Glascock et al 2018, , Rao et al 2018*).
  - In SMA type 1, untreated patients have severe weakness and hypotonia and never gain the ability to sit unsupported. Patients with SMA type 1 typically have an onset of symptoms between the age of 0 and 6 months, and have a typical lifespan of < 2 years without permanent ventilation.
  - Patients with SMA type 2 (intermediate), 3 (mild), or 4 (adult-onset) experience a later onset and less severe symptoms usually characterized by varying degrees of muscle weakness. Type 0 (prenatal) is the rarest and most severe form, with newborns typically living for < 6 months.
- SMA type 1 is the most common form, affecting approximately 58% of patients. Type 2 and type 3 occur in approximately 29% and 13% of patients, respectively, and type 4 is less common (< 5%) (*Food and Drug Administration [FDA] medical review 2016*). Mothers may notice a decrease of fetal movement in late pregnancy, and some experts classify prenatal onset as type 0 SMA, which is very rare (*Bodamer 2020, FDA medical review 2016*).
- Management of SMA has historically been limited to supportive measures, focusing on providing nutrition and respiratory assistance and preventing or treating the complications of weakness. Nonpharmacologic treatments include physical therapy, spinal bracing, chest physiotherapy, and respiratory support (*Bodamer 2020, Finkel et al 2018, Mercuri et al 2018[a]).*
- In December 2016, Spinraza (nusinersen) became the first FDA-approved product for the treatment of SMA. The FDA granted nusinersen Fast Track designation, Orphan Drug designation, and Priority Review (*FDA 2016*).
  - Nusinersen is an antisense oligonucleotide designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Nusinersen binds to sites within *SMN2* pre-mRNA, promoting inclusion of exon 7 in *SMN2* mRNA transcripts and increasing production of full-length, functional SMN protein (*Finkel et al 2016*).
- Zolgensma (onasemnogene abeparvovec-xioi; referred to as onasemnogene abeparvovec), approved by the FDA in May 2019, is the second FDA-approved product for the treatment of SMA. Onasemnogene abeparvovec was granted Priority Review by the FDA, and received Breakthrough Therapy, Fast Track, and Orphan Drug designations (*FDA 2019*).
  - Onasemnogene abeparvovec is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein. The virus enters the nucleus of neurons and forms an episome (a DNA molecule that replicates independently of chromosomal DNA). The episome is transcribed and translated to produce the missing SMN protein.
- Evrysdi (risdiplam), approved by the FDA in August 2020, is the third FDA-approved product for the treatment of SMA. Risdiplam was granted Priority Review by the FDA, and received Fast Track and Orphan Drug designations.
  - Risdiplam is a splicing modifier that increases exon 7 inclusion in the *SMN2* mRNA transcripts, thereby increasing production of full-length SMN protein (*Evrysdi prescribing information 2020*).

- Medispan class: Spinal Muscular Atrophy Agents
- Medispan class: Spinal Muscular Atrophy – Gene Therapy Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Evrysdi (risdiplam)	-
Spinraza (nusinersen)	-
Zolgensma (onasemnogene abeparvovec-xioi)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evrysdi (risdiplam)	Spinraza (nusinersen)	Zolgensma (onasemnogene abeparvovec-xioi)
Treatment of SMA in patients 2 months of age and older	✔		
Treatment of SMA in pediatric and adult patients		✔	
Treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene			✔ *

* Limitations of use: The safety and effectiveness of repeat administration of onasemnogene abeparvovec have not been evaluated. The use of onasemnogene abeparvovec in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

- 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

Zolgensma (onasemnogene abeparvovec-xioi)

- The safety and efficacy of onasemnogene abeparvovec were evaluated in 3 clinical trials, START, STR1VE and SPR1NT.
  - START was a phase 1, open-label trial of 15 patients with SMA type 1 who had 2 copies of *SMN2.* Two cohorts were treated: 3 patients in cohort 1 received a low dose of Zolgensma, while 12 patients in cohort 2 received a high dose of Zolgensma. After 24 months of treatment, all patients in cohort 2 were alive and none required permanent ventilation (described as ≥ 16 hours per day of required ventilatory support for 14 consecutive days in the absence of acute reversible illness or perioperative change). One patient in group 1 reached a pulmonary event at 28.8 months of age. Patients also had improvement in meeting certain motor milestones, with the majority gaining the ability to sit unassisted, roll over, and achieve head control. Gains in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) were also noted (*Al-Zaidy et al 2019*, *Mendell et al 2017)*.
    - Ten of the 12 patients in cohort 2 enrolled in the START long-term follow-up (LTFU) study. As of December 31, 2019, all 10 patients were alive and free of permanent ventilation, no previously--achieved motor milestone had been lost, and 2 patients gained a new milestone of standing with assistance. There were no new treatment-related serious adverse effects (AEs) and no AEs of special interest during the LTFU study. Some of the patients in the LTFU study have received subsequent therapy with nusinersen (*Novartis 2020[a]*).
  - STR1VE was an open-label, single-arm, multicenter trial in the U.S that evaluated the safety and efficacy of Zolgensma in patients with SMA type 1 who were < 6 months of age at the time of gene therapy, with 1 or 2 copies of *SMN2* and who had bi-allelic *SMN1* gene deletion or point mutations.
    - Data as of March 8, 2019 (median duration of follow-up, 10.2 months) showed that of 20 patients who reached 10.5 months of age or discontinued the study prior to 10.5 months of age, 19 (95%) were surviving without permanent

ventilation. Of 15 patients who had reached 13.6 months of age or discontinued prior to 13.6 months, 13 (87%) were surviving without permanent ventilation (*Day et al 2019*).
    - According to updated data provided by the manufacturer in March 2020, 20 of 22 patients (91%) met the co-primary endpoint of event-free survival at 14 months, and 13 of 22 patients (59%) met the co-primary endpoint of functional sitting for ≥ 30 seconds at 18 months of age. Sustained improvements in CHOP-INTEND scores were also noted (*Novartis 2020[a]*).
  - SPR1NT is an ongoing, Phase 3, open-label, single-arm, multicenter trial designed to evaluate the safety and efficacy of Zolgensma in pre-symptomatic patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age. The primary outcome measure for patients with 2 copies of *SMN2* is independent sitting for ≥ 30 seconds by 18 months. The primary outcome measure for patients with 3 copies of *SMN2* is standing without support for at least 3 seconds by 24 months (*Avexis 2019, Strauss et al 2019)*.
    - As of December 31, 2019, 14 patients with 2 copies of *SMN2* and 15 patients with 3 copies of *SMN2* had been treated. In the 2-copy cohort, 8 patients so far were able to sit independently for ≥ 30 seconds (range, 5.7 to 11.8 months of age), and 4 patients were able to walk independently. Of the patients with 3 copies of *SMN2*, 4 patients were able to stand alone without support for ≥ 3 seconds (9.5 to 12.4 months of age) and 3 patients were able to walk independently (12.2 to 15.1 months of age). Patients in both cohorts who had not achieved these milestones yet were still within the normal age development window for these milestones (*Novartis 2020[a]*).
- Zolgensma is still being studied in a number of trials in pursuit of expanding patient populations. Of note, the STRONG trial is a Phase 1 trial investigating intrathecal delivery in children with SMA type 2 aged 6 months to 5 years (*Clinicaltrials.gov 2020*). Based on their review of data from STRONG, the FDA has notified the manufacturer that they recommend a pivotal confirmatory study to supplement the STRONG data in order to support a regulatory submission for intrathecal use (*Novartis 2020[b])*.

Spinraza (nusinersen)

- Key clinical trials supporting the safety and efficacy of nusinersen include ENDEAR, CHERISH, and NURTURE.
  - The pivotal trial ENDEAR (N = 121) was a 13-month, Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients 7 months or younger who had an onset of SMA symptoms at ≤ 6 months of age and had homozygous deletion or mutation of *SMN1* and 2 copies of the *SMN2* gene (*Finkel et al 2017).*
    - At interim analysis, a higher proportion of patients treated with nusinersen had a motor milestone response than those in the control group (41% vs 0%, p < 0.001), prompting early termination of the trial. The final analysis showed that 51% of the nusinersen-treated group had a motor milestone response, compared with no patients in the control group. Motor milestones reached included achievement of full head control (22%), ability to roll over (10%), ability to sit independently (8%), and ability to stand (1%).
    - A co-primary endpoint of event-free survival also favored nusinersen vs placebo (61% vs 32%; p = 0.005).
    - Patients in the nusinersen group also had a 63% lower risk of death compared with the control group (hazard ratio, 0.37; 95% confidence interval [CI], 0.18 to 0.77; p = 0.004).
  - CHERISH (N = 126) was a Phase 3, randomized, sham-controlled, double-blind, multicenter trial in patients aged 2 to 12 years with later-onset SMA. The primary endpoint was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE) score at 15 months of treatment (*Mercuri 2018[b]).*
    - In the pre-planned interim analysis, there was a significant improvement in the HFMSE from baseline to 15 months in the nusinersen group vs the control group (mean difference in change, 5.9 points; 95% CI, 3.7 to 8.1; p < 0.001).
    - Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group vs 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points (p < 0.001), and the overall incidence of AEs was similar in the nusinersen group and the control group (93% vs 100%, respectively).
  - The NURTURE study is an ongoing, Phase 2, open-label, single-arm trial to evaluate the use of nusinersen in patients with SMA and 2 or 3 copies of *SMN2* who were ≤ 6 weeks of age and asymptomatic at the time of treatment initiation The primary endpoint was time to death or respiratory intervention (invasive or non-invasive for ≥ 6 hours per day continuously for ≥ 7 days or tracheostomy). At an interim analysis published in 2019, 25 patients had been enrolled, of whom 15 had 2 *SMN2* copies and 10 had 3 *SMN2* copies. At the time of the interim analysis, 4 participants (16%) had utilized a respiratory intervention. All patients were alive and none required permanent ventilation. Efficacy was further supported by the achievement of motor milestones by HINE-2 and motor function by CHOP-INTEND. Of note, all patients achieved the milestone of “sitting without support” and 23 of 25 patients (92%) achieved “walking with assistance” (*De Vivo et al 2019*).

- In June 2020, the manufacturer reported updated data noting that all children treated pre-symptomatically were alive and none required permanent ventilation after up to 4.8 years of continuous treatment. In addition, patients continued to maintain and make progressive gains in motor function. The study has been extended by an additional 3 years to allow the collection of continued data (*Biogen 2020*).

- The FDA-approved indication for nusinersen does not limit its use to certain ages or SMA types. The FDA medical review noted that the underlying cause of SMA (a shortage of SMN protein) is common to patients with all SMA types, and it is reasonable to expect that nusinersen should provide clinical benefits in all SMA types. Open-label studies included patients 2 to 17 years of age with 2 to 5 *SMN2* copies and symptom onset corresponding to types 2 and 3 SMA; these results plus the initial summary of the sham-controlled trial in later-onset patients support the conclusion that nusinersen provides clinical benefits to patients with types 2 and 3 SMA and allow reasonable extrapolation to these populations. Given the invasive nature of nusinersen administration, patients with milder forms of SMA (type 4) may need to weigh potential benefits, risks and discomfort, and relative symptom severity to make individual treatment decisions (*FDA medical review 2016*).

Evrysdi (risdiplam)

- Evidence for the safety and efficacy of risdiplam is available from results of 2 clinical trials, FIREFISH and SUNFISH. Both studies are still ongoing.
  - FIREFISH is a 2-part, Phase 2/3, open-label, multicenter, dose-escalation study assessing the safety and tolerability of risdiplam in infantile-onset SMA type 1 patients aged 1 to 7 months.
    - In part 1, 21 infants were assigned to group A (n = 4) receiving a low dose or group B (n = 17) recieiving a high dose that was adjusted up to the recommended dose of 0.2 mg/kg/day. Of the infants who were treated with the recommended dosage of risdiplam 0.2 mg/kg/day, 7 of 17 (41%) were able to sit independently for ≥ 5 seconds as assessed by the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) after 12 months of treatment, a milestone beyond that expected in the natural history of the disease. Additionally, 90% of patients (19/21) were alive without permanent ventilation (and reached 15 months of age or older) (*Evrysdi prescribing information 2020*). The most common AEs included pyrexia, upper respiratory tract infections, rash, diarrhea, vomiting, pneumonia and constipation (*Evrysdi AMCP Dossier 2020).*
      - The manufacturer announced 2-year data for FIREFISH part 1, noting that an estimated 88% of patients were alive and required no permanent ventilation after 2 years. Patients continued to achieve motor milestones, including 59% (10/17) sitting without support for ≥ 5 seconds, 65% (11/17) maintaining upright head control, 29% (5/17) turning over, and 30% (5/17) standing either supporting weight or with support. No new safety signals were identified (*Genentech 2020*).
    - Part 2 is a pivotal single-arm study evaluating the use of risdiplam in 41 infants with SMA type 1 for 24 months. Infants received risdiplam at a dose of 5 mg once daily for patients with a body weight ≥ 20 kg or 0.25 mg/kg for patients with a body weight < 20 kg. The primary outcome is the proportion of infants sitting without support for ≥ 5 seconds after 12 months on treatment as assessed by BSID-III. A primary analysis at 12 months (November 2019) showed that 12/41 infants (29%; 90% CI, 17.8% to 43.1%) were sitting without support for ≥ 5 seconds. After 24 months in part 2, infants will continue in a open-label extension phase (*Evrysdi AMCP Dossier 2020*).
  - SUNFISH is a 2-part, double-blind, placebo-controlled trial in children and young adults aged 2 to 25 years old with SMA type 2 and 3 (*Evrysdi AMCP Dossier 2020*).
    - Part 1 (N = 51) was a dose-finding phase evaluating safety and tolerability of risdiplam. Patients received risdiplam or placebo for a minimum of 12 weeks, followed by open-label use of risdiplam at the dose selected for Part 2. Exploratory results at 12 months showed improvements in motor function compared to natural history.
    - In Part 2, 180 patients were randomized (type 2, 71%; type 3, 29%) to risdiplam or placebo for 24 months followed by an open-label extension period. The primary endpoint was the change from baseline in motor function measure 32 scale (MFM-32) at month 12; the average baseline MFM-32 score was 45 in the risdiplam group vs 47 in the placebo group. The primary analysis showed a statistically significant 1.36-point increase from baseline MFM-32 score in the risdiplam group (95% CI, 0.61 to 2.11) compared to a -0.19-point change in the placebo group (95% CI, -1.22 to 0.84). The most common AEs that occurred in > 10% of risdiplam-treated patients and more commonly than with placebo were fever, diarrhea, and headache. The most common serious AE in the risdiplam arm was pneumonia in 9 patients. There was a trend for more grade 3 to 4 AEs in the risdiplam group.
- Additional studies of risdiplam are ongoing (*Evrysdi AMCP Dossier 2020*). JEWELFISH is a Phase 2, open-label, exploratory study investigating the safety, pharmacokinetics, and pharmacodynamics of risdiplam in 174 patients 6

months to 60 years of age with SMA who had previously been treated with nusinersen, onasemnogene abeparvovec, or certain other investigational SMA therapies. RAINBOWFISH, which is currently enrolling patients, is a Phase 2, open-label study evaluating the use of risdiplam in pre-symptomatic SMA patients up to 6 weeks of age at the time of treatment initiation.

Other studies

- A recent observational cohort study showed benefit of nusinersen for adults aged 16 to 65 years with SMA. A clinically meaningful improvement (defined as an increase of 3 points or more in the HFMSE score compared to baseline) was observed with nusinersen treatment at 6 months in 35 of 124 patients (28%), at 10 months in 33 of 92 patients (36%), and at 14 months in 23 of 57 patients (40%) (*Hagenacker 2020*).
- A Cochrane review of 2 randomized controlled trials assessed the safety and efficacy of drug therapies (nusinersen and riluzole) designed to slow or stop the progression of SMA type 1. Riluzole is not indicated for the treatment of SMA. Authors concluded that intrathecal nusinersen probably prolongs ventilation-free and overall survival in infants with SMA type 1. Additionally, a greater proportion of infants treated with nusinersen achieved motor milestones. In the riluzole trial, 3 of 7 children treated with riluzole were still alive at the ages of 30, 48, and 64 months, whereas all 3 children in the placebo group died. None of the children in the riluzole or placebo group developed the ability to sit, which was the only milestone reported in the study (*Wadman et al 2019*).
- A Cochrane review of 14 randomized controlled trials evaluated the efficacy of various drug treatments, most of which are not indicated for the treatment of SMA, to slow the disease progression of SMA types 2 and 3. The trials evaluated gabapentin, hydroxyurea, nusinersen, olesoxime, phenylbutyrate, somatropin, thyrotropin-releasing hormone, valproic acid, and combination valproic acid/acetyl-L-cartinine. Treatment varied from 3 to 24 months. Overally, no treatment showed a clinically important effect on motor function in SMA types 2 or 3, except for intrathecal nusinersen, which showed a 3.7-point improvement in motor function in children with SMA type 2 based on the HFMSE scale with moderate quality evidence (*Wadman et al 2020*).

CLINICAL GUIDELINES

- **SMA Newborn Screening Working Group.** Treatment algorithm for infants diagnosed with SMA through newborn screening (*Glascock et al 2018*)
  - Clinical and preclinical data indicate that early treatment will be critical in order to modulate the rapid, progressive degeneration seen in SMA, particularly SMA type 1. Animal studies also show that the best results occur when drugs are given as early as possible.
  - Recommendations for the use of SMN-upregulating treatment for patients with a confirmed positive result for SMA on newborn screening are based on the number of *SMN2* copies, as follows:
    - 1 *SMN2* copy: probable SMA type 0. Treatment is recommended if the patient is truly pre-symptomatic. If symptoms are present, physician discretion is recommended. (Most patients with 1 copy of *SMN2* will be symptomatic at birth.)
    - 2 *SMN2* copies: probable SMA type 1. Treatment is recommended.
    - 3 *SMN2* copies: probable SMA type 2 or type 3. Treatment is recommended.
    - ≥ 4 *SMN2* copies: probable SMA type 3 or type 4. Waiting to treat is recommended; patients should be monitored and treated upon the onset of symptoms. (The committee was divided on this recommendation.)
  - In patients with ≥ 4 copies of *SMN2*, who are not immediately treated with a disease-modifying therapy for SMA, the following key recommendations are made:
    - Infants identified as having ≥ 4 *SMN2* copies should be referred to someone who can identify their exact copy number (some commercial laboratories report the result only as "≥ 4").
    - Routine follow-up care should ideally occur every 3 to 6 months until the patient reaches 2 years of age, and every 6 to 12 months thereafter. This would ensure the detection of very rare cases in which children with ≥ 4 *SMN2* copies have SMA type 1 or 2.
    - Certain follow-up assessments recommended include electromyography (EMG), compound muscle action potential (CMAP), myometry, physical examinations, and motor function scales.
  - The working group acknowledges that the future availability of new FDA-approved therapies will prompt the need for additional consideration by physicians and patients, as each drug will present unique benefits, risks, and burdens.

- **SMA Care Group**. Diagnosis and management of SMA. Part 1: recommendations for diagnosis, rehabilitation, orthopedic, and nutritional care (*Mercuri et al 2018[a])* and Part 2: pulmonary and acute care; medications, supplements, and immunizations; other organ systems; and ethics (*Finkel et al 2018*). The following recommendations outline aspects associated with supportive pharmacological care:
  - Over the last decade, the approach to treating the pulmonary manifestations of SMA has become more proactive, with introduction of therapies earlier in the disease process. Respiratory support should be the highest priority.
    - Management may include airway clearance, noninvasive positive pressure ventilation, and tracheotomy ventilation in select patients. Continuous positive airway pressure (CPAP) should not be used routinely.

- **European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy** *(Kirschner et al 2020*). With the recent approval of Zolgensma, many patients could be eligible for the gene therapy with the broadly defined approved indication. However, clinical trials studied very specific patient groups for gene therapy (eg, SMA type, age and weight), thus individual treatment decisions should be made on a case-by-case basis. The statement of 11 points highlights 3 areas including selection criteria, structural requirements for administration, and generation of additional evidence. Key points are as follows:
  - *Selection criteria*:
    - Traditional SMA types (0 to 4) alone are not enough to define patients who would most benefit from gene therapy. Age at onset, disease duration, and motor function status are key factors that predict response to treatment in symptomatic patients, whereas treatment decisions for presymptomatic patients should primarily be based on *SMN2* copy number. Although the approval of Zolgensma is based on clinical trials in patients ≤ 6 months old weighing less than 8.4 kg, it is indicated in patients up to 2 years old. However, little is known about the safety and efficacy in older and heavier patients; in these cases nusinersen is available as a treatment option. When administered after the age of 6 months and/or in advanced stages of the disease, caregivers should be made aware that there are no published data on efficacy and safety. It is important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.
    - In patients presenting with severe symptomatic disease, there is a high risk of living with severe disability despite the use of gene therapy. Palliative care is recommended as an alternative treatment option in these patients.
    - There is no evidence that combination therapy (eg, Zolgensma plus nusinersen) is superior to any single treatment alone. Before more evidence is available, combination of both approved therapies should not be part of routine care.
  - *Structural requirements for administration*: Providers performing gene therapy should have broad expertise in the assessment and treatment of SMA according to international standards. The ideal time between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive nature of the disease.
  - *Generation of additional evidence*: Data regarding safety and effectiveness should be collected for all treated patients. Institutions using Zolgensma should be adequately equipped with resources to safely administer the therapy and provide care and long-term monitoring. The statement suggests that patients weighing ≥ 13.5 kg may be best treated with Zolgensma in a clinical trial setting only.

SAFETY SUMMARY

- Contraindications
  - Evrysdi: none
  - Spinraza: none
  - Zolgensma: none
- Boxed Warning
  - Evrysdi: none
  - Spinraza: None
  - Zolgensma: acute serious liver injury, elevated amintransferases; higher risk in patients with pre-existing liver impairment
- Warnings and precautions
  - Evrysdi: none
  - Spinraza: thrombocytopenia, coagulation abnormalities, renal toxicity
  - Zolgensma: thrombocytopenia, elevated troponin

- AEs
  - Evrysdi:
    - Common AEs in infantile-onset SMA (≥ 10%): upper respiratory tract infection, pneumonia, constipation, vomiting, fever, diarrhea, and rash
    - Common AEs in later-onset SMA (≥ 10%): fever, diarrhea, and rash
  - Spinraza:
    - The most common AEs (≥ 20% of Spinraza-treated patients and occurred at least 5% more frequently vs placebo-treated patients) include:
      - Infantile-onset SMA: lower respiratory infection and constipation
      - Later-onset SMA: pyrexia, headache, vomiting, and back pain
  - Zolgensma
    - The most common AEs (≥ 5%) include: elevated aminotransferases and vomiting
- Use in specific populations:
  - Spinraza and Evrysdi, Pregnancy: may cause fetal harm (based on animal data).
  - Evrysdi, Hepatic impairment: Use should be avoided in patients with hepatic impairment.
  - Zolgensma, Pediatric use: Use in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evrysdi (risdiplam)	Powder for reconstitution (oral solution)	Oral	Once daily	Administer dose after a meal using the provided oral syringe.
Spinraza (nusinersen)	Injection	Intrathecal	4 loading doses: first 3 doses at 14-day intervals, 4th dose 30 days after the 3rd Maintenance dose every 4 months thereafter	To be given by, or under the direction of, healthcare professionals experienced in performing lumbar punctures; administered as an intrathecal bolus over 1 to 3 minutes; sedation should be considered as indicated by the clinical condition of the patient; ultrasound or other imaging techniques should be considered to guide administration, particularly in younger patients.
Zolgensma (onasemnogene abeparvovec-xioi)	Injection	IV	One-time administration; 1.1 x 10^{14} vector genomes (vg)/kg	Administered over 60 minutes using a syringe pump. There are a total of 22 kit configurations, consisting of 2 to 9 vials (5.5 mL and/or 8.3 mL), to treat patients weighing 2.6 to 13.5 kg.

See the current prescribing information for full details

- Zolgensma: vials are shipped frozen and are stable under refrigeration for 14 days after receipt.

CONCLUSION

- SMA is a serious neuromuscular disease characterized by degeneration of motor neurons in the spinal cord and brainstem. Clinical features include progressive muscular atrophy and weakness.
  - SMA is caused by an inherited genetic mutation affecting the *SMN1* gene, causing a deficiency of the critical SMN protein.
  - Several subtypes of SMA exist, with varying severity and ages of onset.

- Zolgensma has the potential to significantly improve the disease course of SMA with a 1-time IV dose. Published efficacy data are limited to approximately 15 patients, all of whom had SMA type 1 and 2 copies of a modifying gene, *SMN2*.
  - Zolgensma is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein.
  - The main safety risks include elevated transaminases and potential acute serious liver injury.
- Nusinersen has demonstrated efficacy in patients with SMA types 1, 2, and 3 and in pre-symptomatic patients; however, nusinersen requires intrathecal dosing several times per year throughout the patient's lifetime.
- In pivotal trials, risdiplam improved motor function in people living with SMA over a large range of ages and levels of disease severity including types 1, 2, and 3.
  - Risdiplam helped infants survive longer without the need for permanent ventilation and sit without support for ≥ 5 seconds, a key motor milestone not normally seen in the natural course of the disease.
  - Risdiplam is an oral medication that is administered by the patient/caregiver, compared to intrathecal (nusinersen) and IV (Zolgensma) which require a healthcare professional.
- The specific place in therapy for each SMA agent, including the potential role for sequential treatment, requires further study.

APPENDIX

- **Bayley Scales of Infant and Toddler development Third Edition (BSID-III**) (*Evrydsi dossier 2020*)
  - BSID-III is intended for children age 1 to 42 months. The assessment is completed over 30 to 90 minutes and measures 5 developmental domains: adaptive behavior, cognition, language, motor, and social-emotional. Raw scores of each successfully completed item are converted to subtest scaled scores and to a composite standard score. The scores determine the child's performance compared with typically developing children of their age. While it is not a disease-specific measure, the BSID-III has high reliability and validity.
- **Hammersmith Functional Motor Scale – Expanded (HFMSE)** (*Spinraza dossier 2016*)
  - Expanded version of the original 20-item Hammersmith Functional Motor Scale that incorporates 13 items from the Gross Motor Function Measure assessment.
  - Consists of 33 items evaluating the child's ability to perform activities. Each item is scored on a 3-point scale, with a score of 2 for "performs without modification," 1 for "performs with modification/adaptation," and 0 for "unable to perform."
  - The total score can range from 0 (all activities failed) to 66 (all activities achieved).
  - A clinically meaningful change has been estimated to be a 3-point change at 6 months.
- **Hammersmith Infant Neurological Examination (HINE)** (*De Sanctis 2016, Spinraza dossier 2016, FDA Medical Review 2016, Together in SMA 2016*)
  - Measures functional ability and achievement of motor milestones.
  - Contains 26 items; total possible score is 78. Healthy-term infants should have a median score ≥ 67 at 3 months and ≥ 70 at 6 months. At 9 or 12 months, scores ≥ 73 are regarded as optimal.
    - Section 1 is based on the neurological exam (postures, cranial nerve function, reflexes, tone, and movements).
    - Section 2 (HINE-2) evaluates development of motor function based on 8 items (head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling, standing, and walking); each item is scored between 0 and 2 to 4, for a maximum score of 26.
    - Section 3 evaluates the state of behavior (consciousness, social orientation, and emotional state).
- **Motor Function Measure 32 (MFM-32**) (*Evrydsi dossier 2020*)
  - MFM-32 is typically used in people older than 6 years; however it has been validated in children as young as 2 years old. The assessment typically takes around 30 to 40 minutes to complete. Each item of the MFM is scored using a 4-point Likert scale, ranging from 0 to 3, based on the subject's maximal abilities without assistance. The scores on each of the 32 items are summed and converted to a 0 to 100 total score; the lower the total score, the more severe the impairment.
- **Upper Limb Module (ULM)** (*Spinraza dossier 2016*)
  - Designed to assess upper limb functional abilities in patients with SMA, including young children and patients with severe contractures in the lower limbs.
  - Consists of 9 upper limb performance items that reflect activities of daily living.
  - The total score ranges from 0 to 18 points, with higher scores indicating greater functional abilities.
  - An increase of ≥ 2 points is considered clinically meaningful.

- A revised version of the ULM consists of 20 upper limb performance items.

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Therapeutic Class Overview

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators and dornase alfa

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 300 have been confirmed to cause CF (*CFTR2 2019*, *Quon and Rowe 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*). The most common *CFTR* mutation leading to CF is the *F508del* mutation; approximately 50% of patients with CF are homozygous for this mutation, and 90% carry at least 1 copy (*Katkin 2019*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon and Rowe 2016*).
  - Inhaled antibiotics have commonly been used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF. A reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, and oral macrolide antibiotics and high-dose ibuprofen have been used to reduce inflammation (*Quon and Rowe 2016*).
    - Pulmozyme (dornase alfa), initially approved by the Food and Drug Administration (FDA) in 1993, is a recombinant DNase enzyme. In CF patients, retention of viscous purulent secretions in the airways contributes to reduced pulmonary function and to exacerbations of infection. Dornase alfa hydrolyzes deoxyribonucleic acid (DNA) in the sputum of CF patients, reducing sputum viscoelasticity. Guidelines recommend the use of dornase alfa for patients with CF aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations) (*Drugs@FDA 2020, Mogayzel et al 2013*).
- More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) (*Drugs@FDA 2020, Elborn 2016*). The CFTR modulators facilitate processing and trafficking of CFTR to the cell surface (CFTR correctors [tezacaftor, lumacaftor, and elexacaftor]) or facilitate increased chloride transport at the cell surface (CFTR potentiator [ivacaftor]). Eligibility for CFTR modulator therapy depends on the patient's age and CF-causing mutation(s).
  - In 2018, prior to the approval of Trikafta and some age expansions for the other CFTR modulators, it was estimated that only 55% of patients with a known genotype were eligible for CFTR modulator therapy (*Vertex CF portfolio guide 2018*). The approval of Trikafta may provide the opportunity for up to 90% of CF patients to be eligible for CFTR modulator therapy in the future (*Vertex 2019*).
  - The CFTR modulators are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the 4 available CFTR modulators and dornase alfa.
- Medispan Class: CF Agents, CFTR Potentiators (Kalydeco); CF Agents, CF Agent-Combinations (Orkambi, Symdeko, and Trikafta); and CF Agents, Hydrolytic Enzymes (Pulmozyme)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
CFTR Modulators	

Drug	Generic Availability
Kalydeco (ivacaftor)	-
Orkambi (lumacaftor/ivacaftor)	-
Symdeko (tezacaftor/ivacaftor)	-
Trikafta (elexacaftor/tezacaftor/ivacaftor)	-
DNase enzyme	
Pulmozyme (dornase alfa)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	CFTR Modulators				DNase Enzyme
	Kalydeco (ivacaftor)	**Orkambi** (lumacaftor/ ivacaftor)	**Symdeko** (tezacaftor/ ivacaftor)	**Trikafta** (elexacaftor / tezacaftor/ ivacaftor)	**Pulmozyme** (dornase alfa)
Treatment of CF in patients aged 6 months and older who have 1 mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data*	✔				
Treatment of CF in patients aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene		✔			
Treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in the *CFTR* gene that is responsive to tezacaftor/ ivacaftor based on *in vitro* data and/or clinical evidence†			✔		
Treatment of CF in patients aged 12 years and older who have at least 1 *F508del* mutation in the *CFTR* gene				✔	
For daily administration in conjunction with standard therapies for the management of CF patients to improve pulmonary function‡					✔

* The following 38 mutations are included: *E56K, P67L, R74W, D110E, D110H, R117C,* ***R117H***, ***G178R***, *E193K, L206W, R347H, R352Q, A455E,* ***S549N***, ***S549R***, ***G551D***, ***G551S***, *D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T,* ***G1069R***, ***R1070Q***, *R1070W, F1074L, D1152H,* ***G1244E***, ***S1251N***, ***S1255P***, *D1270N,* ***G1349D***, *2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: Bolded mutations are unique to the indication for Kalydeco and are not covered by another CFTR modulator.

† The following 27 mutations are included (patients must have 2 copies of the *F508del* mutation, or at least 1 copy of another listed medication, for Symdeko to be indicated): *E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, F508del, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: All of these mutations are also covered by either Kalydeco or Orkambi.

‡ In CF patients with a forced vital capacity (FVC) ≥ 40% of predicted, daily administration of dornase alfa has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

(*Prescribing information: Kalydeco 2019, Orkambi 2018, Pulmozyme 2018, Symdeko 2019, Trikafta 2019*)

- 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

CFTR Modulators

Note: The following is a brief overview of the clinical evidence supporting the efficacy of the CFTR modulators. Appendix A provides an overview of key clinical trials for CFTR modulators in a table format. Appendix B provides a description of study endpoints.

- The safety and efficacy of ivacaftor have been evaluated in a number of trials in patients with a variety of *CFTR* mutations. In addition to the clinical evidence available, ivacaftor has been FDA-approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 48-week, double-blind trial demonstrated improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and exacerbations for ivacaftor vs placebo in 167 patients with CF aged ≥ 12 years with ≥ 1 *G551D* mutation (*Ramsey et al 2011*). A separate, placebo-controlled, 48-week double-blind trial in 52 patients aged 6 to 11 years with this mutation demonstrated improvement in $ppFEV_1$ (*Davies et al 2013*), and an open-label extension study of these 2 trials demonstrated sustained $ppFEV_1$ improvement over 96 weeks (*McKone et al 2014*).
  - A placebo-controlled crossover trial with two 8-week treatment periods demonstrated improved $ppFEV_1$ with ivacaftor in 39 patients with CF aged ≥ 6 years with a non-*G551D* gating mutation (*De Boeck et al 2014*).
  - A 24-week, double-blind, placebo-controlled trial evaluated the safety and efficacy of ivacaftor vs placebo in 69 patients aged ≥ 6 years with an *R117H* mutation (*Moss et al 2015*). In this trial, improvement in $ppFEV_1$ was demonstrated in adults but not in children aged 6 to 11 years; the authors suggested that the lack of effect may have been related to the high baseline $ppFEV_1$ in the pediatric patients enrolled.
  - A crossover study with two 8-week treatment arms enrolled a total of 246 patients aged ≥ 12 years with CF who were heterozygous for *F508del* and a residual function mutation (*Rowe et al 2017*). A comparison of the ivacaftor and placebo arms demonstrated an improvement in $ppFEV_1$ with ivacaftor. (See the tezacaftor/ivacaftor section below for information on comparisons of tezacaftor/ivacaftor to ivacaftor and placebo in this study.)
  - An open-label study in 34 patients aged 2 to 5 years with CF and ≥ 1 *CFTR* gating mutation evaluated weight-based dosing of ivacaftor in this age group (*Davies et al 2016*). Patients weighing < 14 kg received a dose of 50 mg and those ≥ 14 kg received a dose of 75 mg. Pharmacokinetic analyses demonstrated that exposure was similar to that reported with the approved dosing in adults. Improvements were also seen in weight and sweat chloride concentrations (a pharmacodynamic endpoint that reflects changes in CFTR function). No meaningful data on lung function were available, as the accuracy of spirometry results is limited in this age group.
  - The efficacy of ivacaftor in patients aged 6 to < 24 months was extrapolated from data in patients aged ≥ 6 years with support from pharmacokinetic analyses showing similar drug exposure levels to adults. Safety of ivacaftor in this age group was derived from a cohort of 11 patients aged 6 months to < 12 months and a cohort of 19 patients aged 12 months to < 24 months in a 24-week, open-label study, which demonstrated that the safety profile was similar in this age group to that observed in patients aged ≥ 24 months. The study also demonstrated improvements in sweat chloride and markers of pancreatic function in patients aged 12 months to < 24 months (*Kalydeco prescribing information 2018, Rosenfeld et al 2018*).
  - A systematic review and meta-analysis evaluated the use of ivacaftor vs placebo in patients with CF (*Skilton et al 2019*). The review included 5 trials evaluating ivacaftor in patients with the *F508del* mutation (1 trial, N = 140), the *G551D* mutation (3 trials, N = 238), or the *R117H* mutation (1 trial, N = 69). Primary outcomes included survival, quality of life as assessed by the CF questionnaire-revised (CFQ-R), and FEV_1. Overall, the authors found evidence supporting the efficacy of ivacaftor in patients with the *G551D* mutation, but not the *F508del* or *R117H* mutations. Key findings from the review were as follows:
    - No survival data or deaths were reported in any of the included trials.
    - In studies of patients with the *F508del* mutation, no improvement was demonstrated in CFQ-R or FEV_1.
    - In studies of patients with the *G551D* mutation, improvement was demonstrated in both CFQ-R and FEV_1, although improvements in CFQ-R were not statistically significant at all time points.
    - In studies of patients with the *R117H* mutation, improvement was demonstrated in CFQ-R (in adults but not children), and there was no improvement in FEV_1.
  - Support for ivacaftor's efficacy for additional mutations is available from *in vitro* assay data (*Kalydeco prescribing information 2018*). This assay was based on CFTR chloride transport in Fisher Rat Thyroid cells expressing mutant

CFTR. An increase in chloride transport of ≥ 10% was designated as the response threshold because it is predictive or reasonably expected to predict clinical benefit. Mutations meeting this threshold were considered responsive, and a patient must have at least 1 responsive mutation in order for ivacaftor to be indicated.

- A number of trials have evaluated the safety and efficacy of lumacaftor/ivacaftor for the treatment of patients with CF homozygous for the *F508del* mutation.
  - Two 24-week, double-blind, placebo-controlled trials evaluated the efficacy of lumacaftor/ivacaftor in a total of 1122 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Wainwright et al 2015*). Pooled data demonstrated an improvement in ppFEV$_1$ as well as exacerbations. Based on a 96-week open-label extension study, the ppFEV$_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor; however, the improvement was not statistically significant (*Konstan et al 2017*).
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 46 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation and had severe lung disease (ppFEV$_1$ < 40) (*Taylor-Cousar et al 2018*). Dose modification to half the usual dose for 1 to 2 weeks at treatment initiation was permitted; 28 patients initiated treatment at full dose (400 mg/250 mg twice daily) and 18 patients initiated at half dose (200 mg/125 mg twice daily). The primary endpoints were safety and tolerability, which demonstrated that the most common adverse events (AEs) were respiratory in nature; patients initiating treatment at the reduced dose had less frequent respiratory events. Following an initial reduction, ppFEV$_1$ from week 4 to the end of the study was similar to baseline.
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 58 patients with CF aged 6 to 11 years who were homozygous for *F508del* (*Milla et al 2017*). At 24 weeks, there was a small improvement in ppFEV$_1$ that failed to reach statistical significance (p = 0.0671); the authors suggested that the lack of a significant effect might have been due to the small sample size and relatively mild lung disease in this population. A separate double-blind, placebo-controlled trial in 206 patients in this age group demonstrated a small but statistically significant effect on ppFEV$_1$ (*Ratjen et al 2017*).
  - An open-label, Phase 3 study evaluated the use of lumacaftor/ivacaftor in patients with CF aged 2 to 5 years who were homozygous for *F508del* (*McNamara et al 2019*). Patients weighing between 8 and 14 kg received a dose of 100 mg/125 mg and patients weighing ≥ 14 kg received a dose of 150 mg/188 mg, each given twice daily. A total of 12 patients were enrolled in part A of the study (assessing pharmacokinetics and safety over 15 days) and 60 were enrolled in part B (assessing pharmacokinetics, safety, pharmacodynamics, and efficacy over 24 weeks). The study demonstrated a reduction in mean sweat chloride concentrations, improvement in biomarkers of pancreatic function, and increased growth parameters. Safety and pharmacokinetics were consistent with previous studies of lumacaftor/ivacaftor.
- Two published Phase 3 trials have evaluated the safety and efficacy of tezacaftor/ivacaftor in patients with CF aged ≥ 12 years, and efficacy has been extrapolated to patients aged 6 to < 12 years. As with ivacaftor, tezacaftor/ivacaftor has additionally been FDA approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 24-week, double-blind trial compared tezacaftor/ivacaftor to placebo in 509 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Taylor-Cousar et al 2017*). The improvement in ppFEV$_1$ was greater with tezacaftor/ivacaftor vs placebo, and the rate of pulmonary exacerbations also favored tezacaftor/ivacaftor treatment.
  - A double-blind, crossover trial with two 8-week treatment periods evaluated tezacaftor/ivacaftor, ivacaftor monotherapy, and placebo in 246 patients with CF aged ≥ 12 years who were heterozygous for *F508del* and a second allele with a residual function mutation (*Rowe et al 2017*). Both tezacaftor/ivacaftor and ivacaftor monotherapy improved ppFEV$_1$ vs placebo, with tezacaftor/ivacaftor having a slightly larger effect than ivacaftor alone.
  - The efficacy of tezacaftor/ivacaftor in patients aged 6 to < 12 years was extrapolated from patients aged ≥ 12 years with support from population pharmacokinetic analyses showing similar tezacaftor and ivacaftor exposure levels in patients aged 6 to < 12 years to older patients. Safety of tezacaftor/ivacaftor in this population was derived from a 24-week, open-label trial in 70 patients aged 6 to < 12 years (*Symdeko prescribing information 2019*).
- Two published Phase 3 trials have evaluated the safety and efficacy of elexacaftor/tezacaftor/ivacaftor in patients with CF.
  - A 24-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor vs placebo in 403 patients ≥ 12 years of age with a single *F508del* mutation and a minimal function mutation (ie, a mutation that is nonresponsive to ivacaftor and tezacaftor/ivacaftor) (*Middleton et al 2019*). The primary endpoint, the absolute change from baseline in ppFEV$_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs placebo, with a difference of 13.8 percentage points (95% confidence interval [CI], 12.1 to 15.4; p < 0.001). Differences also favored elexacaftor/tezacaftor/ivacaftor in the change from baseline in ppFEV$_1$ through week 24, number of pulmonary

exacerbations through week 24, and changes in CFQ-R respiratory domain score, body mass index (BMI), and sweat chloride concentration.
  - A 4-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor to tezacaftor/ivacaftor in 107 patients ≥ 12 years of age who were homozygous for the *F508del* mutation (*Heijerman et al 2019*). All patients received tezacaftor/ivacaftor in a 4-week run-in period that preceded the 4-week intervention period, and baseline measurements for the intervention period reflected measurements taken after the tezacaftor/ivacaftor run-in period. The primary endpoint, the absolute change from baseline in ppFEV$_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs the tezacaftor/ivacaftor group, with a difference of 10.0 percentage points (95% CI, 7.4 to 12.6). Differences also favored elexacaftor/tezacaftor/ivacaftor in sweat chloride concentration and CFQ-R respiratory domain score.
- A systematic review and meta-analysis evaluated the use of CFTR correctors, alone or in combination with ivacaftor, vs placebo in patients with CF and class II mutations (predominantly patients homozygous for the *F508del* mutation) (*Southern et al 2018*). The authors found insufficient evidence that monotherapy with a CFTR corrector has any clinically important effects in patients homozygous for *F508del*. Lumacaftor/ivacaftor and tezacaftor/ivacaftor each resulted in similar, small improvements in clinical outcomes, including quality of life, respiratory function, and pulmonary exacerbations. With respect to tolerability, lumacaftor/ivacaftor was associated with an increase in early, transient shortness of breath and longer-term increases in blood pressure, neither of which was observed with tezacaftor/ivacaftor. The authors concluded that tezacaftor/ivacaftor has a better safety profile compared to lumacaftor/ivacaftor; however, the 2 combinations have not been directly compared.
- An additional systematic review and meta-analysis evaluated the use of CFTR modulators in patients with various genetic mutations (*Habib et al 2019*). A total of 14 trials (8 Phase 3 and 6 Phase 2) were included in the review; the elexacaftor/tezacaftor/ivacaftor triple therapy was not included.
  - The authors found that the largest improvement in ppFEV$_1$ vs placebo was demonstrated in patients with the *G551D* mutation treated with ivacaftor, with a weighted absolute mean difference of 10.8% (95% CI, 9.0 to 12.7). Patients with this mutation treated with ivacaftor also had the greatest reduction in pulmonary exacerbations.
  - Patients aged ≥ 12 years who were homozygous for the *F508del* mutation had smaller improvements vs placebo when treated with lumacaftor/ivacaftor or tezacaftor/ivacaftor. Improvements with each of these combination products were similar: 3.4% (95% CI, 2.4 to 4.4) with lumacaftor/ivacaftor and 4.0% (95% CI, 3.2 to 4.8) with tezacaftor/ivacaftor. Lumacaftor/ivacaftor and tezacaftor/ivacaftor also significantly reduced the risk of exacerbations vs placebo in patients with this genotype, but the risk reduction was less than that observed with ivacaftor in patients with the *G551D* mutation. Patients treated with lumacaftor/ivacaftor had more respiratory-related AEs leading to treatment discontinuation vs placebo.

Dornase alfa

- Pivotal trials have been conducted in CF patients with an FVC > 40% predicted and in patients with advanced lung disease (FVC < 40% predicted) (*Fuchs et al 1994, McCoy et al 1996*).
  - A 24-week, randomized, double-blind, placebo-controlled trial was conducted in 968 adults and children aged ≥ 5 years with clinically stable CF and FVC > 40% predicted (*Fuchs et al 1994*). Patients received dornase alfa 2.5 mcg once daily, dornase alfa 2.5 mcg twice daily, or placebo. A T-Updraft II Nebu-u-mist nebulizer with PulmoAide compressor was used for drug administration.
    - The administration of dornase alfa once or twice daily reduced the risk of an exacerbation requiring parenteral antibiotic treatment, although only the reduction with twice-daily dosing was statistically significant. Exacerbations requiring parenteral antibiotic therapy occurred in 27%, 22%, and 19% of patients in the placebo, once-daily, and twice-daily groups, respectively. The relative risk vs placebo was 0.78 (95% CI, 0.57 to 1.06; p = 0.11) in the once-daily dornase alfa group and 0.66 (95% CI, 0.48 to 0.91; p = 0.01) in the twice-daily group. When adjusted based on the estimated relative risk of exacerbation by patient age, the exacerbation reduction was statistically significant with both dose regimens (once daily: relative risk, 0.72; 95% CI, 0.52 to 0.98; p = 0.04; twice daily: relative risk, 0.63; 95% CI, 0.46 to 0.87; p < 0.01).
    - Dornase alfa also improved pulmonary function. FEV$_1$ improved an average of 5.8% and 5.6% with once- and twice-daily dosing, respectively, throughout the study, while placebo-treated patients did not improve (change of 0.0%) (p < 0.01 for both dose regimens vs placebo).
    - Dornase alfa also improved quality of life compared to placebo.

- A 12-week, randomized, double-blind, placebo-controlled trial was conducted in 320 patients (age range, 7 to 57 years) with clinically stable CF and FVC < 40% predicted (*McCoy et al 1996*). Patients received dornase alfa 2.5 mg once daily or placebo.
  - There were no statistically significant differences in the incidence of pulmonary exacerbations; the age-adjusted relative risk for patients treated with dornase alfa vs placebo was 0.925 (95% CI, 0.69 to 1.21; p = 0.52). However, the study may have been underpowered to detect a difference.
  - Dornase alfa significantly improved pulmonary function. The mean improvements in FEV_1 were 9.4% and 2.1% in the dornase alfa and placebo groups, respectively (p < 0.001), and the mean improvements in FVC were 12.4% and 7.3%, respectively (p < 0.01).
  - No differences were observed in dyspnea scores.
- A 2-year, randomized, double-blind, placebo-controlled trial was conducted in 474 children aged 6 to 10 years with CF and mild lung function abnormalities (FVC ≥ 85% predicted) (*Quan et al 2001*). Patients received dornase alfa 2.5 mg daily or placebo with a jet nebulizer and compressor.
  - After 2 years of therapy, patients treated with dornase alfa maintained their $ppFEV_1$ (mean change from baseline, 0.04% predicted), whereas patients treated with placebo had a decrease from baseline of 3.2% predicted (p = 0.006). Lung function benefit was also shown for the forced expiratory flow between 25% and 75% of vital capacity (difference, 7.9% predicted; p = 0.0008) and maximal expiratory flow rate at 50% of vital capacity (difference, 8.2% predicted; p = 0.0002); however, the treatment difference in FVC was not statistically significant (difference, 0.7% predicted; p = 0.51).
  - Use of dornase alfa also reduced pulmonary exacerbations. In the dornase alfa group, 40 patients (17%) had a total of 62 exacerbations, compared to 56 patients (24%) and 92 exacerbations in the placebo group (relative risk, 0.66; 95% CI, 0.44 to 1.00; p = 0.048).
- A randomized crossover study in 87 patients with CF aged ≥ 6 years compared administration of dornase alfa via a jet nebulizer to administration using the Pari eRapid electronic nebulizer (*Sawicki et al 2015*). The 2 devices led to comparable efficacy and safety, while the eRapid nebulizer was associated with shorter administration times and higher patient preference.
- A systematic review and meta-analysis evaluated the use of dornase alfa in patients with CF (*Yang and Montgomery 2018*). The review included randomized and quasi-randomized controlled trials comparing dornase alfa to placebo, standard therapy, or other medications that improve airway clearance. In all, 19 trials (N = 2565) were included, most of which compared dornase alfa to placebo. Trial duration ranged from 6 days to 3 years. Of the 19 trials included in the qualitative synthesis, 13 trials were included in the meta-analysis.
  - Compared to placebo or no dornase alfa treatment, dornase alfa was demonstrated to improve FEV_1 at various time points ranging from 1 month to 2 years. Results for efficacy at 1 month of treatment were pooled from 4 trials and demonstrated a mean improvement vs placebo of 9.51% (95% CI, 0.67 to 18.35). Results for later time points were based on a smaller number of trials and generally showed smaller improvements.
  - Pooled data for pulmonary exacerbations from 3 trials found a significant exacerbation reduction, with a risk ratio of 0.78 (95% CI, 0.62 to 0.96).
  - Effects on quality-of-life measurements such as symptoms, activity limitation, fatigue, and emotional well-being varied among trials, with some (but not all) showing significant benefits.
  - Based on 7 trials, mortality was not significantly different between dornase alfa and control groups (risk ratio, 1.7; 95% CI, 0.70 to 4.14). The majority of deaths were reported from trials in patients with severe lung disease.
  - Overall, voice alteration and rash were the only AEs associated with dornase alfa.
  - Evidence comparing dornase alfa to other medications was limited.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF). Pulmonary guidelines: use of CFTR modulator therapy in patients with CF** (*Ren et al 2018*); endorsed by the American Thoracic Society
  - This guideline provides recommendations focused on 3 main questions:
    - 1: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to gating mutations other than *G551D* or *R117H* (ie, *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*)?
    - 2: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to the *R117H* mutation?

- 3: Should lumacaftor/ivacaftor combination (vs no CFTR modulator treatment) be used in individuals with 2 copies of the *F508del* mutation?

○ A total of 30 recommendations were provided, based on the questions above and patients' age and ppFEV$_1$. These recommendations are listed in Table 3.

○ The committee chose not to address clinical situations for which recommendations have already been published (see *Mogayzel et al 2013* and *Lahiri et al 2016)* or if the question was of low priority and unlikely to change practice.

Table 3. CFF recommendations for CFTR modulators in CF treatment (2018)

Patient Age (years)	ppFEV$_1$	Certainty	Recommendation
Question 1: Ivacaftor use in patients with gating mutation other than *G551D* or *R117H*			
2 to 5	Not applicable	Not applicable	Recommended*
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Low	Conditional for
6 to 11	> 90	Low	Conditional for
12 to 17	< 40	Low	Conditional for
12 to 17	40 to 90	Moderate	Conditional for
12 to 17	> 90	Moderate	Conditional for
≥ 18	< 40	Low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Moderate	Conditional for
Question 2: Ivacaftor use in patients with *R117H* mutation			
≤ 5	Not applicable	Very low	Conditional against
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Low	Conditional against
12 to 17	< 40	Very low	Conditional for
12 to 17	40 to 90	Very low	Conditional for
12 to 17	> 90	Very low	Conditional against
≥ 18	< 40	Very low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Low	Conditional for
Question 3: Lumacaftor/ivacaftor use in patients with 2 copies of *F508del*			
≤ 5	Not applicable	Not applicable	No recommendation
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Very low	Conditional for
12 to 17	< 40	Moderate	Strong for
12 to 17	40 to 90	Moderate	Strong for
12 to 17	> 90	Low	Conditional for
≥ 18	< 40	Moderate	Strong for
≥ 18	40 to 90	Moderate	Strong for
≥ 18	> 90	Low	Conditional for

*Based on the Cystic Fibrosis Preschool Guidelines recommendations

- **CFF. CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)

○ This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. It has not been updated since 2013 and thus does not include recommendations for combination CFTR modulators; recommendations also do not reflect the expanded indications for ivacaftor.

○ For these guidelines, the severity of lung disease is defined by ppFEV$_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.

- The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
- Recommendations specific to CFTR modulators and dornase alfa are shown in Table 4.

Table 4. CFF recommendations for CFTR modulators and dornase alfa in CF treatment (2013)

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Dornase alfa – moderate-to-severe disease	For individuals with CF aged ≥ 6 years with moderate-to-severe lung disease, the CFF strongly recommends the chronic use of dornase alfa to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa – mild disease	For individuals with CF aged ≥ 6 years with asymptomatic or mild lung disease, the CFF recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
2013 new or modified recommendations				
Ivacaftor	For individuals with CF aged ≥ 6 years with at least 1 *G551D CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial.
B: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

- **CFF. Clinical practice guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children aged 2 to 5 years with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 5 highlights recommendations relevant to CFTR modulators and dornase alfa. The guideline does not include the more recent expanded indications for ivacaftor or recommendations for lumacaftor/ivacaftor.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force.

Table 5. CFF recommendations for CFTR modulators and dornase alfa in preschoolers aged 2 to 5 with CF (2016)

Topic	Recommendation	Grade or Consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Dornase alfa	The CFF recommends that dornase alfa be selectively offered to patients based on individual circumstances.	Moderate	Low	C
Ivacaftor	The Preschool Guidelines Committee recommends the routine use of ivacaftor in those with specific gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, and *S549R*), and a consideration for those with a confirmed diagnosis of CF and a *R117H* mutation.	Consensus Recommendation		

***C**: The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

- **Clinical Decision Support Resource: UptoDate Topic Review**
  CF: Treatment with CFTR modulators (*Simon 2019*)
  - The use of a CFTR modulator is recommended for most individuals with CF who are ≥ 12 years old and have responsive *CFTR* variants, and suggested for most younger patients with CF for whom sufficient evidence is available to allow FDA approval. Selection of a specific CFTR modulator depends on the patient's genotype and age.
  - Table 6 provides an overview of recommendations for the use of CFTR modulators. Gating and residual function mutations are listed in the boxes below the table.
    - These recommendations reflect the indications for each CFTR modulator as of October 2019 and consideration of each drug's efficacy, AEs, and potential for drug-drug interactions. Many of the recommendations were based upon comparisons of efficacy and safety data from clinical trials in which each treatment was studied independently rather than by direct comparison of multiple treatments within a single study. These recommendations are likely to change as new evidence becomes available.

Table 6. Recommendations for CFTR modulator therapy in patients with CF

Genotype	Age group	Kalydeco (ivacaftor)	Orkambi (lumacaftor/ ivacaftor)	Symdeko (tezacaftor/ ivacaftor)	Trikafta (elexacaftor/ tezacaftor/ ivacaftor)	None available
F508del homozygote	2 to 5 yrs		✔			
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
F508del heterozygote without a gating or residual function mutation	< 12 yrs					✔
	≥ 12 yrs				✔	
F508del heterozygote with gating mutation at other allele*	6 mos to 11 yrs	✔				
	≥ 12 yrs				✔	
F508del heterozygote with residual function mutation at other allele*	6 mos to 5 yrs	✔				
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
Gating mutation without *F508del*	≥ 6 mos	✔				
Residual function mutation without *F508del*	6 mos to 5 yrs	✔				
	≥ 6 yrs			✔		

Abbreviations: **mos** = months; **yrs** = years
*For patients heterozygous for *F508del* who also have gating or residual function variants, Trikafta is suggested if it is available and the patient is eligible (≥ 12 years) because the triple combination therapy is likely to be more effective than monotherapy or dual therapy.

Gating mutations approved by FDA for Kalydeco (but not Symdeko):
G1244E, G1349D, G178R, G551D, G551S, R117H, S1251N, S1255P, S549N, S549R, G1069R, R1070Q**
*Although *G1069R* and *R1070Q* are not considered prototypic gating variants, *in vitro* studies showed that ivacaftor increased their CFTR functional activity; these findings led to the FDA approval for ivacaftor.

Residual function mutations approved by FDA for Kalydeco and Symdeko:
A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G → A, 3272-26A → G, 3849+10kbC → T, 711+3A → G

SAFETY SUMMARY

- **Kaldeco (ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been reported. It is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests (LFTs) should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Kalydeco with strong cytochrome P450 (CYP) 3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor and is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Kalydeco treatment.
  - The most common adverse reactions (≥ 8% in patients with CF who have a *G551D* mutation) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.
- **Orkambi (lumacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Orkambi should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, the patients should be closely monitored and the dose should be reduced.
    - Serious adverse reactions related to elevated transaminases have been reported; in some cases associated with concomitant elevations in total serum bilirubin. ALT, AST, and bilirubin should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase or bilirubin elevations.
    - Respiratory events (eg, chest discomfort, dyspnea, and abnormal respiration) were observed more commonly in patients during initiation of Orkambi compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease ($ppFEV_1 < 40$). Clinical experience in patients with $ppFEV_1 < 40$ is limited, and additional monitoring of these patients is recommended during initiation of therapy.
    - Increased blood pressure has been observed in some patients treated with Orkambi. Blood pressure should be monitored periodically.
    - Drug interactions:
      - Lumacaftor is a strong inducer of CYP3A. Administration of Orkambi may decrease systemic exposure of CYP3A substrates. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.
      - Orkambi may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, eg, amenorrhea, dysmenorrhea, menorrhagia, and irregular menstruation (27% in women using hormonal contraceptives compared with 3% in women not using hormonal contraceptives). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.
      - Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of Orkambi with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure and is not recommended.
      - See the prescribing information for full details on drug interactions.

- Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Orkambi treatment.
- The most common adverse reactions (≥ 5% in patients with CF who are homozygous for the *F508del* mutation) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, abnormal respiration, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza.

- **Symdeko (tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Symdeko. Assessments of ALT and AST are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and may decrease exposure to tezacaftor; co-administration is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with Symdeko. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Symdeko.
  - The most common adverse reactions (≥ 3% of patients) were headache, nausea, sinus congestion, and dizziness.

- **Trikafta (elexacaftor/tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Trikafta. Bilirubin elevations have also been observed. Assessments of ALT, AST, and bilirubin are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of hepatobiliary disease or LFT elevations. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and would be expected decrease exposure to tezacaftor and elexacaftor; co-administration is not recommended.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Trikafta.
  - The most common adverse reactions (≥ 5% of patients and more frequently than with placebo by ≥ 1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increased ALT, nasal congestion, increased blood creatine phosphokinase, increased AST, rhinorrhea, rhinitis, influenza, sinusitis, and increased blood bilirubin.

- **Pulmozyme (dornase alfa):**
  - Contraindications: patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product
  - Warnings/precautions: None
  - The most common adverse reactions (≥ 3% of patients) were voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥ 10%, fever, and dyspnea.

DOSING AND ADMINISTRATION

Table 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
CFTR Modulators				
Kalydeco (ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Orkambi (lumacaftor/ ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced for the first week of Orkambi treatment when co-administered with strong CYP3A inhibitors.
Symdeko (tezacaftor/ ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 1 tezacaftor/ivacaftor combination tablet and the evening dose is 1 ivacaftor tablet. • Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Trikafta (elexacaftor/ tezacaftor/ ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 2 elexacaftor/tezacaftor/ ivacaftor combination tablets and the evening dose is 1 ivacaftor tablet. • Dose should be reduced if used in patients with moderate hepatic impairment (to be used only if benefits outweigh risks). Trikafta should not be used in patients with severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
DNase Enzyme				
Pulmozyme (dornase alfa)	Inhalation solution	Inhalation (with nebulizer)	Once daily; some patients may benefit from twice-daily administration	• Administered using a recommended jet nebulizer/compressor system or eRapid Nebulizer System.

See the current prescribing information for full details.

CONCLUSION

- The CFTR modulators, Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor), are used in the long-term management of CF in patients eligible for such treatment based on their age and specific *CFTR* mutations. These products act to facilitate processing and trafficking of CFTR to the cell surface or to increase chloride transport at the cell surface. These products have been demonstrated to improve lung function; some trials also demonstrated improvement in reducing pulmonary exacerbations and/or improving quality of life.
  - The approval of Trikafta expanded the population of patients eligible for highly effective CFTR modulator therapy. As a result of the Trikafta approval and expanded indications for existing agents, the majority of patients with CF have become eligible for CFTR modulator therapy.
  - Key warnings/precautions with the CFTR modulators include the risk of elevated transaminases, cataracts, and drug interactions. A key additional warning for Orkambi is the risk of respiratory events (eg, chest discomfort, dyspnea, and

abnormal respiration). Orkambi has also been associated with worsening of liver function in patients with advanced liver disease, and has more significant drug interactions than the other CFTR modulators.
  - The CFTR modulators are dosed orally twice daily.
- Pulmozyme (dornase alfa) is another key treatment used in the long-term management of CF. It works to reduce sputum viscoelasticity. Guidelines recommend its use in patients aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations).
  - Pulmozyme has no warnings/precautions listed in its prescribing information.
  - Pulmozyme is administered by inhalation with a nebulizer. Recommended dosing is once daily, although some patients may benefit from twice-daily administration.

APPENDICES

Appendix A: Additional Information on CFTR Modulators

Table 8. Overview of Key Clinical Trials for CFTR Modulators

Trial/Reference	Design/Population	Key Results	Comments/ Additional Data
Kalydeco (ivacaftor)			
STRIVE *Ramsey et al 2011*	Phase 3, 48-week, DB, PC trial in 167 patients aged ≥ 12 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 10.4 percentage points from baseline; difference from placebo, 10.6 percentage points (95% CI, 8.6 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, and sweat chloride. Improvements were maintained through week 48.
ENVISION *Davies et al 2013*	Phase 3, 48-week, DB, PC trial in 52 patients aged 6 to 11 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 12.6 percentage points from baseline; difference from placebo, 12.5 percentage points (95% CI, 6.6 to 18.3; p < 0.0001)	Secondary endpoints: Improvements were observed in weight and sweat chloride. The improvement in CFQ-R (child version) did not reach statistical significance (TD, 6.0 points; p = 0.109); however, the parent/caregiver version did (TD, 5.9 points; p = 0.033). No statistically significant difference in exacerbations was demonstrated.
PERSIST *McKone et al 2014*	Phase 3, 96-week, OLE study of STRIVE and ENVISION; enrolled 192 patients aged ≥ 6 yrs with ≥ 1 *G551D* mutation; all received ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate and resolved during the reporting period; safety was consistent with the PC period of the trial $ppFEV_1$ (secondary endpoint): Improvements in FEV_1 were sustained through the 96-week extension period	Additional secondary endpoints: Improvements were sustained for weight gain, CFQ-R, and exacerbation rate.

KONNECTION *De Boeck et al 2014*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 39 patients aged ≥ 6 yrs with non-*G551D* gating mutation	$ppFEV_1$: 8 weeks: 7.5 percentage points from baseline; difference from placebo, 10.7 percentage points (95% CI, 7.3 to 14.1; p < 0.0001)	Secondary endpoints: Improvements were observed in weight, sweat chloride, and CFQ-R.
KONDUCT *Moss et al 2015*	Phase 3, 24-week, DB, PC trial in 69 patients aged ≥ 6 yrs with *R117H* mutation	$ppFEV_1$: 24 weeks: 2.6 percentage points from baseline; difference from placebo, 2.1 percentage points (95% CI, -1.13 to 5.35; p = 0.20); in a pre-specified subgroup analysis, $ppFEV_1$ significantly improved with ivacaftor in patients aged ≥ 18 yrs, with a TD vs placebo of 5.0 percentage points (95% CI, 1.15 to 8.78), but not in patients aged 6 to 11 yrs, with a TD vs placebo of -6.3 percentage points (95% CI, -11.96 to -0.71; p = 0.03)	Secondary endpoints: Improvements were observed in sweat chloride and CFQ-R. The lack of effect for $ppFEV_1$ in the pediatric and overall populations may be related in part to the fact that pediatric patients had a high baseline $ppFEV_1$. Most patients (N = 65) entered a washout period followed by an OLE period; at a 12-week analysis, patients in both the placebo-to-ivacaftor and ivacaftor-to-ivacaftor groups showed a significant $ppFEV_1$ improvement from post-washout baseline (5.0 [p = 0.0005] and 6.0 [p = 0.0006] percentage points, respectively).
EXPAND *Rowe et al 2017* *(ivacaftor and placebo arms)*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation (of these, 157 and 162 patients were treated with ivacaftor and placebo, respectively)	$ppFEV_1$: Average of 4 and 8 week assessments: difference from placebo, 4.7 percentage points (95% CI, 3.7 to 5.8; p < 0.001)	Secondary endpoint: Improvements were observed for ivacaftor vs placebo for CFQ-R. Benefits were also observed for other secondary endpoints, but statistical significance cannot be claimed due to the statistical design.
KIWI *Davies et al 2016*	Phase 3, 24-week, OL study in 34 patients aged 2 to 5 yrs with ≥ 1 *CFTR* gating mutation; patients received a dose of 50 mg (weight 8 to 14 kg) or 75 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposure was similar to that reported with the approved dosing in adults Safety: Safety was similar to use in adults, although there was an increased incidence of LFT elevations; most AEs were mild or moderate; common AEs included cough and vomiting	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. No meaningful data on lung function were available (spirometry results are limited in this age group).

ARRIVAL *Rosenfeld et al 2018*	Phase 3, 24-week, OL study in 19 patients aged 12 to < 24 months with a *CFTR* gating mutation on ≥ 1 allele (study part B); patients received a dose of 50 mg (weight 7 to 14 kg) or 75 mg (weight ≥ 14 to < 25 kg), each given twice daily	Pharmacokinetics: Exposure of ivacaftor was similar to that in older children in adults The safety profile was consistent with experience in older children; most AEs were mild or moderate and considered unlikely to be (nor not) related to ivacaftor; 27.8% of patients had elevated ALT and/or AST > 3 x ULN	Secondary endpoint: Improvements were demonstrated in sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Mean serum lipase and amylase were elevated at baseline and decreased rapidly with ivacaftor. Growth status was generally well maintained.
Orkambi (lumacaftor/ivacaftor)			
TRAFFIC and **TRANSPORT** *Wainwright et al 2015*	Two Phase 3, 24-week, DB, PC trials in 1122 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks, pooled data: 2.5 percentage points from baseline; difference from placebo, 2.8 percentage points (95% CI, 1.8 to 3.8; p < 0.001)	Secondary endpoints: In the pooled analysis, there were improvements in weight and exacerbations. The difference in CFQ-R did not reach statistical significance, with an improvement of 2.2 (95% CI, 0.0 to 4.5; p = 0.05).
PROGRESS *Konstan et al 2017*	Phase 3, 96-week, OLE study of TRAFFIC and TRANSPORT; enrolled 1030 patients aged ≥ 12 yrs homozygous for *F508del*; all received lumacaftor/ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate; rates of AEs were similar or reduced to rates during the PC period of the trial; an increase in blood pressure was noted $ppFEV_1$ (secondary endpoint): Mean $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor, but the improvement was not statistically significant	Additional secondary endpoints: The pulmonary exacerbation rate remained low. Improvements in BMI and CFQ-R continued throughout the study. Analysis of lung function change over time showed a slower rate of decline compared to matched registry patients.
Taylor-Cousar et al 2018	Phase 3b, 24-week, OL study in 46 patients aged ≥12 yrs homozygous for *F508del* who had advanced lung disease ($ppFEV_1$ < 40); 28 received lumacaftor/ivacaftor at the usual dose (400 mg/250 mg twice daily) and 18 patients initiated at half-dose (200 mg/125 mg twice daily) for	Safety/tolerability: The most common AEs were respiratory in nature (infective pulmonary exacerbation, abnormal respiration, cough, dyspnea); patients initiating on half-dose had less frequent respiratory events (56% vs 71%) and events were of shorter duration (median 4 vs 9	Secondary endpoints: There was an initial decrease in $ppFEV_1$ that returned to baseline at week 4 and remained near baseline throughout the remainder of the study. Improvements vs baseline were seen in sweat chloride and BMI. Reductions in intravenous antibiotics and all-cause hospitalization were shown between the study period and the 24-week period prior to the study.

	1 to 2 weeks before increasing to full-dose	days); 5 patients (11%) had ALT or AST elevation > 3 x ULN	Improvements in CFQ-R were not statistically significant.
Milla et al 2017	Phase 3, 24-week, OL study in 58 patients aged 6 to 11 yrs homozygous for *F508del*	ppFEV$_1$: 24 weeks: 2.5 percentage points from baseline (95% CI, -0.2 to 5.2; p = 0.0671)	Secondary endpoints: Improvements from baseline were seen in sweat chloride, weight, and CFQ-R. The small sample size and relatively mild lung disease in this population may explain the lack of significant effect on ppFEV$_1$. The safety profile was similar to that seen in larger trials in older patients.
Ratjen et al 2017	Phase 3, 24-week, DB, PC trial in 206 patients aged 6 to 11 yrs homozygous for *F508del*	Mean change in lung clearance index (LCI$_{2.5}$; see Appendix B) from baseline to average of all visits up to and including week 24 (primary endpoint): -1.0 with lumacaftor/ivacaftor vs 0.1 with placebo; TD, -1.1 (95% CI, -1.4 to -0.8; p < 0.0001) ppFEV$_1$: Average of all visits up to and including week 24: 1.1 percentage points from baseline; difference from placebo, 2.4 percentage points (95% CI, 0.4 to 4.4; p = 0.0182)	Additional secondary endpoints: Improvements were observed in sweat chloride. Changes in BMI and CFQ-R were not statistically significant.
McNamara et al 2019	Phase 3, 24-week, OL study in 60 patients aged 2 to 5 yrs homozygous for *F508del* (study part B); patients received a dose of 100 mg/125 mg (weight 8 to 14 kg) or 150 mg/188 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposures of both lumacaftor and ivacaftor were within the targeted range for older patients and similar to concentrations previously reported The safety profile was consistent with experience in adults; 10% of patients had respiratory AEs (dyspnea, abnormal respiration, wheezing); 15% had increased ALT and/or AST > 3 x ULN	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Limited data on lung function were available (spirometry results are limited in this age group). LCI$_{2.5}$ demonstrated a numerical, nonsignificant improvement (exploratory/optional endpoint).

Symdeko (tezacaftor/ivacaftor)			
EVOLVE *Taylor-Cousar et al 2017)*	Phase 3, 24-week, DB, PC trial in 509 patients aged ≥ 12 yrs homozygous for *F508del*	ppFEV$_1$: 24 weeks: 3.4 percentage points from baseline; difference from placebo, 4.0 percentage points (95% CI, 3.1 to 4.8; p < 0.001)	Secondary endpoints: Patients treated with tezacaftor/ivacaftor had a reduced number of pulmonary exacerbations. Numerical improvements were seen in BMI, CFR-Q, and sweat chloride. The change in BMI was not statistically significant, and the changes in CFQ-R and sweat chloride were not assessed for statistical significance due to the testing hierarchy. The rate of respiratory AEs was not higher in the tezacaftor/ivacaftor group than the placebo group; this compares favorably to studies with lumacaftor/ivacaftor.
EXPAND *Rowe et al 2017*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation	ppFEV$_1$: 8 weeks: difference for tezacaftor/ivacaftor vs placebo, 6.8 percentage points (95% CI, 5.7 to 7.8; p < 0.0001); difference for tezacaftor/ivacaftor vs ivacaftor, 2.1 percentage points (95% CI, 1.2 to 2.9; p < 0.0001)	Secondary endpoints: Improvement was seen in CFQ-R for tezacaftor/ivacaftor vs placebo; the difference in CFQ-R between tezacaftor/ivacaftor and ivacaftor was not statistically significant. A numerical improvement was observed in sweat chloride, but significance was not assessed due to the statistical hierarchy.
Trikafta (elexacaftor/tezacaftor/ivacaftor)			
VX17-445-102 *Middleton et al 2019*	Phase 3, 24-week, DB, PC trial in 403 patients aged ≥ 12 years heterozygous for *F508del* and a minimal function mutation	ppFEV$_1$: 4 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 13.8 percentage points (95% CI, 12.1 to 15.4; p < 0.001) 24 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 14.3 percentage points (95% CI, 12.7 to 15.8; p < 0.001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, sweat chloride, and BMI.

VX17-445-103 *Heijerman et al 2019*	Phase 3, 4-week, DB, AC trial in 107 patients aged ≥ 12 years homozygous for *F508del*	ppFEV$_1$: 4 weeks: difference for elexacaftor/tezacaftor/ivacaftor vs tezacaftor/ivacaftor: 10.0 percentage points (95% CI, 7.4 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were seen in CFQ-R score and sweat chloride. Exacerbations were not defined as an efficacy endpoint, but were reported as an AE less frequently in the elexacaftor/tezacaftor/ivacaftor group than in the tezacaftor/ivacaftor group. BMI was not defined as an efficacy endpoint but increased more in the elexacaftor/tezacaftor/ivacaftor group (nominal p < 0.0001).

Note: CFQ-R scores refer to the respiratory domain.
Abbreviations: **AC** = active-controlled, **AE** = adverse event, **ALT** = alanine aminotransferase, **AST** = aspartate aminotransferase, **BMI** = body mass index, **CFQ-R** = cystic fibrosis questionnaire-revised, **CI** = confidence interval, **DB** = double-blind, **LCI** = lung clearance index, **LFT** = liver function test, **OL** = open-label, **OLE** = open-label extension, **PC** = placebo-controlled, **ppFEV$_1$** = percent predicted forced expiratory volume in 1 second, **TD** = treatment difference, **ULN** = upper limit of normal, **XO** = crossover, **yrs** = years

Appendix B: Study endpoint descriptions

- **CF Questionnaire (CFQ); CF Questionnaire-Revised (CFQ-R)** (*American Thoracic Society 2002, Quittner et al 2009*)
  - This is a disease-specific quality-of-life instrument designed to measure impact of CF on overall health, daily life, perceived well-being, and symptoms.
  - The CFQ-R has 9 quality-of-life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, and health perceptions) and 3 symptom scales (weight, respiratory, and digestion).
  - Scaling of items uses 4-point Likert scales (eg, always/often/sometimes/never).
  - Each health-related quality-of-life domain is scored. Standardized scores range from 0 to 100, with higher scores indicating better quality of life.
  - The minimal clinically important difference in CFQ-R respiratory scores has been estimated to be approximately 8.5 points in patients experiencing a CF exacerbation and 4.0 points in stable CF patients.
- **Lung Clearance Index (LCI$_{2.5}$)** (*Ratjen et al 2017*)
  - This is a measure of the number of lung volume turnovers required to reach 2.5% of tracer gas concentration.
  - Elevated LCI$_{2.5}$ values reflect increasing unevenness of gas mixing within the lung caused by early lung disease secondary to mucus plugging and airway wall changes.
  - LCI$_{2.5}$ may be more sensitive than FEV$_1$ for the presence of early structural lung abnormalities, particularly in the pediatric population.
- **Sweat chloride test** (*Durmowicz et al 2013, Farrell et al 2017*)
  - This test measures the amount of chloride in a patient's sweat. It is considered the gold standard for diagnosis of CF.
  - A sweat test concentration of ≥ 60 mmol/L indicates a diagnosis of CF, and a concentration of < 30 mmol/L indicates that CF is unlikely. Patients with results in the intermediate range (30 to 59 mmol/L) and certain clinical characteristics (positive newborn screen, symptoms of CF, or a positive family history) may have CF and further testing should be considered.
  - Based on the diagnostic relationship between sweat chloride and CF, change in sweat chloride has been used as a measure of CFTR function and as a pharmacodynamic endpoint in clinical trials. A reduction in sweat chloride has been demonstrated in clinical trials of CFTR modulators. However, a correlation between changes in sweat chloride and improvements in FEV$_1$ has not been consistently demonstrated, and there is no specific improvement in sweat chloride concentration that can predict FEV$_1$ improvement. This may be related to the multiple physiologic, environmental, and genetic factors that modulate CF severity.

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