South Dakota
Department of Social Services

Medicaid P&T Committee Meeting

September 24, 2021

South Dakota Department of Social Services

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DEPARTMENT OF SOCIAL SERVICES
DIVISION OF MEDICAL SERVICES
700 GOVERNORS DRIVE
PIERRE, SD 57501-2291
PHONE: 605-773-3495
FAX: 605-773-5246
WEB: dss.sd.gov

South Dakota Department of Social Services

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

September 24, 2021
1:00 – 3:00 PM

Meeting Link:
https://teams.microsoft.com/l/meetup-join/19%3ameeting_Y2MwMTIxY2UtNjRiNC00NDYzLThjN2QtNTMxODkyYTViYWQ0%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%22b6efd724-b34e-4a86-b34c-e34f07dd4ceb%22%7d

Join with a video conferencing device
425899727@t.plcm.vc
Video Conference ID: 115 934 363 8

Join by phone
+1 952-222-7450
Phone Conference ID: 239 533 389#

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**
- **Atypical Antipsychotic utilization**
- **ADHD utilization**
- **Gabapentin high-dose utilization**
- **Review of PA forms and criteria**
- **Juxtapid**
- **Imcivree**
- **Opioid update**

New business
- **Dermatological PA approval review**
- **Antiviral PA approval review**
- **Cholbam utilization review for diagnosis**
- **Pancreatic enzyme utilization**
- **Hemophilia factor product utilization**
- **Cystic fibrosis medication compliance**
- **Brexafemme**

Public input accepted after individual topic discussion
Next meeting date December 10, 2021 & adjournment

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

Friday, June 11, 2021
1:00 – 3:00 pm CT

Members and DSS Staff

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

Administrative Business

Darger called the meeting to order at 1:04 pm. The minutes of the December meeting were presented. Baack made a motion to approve. Ladwig seconded the motion. The motion was unanimously approved via roll call vote.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity report from January 1, 2021 to March 31, 2021. A total of 1,718 PAs were reviewed of which 168 requests (9.8%) were received via telephone and 952 requests (55.4%) were received via fax, and 598 (34.8%) were reviewed via electronically. There was a 15% increase of PAs received from the previous quarter. Baack requested an in-depth review of dermatological PAs and Van Gilder requested to review antivirals PAs at the next meeting.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from January 1, 2021 to March 31, 2021. The top five therapeutic classes based on paid amount were atypical antipsychotics, disease-modifying anti-rheumatic agents, skin and mucous membrane agents, amphetamines, and cystic fibrosis correctors. The top 15 therapeutic classes make up 24.86 % of total claims. The committee also reviewed the top 50 drugs based on amount paid and number of claims. The top 50 drugs by amount paid make up 9.58 % of total claims. HIV integrase inhibitor antiretrovirals made its debut on the top 15 therapeutic classes. Ladwig requested to review compliance of patients on cystic fibrosis drugs. Darger commented on the utilization of all the hemophilia factor products which combined would sum up to a considerable amount. Jockheck noted the utilization of 3 prescriptions for Hemlibre which should lesson the amount of factor products needed, but increased utilization doesn't seem to support it. Utilization of all factor products were requested to review for the next meeting. Darger requested utilization review for Flovent and generics; and saving opportunities for Creon and Zenpep. Baack requested to review diagnosis submitted for Cholbam, for rare bile acid synthesis disorders.

Old Business

90-Day Fill

Jockheck provided an update on the 90-day fill which was implemented on 10/1/2020. A 90-day supply of generic maintenance medication is allowed after member establishes three monthly fills. Utilization increased to an average about 700 prescriptions per month.

Atypical antipsychotic utilization in children
Committee continued the conversation on the proposed PA criteria for prescribers wanting to add a 3 or more atypical antipsychotics. Stanley commented the diagnoses listed are exceedingly broad. In addition, the criteria for depression should be clarified for atypical antipsychotics to be used as augmentation. Baack was concerned about the age at which the involvement of psychiatrist, developmental pediatrician, child/adolescent psychiatrist or pediatric neurologist involved in care being low. Stanley supported increasing the age edit for requirement for specialist.
Baack requested utilization for members aged 6 to 12 years old on multiple atypical antipsychotics, diagnosis and prescriber information. Committee requested the criteria to be discussed at next meeting. Darger inquired if there was any public comment. There were none.

ADHD utilization
Committee reviewed ADHD utilization in members 21 years and older. They also reviewed the comparison of PMPM and PUPM of other state Medicaid programs. Committee discussed potential PA on Vyvanse for continuation of therapy from minority to maturity age, step therapy requiring dexmethylphenidate first. Committee requesting PA criteria from State B and other Medicaid programs that require step therapy on Vyvanse. Darger inquired if there was any public comment. There were none.

Opioid update
The committee reviewed 1Q2021 opioid outcomes compared to previous quarters from the opioid initiatives. There was a slight increase in opioid utilization and opioid utilizers during first quarter which corresponds to increase in eligible members. The number of members exceeding 180 MED/day continues to decrease quarter over quarter.

Review PA forms and criteria
The committee reviewed all PA criteria currently in effect. Darger made the following recommendations:

- Byvalson – remove PA
- Nucala – add indication for hypereosinophilic syndrome
- Actemera – add indication for systemic sclerosis associated with interstitial lung disease
- Xolair – add indication for Nasal Polyps with a nasal steroid
- Ketoconazole Topical – update title with brand drug names
- Multiple Sclerosis – revaluate Tysabri for Crohns on the MS PA
- Triptans – consolidate the PA forms if possible
- Nuvigil and Provigil – review need for PA
- Onfi – review need for PA
- Oracea – review need for PA
- Qualaquin – review need for PA
- Soma 250 – review need for PA
- Ultram ER – review need for PA
- Uloric – review need for PA

Van Gilder made the following recommendation:

- Non-sedating antihistamines – review need for PA

Darger inquired if there was any public comment. There were none. Ladwig made a motion to incorporate changes as discussed and if more input was needed from the committee for deeper discussion, those are to be brought back for the committee's input. Stanley seconded the motion. Motion was passed unanimously.

New Business

Gabapentin high-dose utilization review

The committee reviewed utilization of all gabapentin claims and especially those over 1,800 mg/day. Committee discussed various way to manage the high-dose usage. Baack requested an in-depth review of members taking over 4,800 mg/day. Ladwig requested to quantify early refills to identify creep. Darger inquired if there was any public comment. There were none.

Opioid-Benzodiazepine-stimulant utilization review

The committee reviewed utilization of medications considered high risk combinations. Current utilization of these combinations is lowered than expected. Darger inquired if there was any public comment. There were none.

Imcivree

Imcivree was reviewed. The committee requested to review the proposed PA at the next meeting. Darger inquired if there was any public comment. There were none.

Juxtapid

Juxtapid was reviewed. The committee requested to review the proposed criteria at the next meeting. Darger inquired if there was any public comment. There were none.

Adjournment

The next meeting is scheduled on September 24, 2021. The December meeting is tentatively scheduled on December 10, 2021. The Committee made a motion to adjourn the meeting and everyone seconded the motion. The motion passed unanimously, and the meeting adjourned at 3:00 pm.

PA Report
4/1/2021 – 6/30/2021

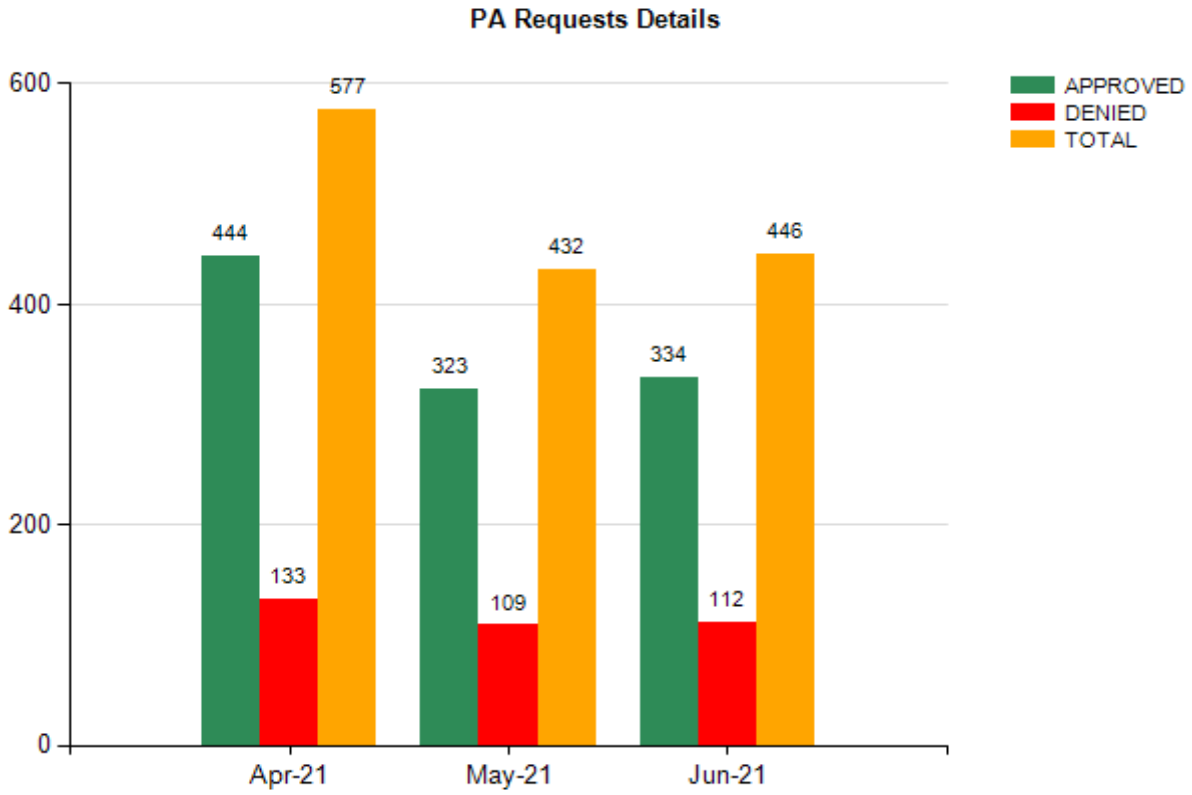
Compliance Summary

Priority	Total PAs	PAs Compliant (Standard - 72 hrs Urgent - 24 hrs)	PAs Not Compliant	% PAs Compliant	% PAs Not Compliant
Standard	1,423	1,423	0	100.00%	0.00%
Urgent	32	32	0	100.00%	0.00%
Grand Total	**1,455**	**1,455**	**0**		

	# of	Phone Requests		Fax Requests		Real-Time PA	
Drug Class	Requests	#	%	#	%	#	%
Total	**1,455**	**141**	**9.7%**	**847**	**58.2%**	**467**	**32.1%**

PA Initial Requests Summary

Month	Approved	Denied	Total
Apr-21	444	133	577
May-21	323	109	432
Jun-21	334	112	446
2Q21	**1,101**	**354**	**1,455**
Percent of Total	**75.67%**	**24.33%**	



Top Therapeutic Classes for PA

Drug Class	Approved	Denied	Total	Approval Rate	% of Total Requests	Most Requested Products
59 - ANTIPSYCHOTICS/ANTIMANIC	195	15	210	92.86%	14.43%	, INVEGA SUSTENNA
65 - ANALGESICS - OPIOID*	102	78	180	56.67%	12.37%	TRAMADOL, HYDROCODONE/APAP
90 - DERMATOLOGICALS*	101	76	177	57.06%	12.16%	SPINOSAD, MALATHION
27 - ANTIDIABETICS*	135	14	149	90.60%	10.24%	, OZEMPIC
58 - ANTIDEPRESSANTS*	116	23	139	83.45%	9.55%	, DESVENLAFAXINE ER
OTHERS -	452	148	600	75.33%	41.24%	
2Q21	**1,101**	**354**	**1,455**	**75.67%**		

PA Drug Class Summary

Drug Class	Approved	Denied	Total	Approval Rate
59 - ANTIPSYCHOTICS/ANTIMANIC AGENTS*	195	15	210	92.86%
27 - ANTIDIABETICS*	135	14	149	90.60%
58 - ANTIDEPRESSANTS*	116	23	139	83.45%
65 - ANALGESICS - OPIOID*	102	78	180	56.67%
90 - DERMATOLOGICALS*	101	76	177	57.06%
49 - ULCER DRUGS/ANTISPASMODICS/ANTICHOLINERG	91	19	110	82.73%
52 - GASTROINTESTINAL AGENTS - MISC.*	52	12	64	81.25%
61 - ADHD/ANTI-NARCOLEPSY/ANTI-OBESITY/ANOREX	39	17	56	69.64%
66 - ANALGESICS - ANTI-INFLAMMATORY*	35	5	40	87.50%
16 - ANTI-INFECTIVE AGENTS - MISC.*	32	4	36	88.89%
67 - MIGRAINE PRODUCTS*	31	22	53	58.49%
41 - ANTIHISTAMINES*	29	5	34	85.29%
72 - ANTICONVULSANTS*	28	5	33	84.85%
54 - URINARY ANTISPASMODICS*	19	8	27	70.37%
50 - ANTIEMETICS*	15	2	17	88.24%
62 - PSYCHOTHERAPEUTIC AND NEUROLOGICAL AGENT	13	1	14	92.86%
21 - ANTINEOPLASTICS AND ADJUNCTIVE THERAPIES	9	1	10	90.00%
39 - ANTIHYPERLIPIDEMICS*	9	1	10	90.00%
75 - MUSCULOSKELETAL THERAPY AGENTS*	8	4	12	66.67%
83 - ANTICOAGULANTS*	8	2	10	80.00%
30 - ENDOCRINE AND METABOLIC AGENTS - MISC.*	6	4	10	60.00%
33 - BETA BLOCKERS*	5	1	6	83.33%
44 - ANTIASTHMATIC AND BRONCHODILATOR AGENTS*	5	1	6	83.33%
60 - HYPNOTICS/SEDATIVES/SLEEP DISORDER AGENT	4	7	11	36.36%
12 - ANTIVIRALS*	3	15	18	16.67%
34 - CALCIUM CHANNEL BLOCKERS*	3	1	4	75.00%
79 - MINERALS & ELECTROLYTES*	2	0	2	100.00%
82 - HEMATOPOIETIC AGENTS*	2	2	4	50.00%
01 - PENICILLINS*	1	0	1	100.00%
40 - CARDIOVASCULAR AGENTS - MISC.*	1	0	1	100.00%
42 - NASAL AGENTS - SYSTEMIC AND TOPICAL*	1	0	1	100.00%
94 - DIAGNOSTIC PRODUCTS*	1	0	1	100.00%
02 - CEPHALOSPORINS*	0	2	2	0.00%
03 - MACROLIDES*	0	1	1	0.00%
04 - TETRACYCLINES*	0	1	1	0.00%
36 - ANTIHYPERTENSIVES*	0	1	1	0.00%
38 - VASOPRESSORS*	0	1	1	0.00%
45 - RESPIRATORY AGENTS - MISC.*	0	1	1	0.00%
86 - OPHTHALMIC AGENTS*	0	2	2	0.00%
2Q21	**1,101**	**354**	**1,455**	
Percent of Total	**75.67%**	**24.33%**		

PA Appeals Summary

Month	Approved	Approved %	Denied	Denied %	Total
April-21	19	86.36%	3	13.64%	22
May-21	14	82.35%	3	17.65%	17
June-21	12	66.67%	6	33.33%	18
2Q21	**45**	**78.95%**	**12**	**21.05%**	**57**

Appeals Detail

Drug Class	Approved	Denied	Total	Approval Rate
LUBIPROSTONE	5	1	6	83.33%
TRAMADOL HCL	4	0	4	100.00%
HYDROCODONE/ACETAMINOPHEN	3	0	3	100.00%
AIMOVIG	2	1	3	66.67%
EMGALITY	2	0	2	100.00%
ABILIFY MAINTENA	1	0	1	100.00%
ARISTADA	1	0	1	100.00%
CLINDAMYCIN/BENZOYL PEROXIDE	1	0	1	100.00%
CLOBAZAM	1	0	1	100.00%
DESVENLAFAXINE ER	1	0	1	100.00%
DIFICID	1	0	1	100.00%
DUPIXENT	1	0	1	100.00%
ENOXAPARIN SODIUM	1	0	1	100.00%
EPIDUO FORTE	1	0	1	100.00%
ESCITALOPRAM OXALATE	1	0	1	100.00%
FENTANYL	1	0	1	100.00%
GENOTROPIN	1	1	2	50.00%
HYDROCODONE BITARTRATE/ACETAMINOPHEN	1	0	1	100.00%
JAKAFI	1	0	1	100.00%
KINERET	1	0	1	100.00%
LANSOPRAZOLE	1	0	1	100.00%
LATUDA	1	0	1	100.00%
LINDANE	1	0	1	100.00%
LYRICA CR	1	0	1	100.00%
MAVYRET	1	3	4	25.00%
MONTELUKAST SODIUM	1	0	1	100.00%
MYRBETRIQ	1	1	2	50.00%
NORDITROPIN FLEXPRO	1	0	1	100.00%
NUCYNTA	1	0	1	100.00%
OXERVATE	1	0	1	100.00%
RYBELSUS	1	0	1	100.00%
SKYRIZI	1	0	1	100.00%
SOOLANTRA	1	0	1	100.00%
STELARA	1	0	1	100.00%
AMITIZA	0	1	1	0.00%
AZELAIC ACID	0	1	1	0.00%
ESZOPICLONE	0	1	1	0.00%
OZEMPIC	0	1	1	0.00%
SYMPAZAN	0	1	1	0.00%
LUBIPROSTONE	5	1	6	83.33%
2Q21	**45**	**12**	**57**	

Top 15 Therapeutic Classes & Top 50 Drugs

TOP 15 THERAPEUTIC CLASSES BASED ON NUMBER OF CLAIMS FROM 4/1/2021 – 6/30/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	13,957	$183,595.35	$13.15	6.68%
2	ANTICONVULSANTS, MISCELLANEOUS	11,404	$1,127,362.15	$98.86	5.46%
3	ATYPICAL ANTIPSYCHOTICS	8,929	$2,670,972.13	$299.13	4.28%
4	SECOND GENERATION ANTIHISTAMINES	7,795	$90,787.55	$11.65	3.73%
5	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,096	$506,924.77	$71.44	3.40%
6	RESPIRATORY AND CNS STIMULANTS	6,497	$483,696.68	$74.45	3.11%
7	AMPHETAMINES	6,478	$1,102,000.49	$170.11	3.10%
8	PROTON-PUMP INHIBITORS	6,300	$199,710.83	$31.70	3.02%
9	ADRENALS	5,919	$651,566.07	$110.08	2.83%
10	OPIATE AGONISTS	5,880	$187,934.87	$31.96	2.82%
11	AMINOPENICILLIN ANTIBIOTICS	5,647	$82,604.43	$14.63	2.70%
12	ANXIOLYTICS, SEDATIVES, AND HYPNOTICS, MISC	4,285	$144,660.53	$33.76	2.05%
13	CONTRACEPTIVES	4,014	$129,098.02	$32.16	1.92%
14	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,709	$277,172.13	$74.73	1.78%
15	THYROID AGENTS	3,581	$74,173.55	$20.71	1.71%
Total		**101,491**	**$7,912,259.55**	**$77.96**	**48.60%**

TOP 15 THERAPEUTIC CLASSES BASED ON AMOUNT PAID FROM 4/1/2021 – 6/30/2021					
	AHFS Description	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	ATYPICAL ANTIPSYCHOTICS	8,929	$2,670,972.13	$299.13	4.28%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	297	$1,710,154.25	$5,758.10	0.14%
3	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	566	$1,357,798.91	$2,398.94	0.27%
4	CYSTIC FIBROSIS (CFTR) CORRECTORS	57	$1,128,991.04	$19,806.86	0.03%
5	ANTICONVULSANTS, MISCELLANEOUS	11,404	$1,127,362.15	$98.86	5.46%
6	AMPHETAMINES	6,478	$1,102,000.49	$170.11	3.10%
7	HEMOSTATICS	42	$1,031,331.71	$24,555.52	0.02%
8	ADRENALS	5,919	$651,566.07	$110.08	2.83%
9	LONG-ACTING INSULINS	1,335	$648,828.80	$486.01	0.64%
10	INCRETIN MIMETICS	726	$609,689.41	$839.79	0.35%
11	ANTINEOPLASTIC AGENTS	282	$573,633.16	$2,034.16	0.14%
12	RAPID-ACTING INSULINS	1,316	$556,883.00	$423.16	0.63%
13	SELECTIVE BETA-2-ADRENERGIC AGONISTS	7,096	$506,924.77	$71.44	3.40%
14	RESPIRATORY AND CNS STIMULANTS	6,497	$483,696.68	$74.45	3.11%
15	GI DRUGS, MISCELLANEOUS	404	$434,396.87	$1,075.24	0.19%
Total		**51,348**	**$14,594,229.44**	**$284.22**	**24.59%**

Total Rx Claims from 4/1/2021 – 6/30/2021	**208,814**

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 4/1/2021 – 6/30/2021						
	AHFS Description	Drug Label Name	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,615	$261,263.78	$56.61	2.21%
2	SECOND GENERATION ANTIHISTAMINES	CETIRIZINE	4,379	$47,532.59	$10.85	2.10%
3	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN	4,208	$54,263.69	$12.90	2.02%
4	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,852	$166,033.64	$43.10	1.84%
5	PROTON-PUMP INHIBITORS	OMEPRAZOLE	3,772	$44,051.60	$11.68	1.81%
6	LEUKOTRIENE MODIFIERS	MONTELUKAST SODIUM	3,393	$46,645.73	$13.75	1.62%
7	ANTICONVULSANTS, MISCELLANEOUS	GABAPENTIN	3,330	$56,895.74	$17.09	1.59%
8	AMPHETAMINES	VYVANSE	3,251	$986,180.81	$303.35	1.56%
9	SEROTONIN MODULATORS	TRAZODONE	3,238	$33,564.49	$10.37	1.55%
10	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE	3,188	$41,416.58	$12.99	1.53%
11	AMPHETAMINES	AMPHETAMINE/DEXTROA	3,063	$93,235.21	$30.44	1.47%
12	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	ESCITALOPRAM	2,993	$38,603.04	$12.90	1.43%
13	THYROID AGENTS	LEVOTHYROXINE	2,915	$50,972.60	$17.49	1.40%
14	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	2,496	$29,743.72	$11.92	1.20%
15	CENTRAL ALPHA-AGONISTS	CLONIDINE	2,385	$23,809.01	$9.98	1.14%
16	ANGIOTENSIN-CONVERTING ENZYME INHIBITOR	LISINOPRIL	2,175	$20,189.67	$9.28	1.04%
17	ANTIDEPRESSANTS, MISCELLANEOUS	BUPROPION	2,160	$42,539.13	$19.69	1.03%
18	ATYPICAL ANTIPSYCHOTICS	ARIPIPRAZOLE	2,072	$35,943.24	$17.35	0.99%
19	OPIATE AGONISTS	HYDROCODONE/APAP	1,981	$29,010.09	$14.64	0.95%
20	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	SERTRALINE	1,969	$24,213.40	$12.30	0.94%
21	HMG-COA REDUCTASE INHIBITORS	ATORVASTATIN CALCIUM	1,966	$23,131.23	$11.77	0.94%
22	SECOND GENERATION ANTIHISTAMINES	LORATADINE	1,905	$21,033.23	$11.04	0.91%
23	CORTICOSTEROIDS (EENT)	FLUTICASONE PROPIONAT	1,765	$26,165.27	$14.82	0.85%
24	SELECTIVE-SEROTONIN REUPTAKE INHIBITORS	FLUOXETINE HCL	1,752	$20,904.54	$11.93	0.84%
25	ATYPICAL ANTIPSYCHOTICS	RISPERIDONE	1,726	$22,022.39	$12.76	0.83%
26	ANTICONVULSANTS, MISCELLANEOUS	LAMOTRIGINE	1,652	$23,996.58	$14.53	0.79%
27	ADRENALS	PREDNISONE	1,633	$16,539.28	$10.13	0.78%
28	ATYPICAL ANTIPSYCHOTICS	QUETIAPINE	1,629	$20,977.73	$12.88	0.78%
29	VACCINES	COVID-19	1,617	$64,106.72	$39.65	0.77%
30	OTHER MACROLIDE ANTIBIOTICS	AZITHROMYCIN	1,606	$27,394.55	$17.06	0.77%
31	COMPOUNDS	-	1,588	$49,653.77	$31.27	0.76%
32	BIGUANIDES	METFORMIN	1,568	$15,625.49	$9.97	0.75%
33	1ST GENERATION CEPHALOSPORIN ANTIBIOTICS	CEPHALEXIN	1,556	$24,901.66	$16.00	0.75%
34	SEL.SEROTONIN, NOREPI REUPTAKE INHIBITOR	DULOXETINE	1,489	$23,113.96	$15.52	0.71%
35	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE ER	1,488	$28,260.38	$18.99	0.71%
36	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE	1,481	$29,505.87	$19.92	0.71%
37	CORTICOSTEROIDS (SKIN, MUCOUS MEMBRAN)	TRIAMCINOLONE ACETON	1,469	$22,316.64	$15.19	0.70%
38	BENZODIAZEPINES (ANTICONVULSANTS)	CLONAZEPAM	1,467	$16,107.38	$10.98	0.70%
39	5-HT3 RECEPTOR ANTAGONISTS	ONDANSETRON ODT	1,463	$21,525.47	$14.71	0.70%
40	AMINOPENICILLIN ANTIBIOTICS	AMOXICILLIN/CLAVULANA	1,420	$26,405.62	$18.60	0.68%
41	ANTICONVULSANTS, MISCELLANEOUS	LEVETIRACETAM	1,323	$28,404.03	$21.47	0.63%
42	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	CYCLOBENZAPRINE	1,219	$12,516.79	$10.27	0.58%
43	ANTIDEPRESSANTS, MISCELLANEOUS	MIRTAZAPINE	1,210	$17,149.01	$14.17	0.58%
44	DIHYDROPYRIDINES	AMLODIPINE	1,208	$11,773.10	$9.75	0.58%
45	OPIATE AGONISTS	TRAMADOL HCL	1,205	$12,680.92	$10.52	0.58%
46	ANTICONVULSANTS, MISCELLANEOUS	TOPIRAMATE	1,178	$17,186.20	$14.59	0.56%
47	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	GUANFACINE	1,174	$22,376.36	$19.06	0.56%
48	VITAMIN D	VITAMIN D	1,167	$11,977.01	$10.26	0.56%
49	3RD GENERATION CEPHALOSPORIN ANTIBIOTIC	CEFDINIR	1,145	$23,930.72	$20.90	0.55%
50	PROTON-PUMP INHIBITORS	PANTOPRAZOLE	1,117	$13,749.52	$12.31	0.53%
	Total Top 50 Drugs		**105,621**	**$2,821,539.18**	**$26.71**	**50.58%**

TOP 50 DRUGS BASED ON AMOUNT PAID FROM 4/1/2021 – 6/30/2021						
	AHFS Description	Drug Label Name	Total Rxs	Pharmacy Due Amount	Paid/Rx	%Total Claims
1	AMPHETAMINES	VYVANSE	3,251	$986,180.81	$303.35	1.56%
2	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA PEN	116	$886,867.14	$7,645.41	0.06%
3	CYSTIC FIBROSIS (CFTR) CORRECTORS	TRIKAFTA	36	$791,382.67	$21,982.85	0.02%
4	ATYPICAL ANTIPSYCHOTICS	INVEGA SUSTENNA	309	$745,820.80	$2,413.66	0.15%
5	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	STELARA	28	$540,600.94	$19,307.18	0.01%
6	ATYPICAL ANTIPSYCHOTICS	LATUDA	407	$514,467.45	$1,264.05	0.19%
7	HEMOSTATICS	ADVATE	12	$458,671.68	$38,222.64	0.01%
8	ATYPICAL ANTIPSYCHOTICS	ARISTADA	173	$438,440.58	$2,534.34	0.08%
9	CYSTIC FIBROSIS (CFTR) CORRECTORS	ORKAMBI	21	$337,608.37	$16,076.59	0.01%
10	ATYPICAL ANTIPSYCHOTICS	VRAYLAR	255	$304,967.78	$1,195.95	0.12%
11	RESPIRATORY AND CNS STIMULANTS	METHYLPHENIDATE	4,615	$261,263.78	$56.61	2.21%
12	MUCOLYTIC AGENTS	PULMOZYME	65	$253,232.72	$3,895.89	0.03%
13	INCRETIN MIMETICS	OZEMPIC	279	$241,425.08	$865.32	0.13%
14	VESICULAR MONOAMINE TRANSPORT2 INHIBIT	INGREZZA	39	$233,318.19	$5,982.52	0.02%
15	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	COSENTYX SENSOREADY	36	$225,832.95	$6,273.14	0.02%
16	ADRENALS	FLOVENT HFA	926	$224,866.01	$242.84	0.44%
17	OTHER MISCELLANEOUS THERAPEUTIC AGENTS	EVRYSDI	10	$223,513.60	$22,351.36	0.00%
18	LONG-ACTING INSULINS	LANTUS SOLOSTAR	542	$220,579.00	$406.97	0.26%
19	INCRETIN MIMETICS	TRULICITY	261	$219,507.38	$841.02	0.12%
20	SOMATOTROPIN AGONISTS	NORDITROPIN FLEXPRO	56	$216,822.92	$3,871.84	0.03%
21	SKIN AND MUCOUS MEMBRANE AGENTS, MISC.	DUPIXENT	68	$214,059.36	$3,147.93	0.03%
22	ANTICONVULSANTS, MISCELLANEOUS	VIMPAT	234	$208,763.90	$892.15	0.11%
23	ATYPICAL ANTIPSYCHOTICS	REXULTI	189	$208,117.92	$1,101.15	0.09%
24	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	HUMIRA	30	$203,834.51	$6,794.48	0.01%
25	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	BIKTARVY	63	$192,114.94	$3,049.44	0.03%
26	HEMOSTATICS	HEMLIBRA	3	$184,880.28	$61,626.76	0.00%
27	SODIUM-GLUC COTRANSPORT 2 (SGLT2) INHIB	JARDIANCE	339	$181,912.14	$536.61	0.16%
28	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ALBUTEROL SULFATE HFA	3,852	$166,033.64	$43.10	1.84%
29	LONG-ACTING INSULINS	TRESIBA FLEXTOUCH	258	$162,280.63	$628.99	0.12%
30	RIFAMYCIN ANTIBIOTICS	XIFAXAN	72	$156,736.25	$2,176.89	0.03%
31	ANTICONVULSANTS, MISCELLANEOUS	EPIDIOLEX	59	$155,065.51	$2,628.23	0.03%
32	HEMOSTATICS	RECOMBINATE	3	$145,033.20	$48,344.40	0.00%
33	HEMOSTATICS	XYNTHA SOLOFUSE	4	$139,984.26	$34,996.07	0.00%
34	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	XYREM	9	$138,676.80	$15,408.53	0.00%
35	RAPID-ACTING INSULINS	INSULIN ASPART FLEXPEN	359	$136,866.26	$381.24	0.17%
36	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	JANUVIA	289	$135,911.21	$470.28	0.14%
37	DIGESTANTS	CREON	74	$134,243.27	$1,814.10	0.04%
38	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	ENBREL SURECLICK	25	$133,974.61	$5,358.98	0.01%
39	GI DRUGS, MISCELLANEOUS	GATTEX	3	$125,022.12	$41,674.04	0.00%
40	GI DRUGS, MISCELLANEOUS	CHOLBAM	6	$124,413.00	$20,735.50	0.00%
41	HIV INTEGRASE INHIBITOR ANTIRETROVIRALS	GENVOYA	36	$119,083.02	$3,307.86	0.02%
42	LONG-ACTING INSULINS	LEVEMIR FLEXTOUCH	238	$118,389.72	$497.44	0.11%
43	ATYPICAL ANTIPSYCHOTICS	ABILIFY MAINTENA	54	$117,712.41	$2,179.86	0.03%
44	VASODILATING AGENTS (RESPIRATORY TRACT)	UPTRAVI	11	$117,579.38	$10,689.03	0.01%
45	ANTINEOPLASTIC AGENTS	SPRYCEL	9	$117,409.14	$13,045.46	0.00%
46	SELECTIVE BETA-2-ADRENERGIC AGONISTS	ADVAIR HFA	312	$117,122.52	$375.39	0.15%
47	ATYPICAL ANTIPSYCHOTICS	INVEGA TRINZA	15	$116,249.59	$7,749.97	0.01%
48	DIRECT FACTOR XA INHIBITORS	ELIQUIS	247	$114,179.46	$462.27	0.12%
49	INTERLEUKIN ANTAGONISTS	DUPIXENT	35	$109,405.50	$3,125.87	0.02%
50	GI DRUGS, MISCELLANEOUS	LINZESS	225	$104,431.42	$464.14	0.11%
	Total Top 50 Drugs		**18,558**	**$12,724,855.82**	**$685.68**	**8.89%**

Old Business

90 Day Fill update

Atypical Antipsychotic PA Criteria:

1. For continuation of atypical antipsychotic agent **OR**

2. Diagnosis of

2.1 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

2.1 Both of the following:

2.1.1 Patient has a diagnosis of depression **AND**

2.1.2 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:

4.1 The patient is unable to swallow **OR**

4.2 The patient failed a standard dosage form from this drug class in the last 30 days

AND

5. For members requesting ***more than 2*** different antipsychotics, the following criteria must be met:

5.1 All antipsychotics involved in the therapeutic duplication are prescribed by or in consultation with a psychiatrist **AND**

5.2 One of the following:

5.2.1 History of at least 4 weeks of dual agent therapy at an adequate dose **OR**

5.2.2 The medications involved in the therapeutic duplication are being cross-tapered and it is the first request for an authorization due to cross-tapering

Multiple Antipsychotic Utilization Members 6 – 12 years

Time frame: 4/1/2021 – 6/30/2021

Review 430 members aged 6 – 12 years old on atypical antipsychotics

- 333 members taking one atypical antipsychotic during 2Q2021
- 25 members taking ≥ 2 *different* atypical antipsychotics during 2Q21; upon further review 11 members taking concurrently
- 72 members taking two or more of the *same* atypical antipsychotics, but *different strengths* during 2Q21; upon further review 26 members taking concurrently

Members taking different drugs – 11 members

aripiprazole & risperidone	aripiprazole & quetiapine	risperidone & quetiapine	olanzapine & quetiapine
• 8 yr female - Psychiatry, Child & Adolescent • 10 yr male - **Physician Assistant**; *Autistic disorder* • 10 yr male - Psychiatry, Child & Adoles • 11 yr female - Psychiatry • 12 yr male - Psychiatry • 13 yr male - Pediatrics; Psychiatry, Child & Adolescent	• 12 yr female - Psychiatry • 12 yr female - Psychiatry, Child & Adolescent • 13 yr female - Psychiatry	• 12 yr male - Psychiatry	• 11 yr male - Psychiatry

Members taking same drug, different strengths – 26 members

aripiprazole 2mg aripiprazole 5mg	aripiprazole 2mg aripiprazole 10mg	aripiprazole 5mg aripiprazole 10mg	olanzapine 5mg olanzapine 10mg	quetiapine 25mg quetiapine 100mg
• 8 yr female - **Nurse Practitioner, Pediatric Care** *ADHD, Autistic disorder, Mixed receptive-expressive language disorder*	• 8 yr male - Psychiatry	• 12 yr male - **Nurse Practitioner** *-pending*	• 12 yr male - Psychiatry, Child & Adolescent	• 11 yr female - Psychiatry • 12 yr female - Psychiatry

risperidone 0.25mg risperidone 0.5mg	risperidone 0.25mg risperidone 1mg	risperidone 0.5mg risperidone 1mg	risperidone 1mg risperidone 2mg	risperidone 2mg risperidone 3mg
• 7 yr male - Psychiatry • 8 yr male - Psychiatry, Child & Adolescent • 12 yr male - Psychiatry • 12 yr male - Psychiatry, Child & Adolescent • 9 yr male – NP Psychiatric/Mental Health *ADHD, Impulse disorder, Adjustment disorder with disturbance of conduct* • 9 yr male - **Student** *ADHD, Adjustment disorder with anxiety, Mixed receptive-expressive language disorder* • 9 yr male - Psychiatry • 10 yr male - **Student** *ADHD, Mood [affective] disorder* • 11 yr male **Student** *Major depressive disorder* • 12 yr male - NP Psychiatric/Mental Health & NP, Family Health *ODD, Adjustment disorder with anxiety*	• 10 yr female - **NP, Pediatric Care** *PDD* • 8 yr male - **Pediatrics; Nurse Practitioner, Pediatric Care** *ADHD, PDD, Mixed receptive-expressive language disorder*	• 9 yr female - **Nurse Practitioner, Family Health** *ADHD, Adjustment disorder with anxiety* • 9 yr male - Psychiatry, Child & Adolescent • 10 yr male - Psychiatry • 10 yr female - Psychiatry, Child & Adolescent	• 8 yr female - Pediatrics *PDD, Childhood emotional disorders, Mixed receptive-expressive language disorder* • 11 yr male - **NP** *ADHD, ODD, PDD* • 11 yr male - **NP, Family Health** *ADHD, GAD, ODD*	• 11 yr male - Psychiatry

*ADHD – Attention deficit hyperactivity disorder

*GAD – Generalized anxiety disorder

*ODD – Oppositional defiant disorder

*PDD – Pervasive developmental disorders

ADHD Utilization

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
- December 2020 P&T meeting – reviewed utilization of members 21 years & older
- March 2021 P&T meeting – reviewed utilization of members 21 years plus & PMPM & PUPM comparison; discussed potential PA on Vyvanse for continuation of therapy from minority to maturity age, step therapy requiring dexmethylphenidate first
- Sept 2021 P&T meeting – review PA criteria from State B and other Medicaid programs that require step therapy on Vyvanse

State Comparison of all utilization, except IHS claims, for all members

Time frame: 4/1/2021 – 6/30/2021

State Medicaid	# ADHD Claims	Plan Paid	PMPM	PUPM	PA Criteria
State A	129,270	$19,017,461	$3.84	$134.05	PA for ≥ 21 years old
State B	9,782	$1,081,647	$1.87	$98.75	Vyvanse PA for adults & children
State C	31,551	$4,076,775	$4.20	$135.01	PA for < 6 years old, PA for ≥ 21 years old
State D	30,497	$5,644,350	$5.26	$164.82	PA for all NP; PA for ≥ 21 years old
South Dakota	16,936	$1,709,241	$3.99	$104.00	

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

1. General Criteria (Children and Adults)
    a. A diagnosis of ADD/ADHD or other FDA approved diagnosis.
    b. Only one long-acting stimulant (amphetamine and methylphenidate products) may be used at a time.
    c. A 30-day transitional overlap in therapy will be allowed.
    d. Other treatable causes of ADD/ADHD have been ruled out.
2. ADD/ADHD Criteria (Children up to age 18 years)
    a. 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 dx on the claim.

Vyvanse Chewable Utilization

Time frame: 6/1/2020 – 7/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range	Age Breakdown
Vyvanse Chew 10 mg	35	$11,602.34	$331.50	22	4 – 36	21 members < 12 years old 1 member 36 years old
Vyvanse Chew 20 mg	54	$18,175.75	$336.59	33	5 – 13	31 members 12 and under 2 members 13 years old
Vyvanse Chew 30 mg	28	$8,356.48	$298.45	15	5 – 15	12 members 12 and under 3 members 13 and over
Vyvanse Chew 40 mg	20	$5,497.89	$274.89	8	9 – 41	6 members 12 and under 1 member 16 years old 1 member 41 years old
Vyvanse Chew 50 mg	7	$1,484.10	$212.01	3	9 – 10	3 members < 12 years old
Vyvanse Chew 60 mg	7	$1,170.89	$195.15	2	14, 18	2 members > 12 years old
Total	**151**	**$46,287.45**	**$306.54**	**75**		

Gabapentin High-Dose Utilization Review

Review members taking > 4,800 mg/day

Time Frame	Dose Per Day	Total Utilizers	Females	Males	Age Range
1Q2021	4,800 mg	1	1		61
1Q2021	5,400 mg – 5,419 mg	3	1	2	50 – 60
1Q2021	6,000 mg – 6,400 mg	2	1	1	39 – 40
2Q2021	4,800 mg	1	1		61
2Q2021	6,000 mg – 7883 mg	6	4	2	18 – 61
2Q2021	9000 mg – 9854 mg	2	2		16, 20

Time frame: 4/1/2021 to 6/30/2021 (partial seizures, postherpetic neuralgia, restless leg syndrome)

	Mbr	Dates of Fill	Dose Per Day	Total Rx	Qty	Paid Amount	Diagnosis	Prescriber Taxonomy
1	61 yr female 1Q2021*	4/29/21 5/16/21 6/14/21	gabapentin 800mg **4,800 mg per day**	3	180 per 30 days	$101.37	Diabetic neuropathy, Fibromyalgia	Cardiology
2	50 yr female 1Q2021*	4/15/21 5/12/21 6/9/21	gabapentin 600mg **5,400 mg per day**	3	180 per 30 days	$87.05	Diabetic neuropathy, Fibromyalgia, Low back pain	Nurse Anesthetist
3	58 yr male 1Q2021*	No fills 2Q21	gabapentin 600mg **5,419 mg per day**	0	now taking pregabalin 150mg/day		Low back pain, Other chronic pain, Unspecified cord compression,	Anesthesiology; Family Practiced changed to 2,700mg/day
4	40 yr male 1Q2021*	5/7/21 6/2/21 6/28/21	gabapentin 600mg **6,000 mg per day**	3	300 per 30 days	$121.84	Diabetic neuropathy, Low back pain	Family Practice
5	39 yr female 1Q2021*	4/28/21 6/1/21	gabapentin 800mg **6,400 mg per day**	2	240 per 30 days	$80.90	Low back pain, Epigastric pain, Pain unspecified	Family Practice
6	18 yr female 2Q2021*	4/12/21 5/12/21 6/27/21	gabapentin 250mg **6,833 mg per day**	3	820 per 30 days	$293.03	Alcohol dependence, Unspecified abdominal pain	Physical Medicine & Rehabilitation, Pediatric
7	14 yr female 2Q2021*	4/8/21 5/4/21 5/24/21 6/14/21	gabapentin 250mg **7,833 mg per day**	4	470 per 14 days	$247.57	Epilepsy	Student in an Organized Health Care Education/ Training Program
8	60 yr female 2Q2021*	4/2/21 4/22/21 4/15/21 5/26/21 6/26/21	gabapentin 250mg **7,833 mg per day**	5	470 per 14 days	$304.32	Other seizures, Recurrent seizures	Geriatric Medicine
9	14 yr male 2Q2021*	5/7/21 6/10/21	gabapentin 250mg **7,883 mg per day**	2	473 per 15 days	$125.30	Partial seizures, Other seizures, Epilepsy	Student in an Organized Health Care Education/ Training Program
10	16 yr female 2Q2021*	4/5/21	gabapentin 250mg **9,000 mg per day**	1	252 per 7 days	$37.73	Low back pain	Student in an Organized Health Care Education/ Training Program
11	20 yr female 2Q2021*	4/20/21 5/6/21 5/18/21 6/2/21 6/22/21	gabapentin 250mg **9,854 mg per day**	5	473 per 12 days	$312.21	Epilepsy, Partial seizures	Pediatrics

*1Q2021 – identified during 1Q2021

*2Q2021 – identified during 2Q2021

Review PA Forms and Criteria
Time frame: 1/1/2021 to 6/30/2021

Nuvigil/Provigil

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
armodafinil	1	$36.03	$36.03	30 per 30 days	1	50
Provigil 200mg	3	$3,818.40	$1,272.80	30 per 30 days	1	43
modafinil 200mg	35	$1,061.56	$30.33	33 per 29.7 days	16	15 – 58
modafinil 100mg	18	$344.13	$19.12	29.6 per 29.6 days	8	19 – 64

*Red font denotes drug is on PA

Nuvigil/Provigl PA Criteria

- Diagnosis of narcolepsy, excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome, or shift work sleep disorder

Off-label Provigil (modafinil)

- ADHD, schizophrenia

Off-label Nuvigil (armodanfinil)

- ADHD, depression, weight loss

Onfi

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Onfi suspension 2.5 mg/ml	2	$1,441.03	$720.52	1,230 per 30 days 240 per 43 days	2	8, 12
clobazam sus 2.5 mg/ml	118	$13,475.61	$114.20	212 per 25 days	39	1 – 24
Onfi 10 mg tab	4	$2,549.44	$637.36	45 per 30 days	2	11, 19
clobazam 10 mg tab	113	$5,069.99	$44.87	84 per 30 days	42	3 – 36
Onfi 20 mg tab	4	$8,400.27	$2,100.07	60 per 30 days	1	17
clobazam 20 mg tab	42	$2,437.30	$58.03	63 per 30.5 days	15	13 – 28
Sympazan MIS 5 mg (film)	3	$3,906.00	$1,302.00	90 per 30 days	1	8
Sympazan MIS 10 mg	3	$7,780.00	$2,953.50	90 per 30 days	1	11

*Red font denotes drug is on PA

Onfi PA Criteria

1. Diagnosis of Lennox-Gastaut syndrome (LGS) or intractable treatment-resistant seizure disorder
2. Must be prescribed by or in consultation with a neurologist

Off-label

- Dravet syndrome (Clinical Pharmacology)

Oracea/Solodyn/Seysara

Drug Name	Total Rx	Paid/Rx	Quantity
Oracea/doxycycline 40 mg cap	0	~$578	#30
Solodyn/minocycline 55mg, 65mg, 80mg, 105mg, 115mg tab	0	~$226 to $801	#30
Seysara (sarecycline) 60mg, 100mg, 150mg tab	0	~$1,110	#30

*Red font denotes drug is on ST

Onfi/Solodyn/Seysara ST Criteria

- 90-day trial of doxycycline monohydrate, doxycycline hyclate, minocycline IR, or tetracycline first in the last 180 days

Proton Pump Inhibitors

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Nexium granules	10	$3,377.27	$337.73	42 per 30 days	5	0 – 11
esomeprazole granules	68	$16,189.65	$238.08	34 per 31 days	32	0 – 42
Protonix Pak	0		~$465	#30		
pantoprazole packet	0		~$465	#30		

*Red font denotes drug is on PA

Nexium oral packet and Protonix Pak PA Criteria

1. Patient is less than 13 years of age OR
2. Diagnosis confirming difficulty in swallowing

Qualaquin

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Qualaquin/quinine 324mg cap	0		~$182	#30		

*Red font denotes drug is on PA

Qualaquin PA Criteria

- Diagnosis of malaria

Off-label

- Babesiosis (Clinical Pharmacology) – An infection of the red blood cells, that is caused by a parasite called Babesia and usually transmitted by tick bite. It may present with high fever, chills, joint pain and headache.
- Leg cramps

Soma 250mg

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Soma/carisoprodol 250mg tab	0		~$188	#67		
carisoprodol 350mg tab	103	$1,411.84	$13.71	67 per 25 days	39	17 – 65

*Red font denotes drug is on ST

Soma 250mg ST Criteria

- 6-month trial of carisoprodol 350 mg within the last 120 days

Ultram ER

Drug Name	Total Rx	Paid Amount	Paid/Rx	Quantity	Utilizers	Age Range
Ultram ER	0		~$84 to $195	#30		
tramadol 100mg ER tab	18	$1,135.66	$63.09	39 per 28 days	8	33 – 60
tramadol 200mg ER tab	4	$296.82	$74.21	30 per 30 days	2	37, 39
tramadol 300mg ER tab	5	$445.76	$89.15	30 per 30 days	2	20, 40
tramadol 50mg tab	1,206	$12,691.79	$10.52	59 per 15 days	590	13 – 89
tramadol 100mg tab	2	$206.25	$103.12	65 per 17 days	2	31, 58

*Red font denotes drug is on ST

Ultram ER PA Criteria

- 30-day trial of immediate release tramadol in the last 120 days

Juxtapid

Time frame: 1/1/2021 to 6/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Juxtapid (lomitapide) cap	0	AWP $1,9992.95 per cap			
Praluent (alirocumab) inj	7	$1,616.88	**$230.98	2	55 – 56
Repatha (evolocumab) inj	35	$17,001.11	$485.75	15	28 – 64

*Red font denotes drug is on PA **1 member had primary insurance

Juxtapid Proposed PA Criteria

1. Diagnosis of homozygous familial hypercholesterolemia (HoFH) **AND**
2. Patient is 18 years of age or older **AND**
3. Patient's baseline LDL-C level is ≥ to 190 mg/dL **AND**
4. Medication is being prescribed by, or in consultation with a cardiologist or endocrinologist **AND**
5. One of the following:
   - **5.1.** Trial and failure of Praluent ***and/or*** Repatha
   - **5.2.** Medical rationale for use of Juxtapid over Praulent or Repatha

Praluent PA Criteria

1. Diagnosis of heterozygous familial hypercholesterolemia (HeFH) **OR** hyperlipidemia in a high-risk member with clinical arteriosclerotic cardiovascular disease (ASCVD); **AND**
2. Patient's baseline LDL-C level is ≥ 70 mg/dL **AND**
   - **3.** Patient is 18 years of age or older **AND**
   - **4.** Medication is being prescribed by, or in consultation with a cardiologist or endocrinologist **AND**
   - **5.** One of the following:
     - **5.1.** Patient has been receiving high dose statin therapy for at least 3 months (i.e., atorvastatin tab 40 mg, atorvastatin tab 80 mg, rosuvastatin tab 20 mg, rosuvastatin tab 40 mg) OR
     - **5.2.** Patient is not a candidate for high dose statin therapy (e.g., labeled contraindication to all statins, patient has experienced rhabdomyolysis or muscle symptoms with statin treatment with creatine kinase elevations greater than 10 times upper limit of normal [ULN])

Repatha PA Criteria

1. One of the following:
   - **1.1.** Diagnosis of homozygous familial hypercholesterolemia (HoFH) **AND** Patient is 13 years of age or older; **OR**
   - **1.2.** Diagnosis of hyperlipidemia in a high-risk member with clinical arteriosclerotic cardiovascular disease (ASCVD) **OR** heterozygous familial hypercholesterolemia (HeFH); **AND** Patient is 18 years of age or older

   AND
2. Patient's baseline LDL-C level is ≥ 70 mg/dL **AND**
3. Medication is being prescribed by, or in consultation with a cardiologist or endocrinologist **AND**
4. One of the following:
   - **4.1.** Patient has been receiving high dose statin therapy for at least 3 months (i.e., atorvastatin tab 40 mg, atorvastatin tab 80 mg, rosuvastatin tab 20 mg, rosuvastatin tab 40 mg) **OR**
   - **4.2.** Patient is not a candidate for high dose statin therapy (e.g., labeled contraindication to all statins, patient has experienced rhabdomyolysis or muscle symptoms with statin treatment with creatine kinase elevations greater than 10 times ULN)

Reauthorization Criteria

Authorization for continued use shall be reviewed at least every 12 months when the following criteria are met:

1. Documentation of positive clinical response to therapy with LDL level less than 70 mg/dl or decreased 30% from baseline.

Imcivree

For the chronic weight management of patients with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes.

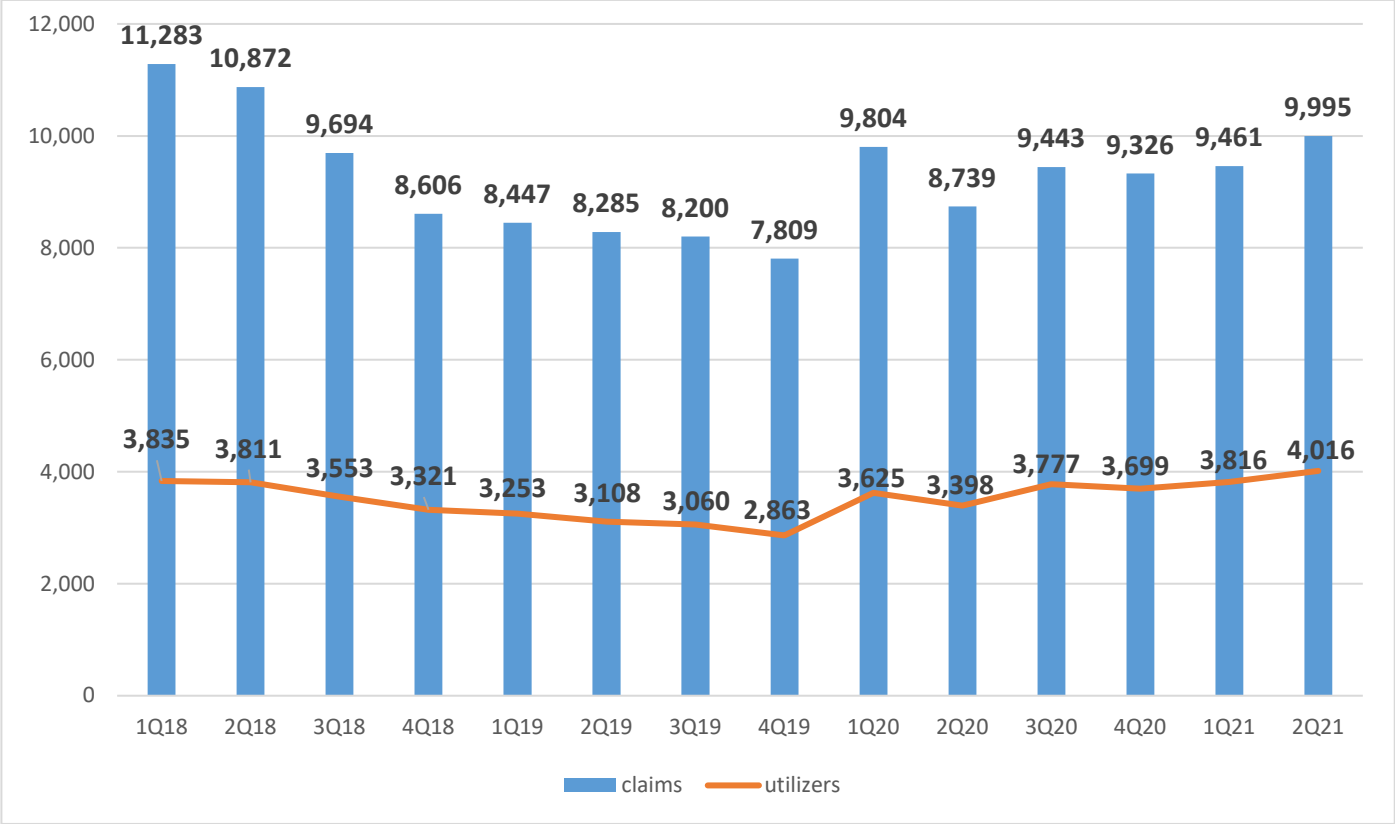
Proposed PA Criteria

- Patient is 6 years of age or older
- Diagnosis of obesity
- Documentation of genetic deficiency (POMC, PCSK1 or LEPR)
- Confirmation that other causes/types of obesity have been ruled out (e.g., other genetic syndromes, polygenic obesity)
- Approval is for 6 months, at which time achieve weight loss will be evaluated to establish efficacy of therapy consistent with clinical trials

Imcivree management by other states

- State A – PA and only covered for ages 6-21; state rule of not covering weight loss agents for 21+
- State B – excluded
- State C – excluded
- State D – excluded

Opioid Summary



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

Total Eligibility and Utilizers

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

SDM 2Q2021

Mar 21 to Jun 21

Opioid Utilization Snapshot

1Q2021

Dec 20 to Mar 21

Opioid Claims **9,995**

3.2% prescription claims filled for an opioid

0.4% higher than Medicaid FFS benchmark

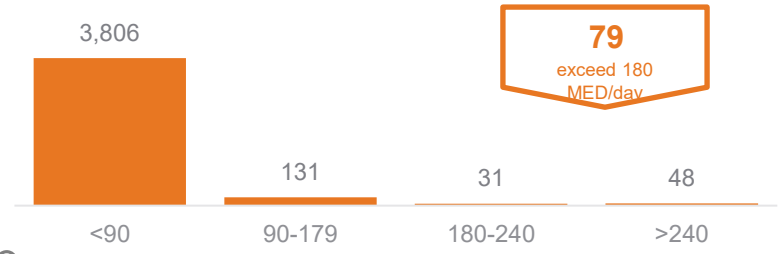
Utilizers **4,016**

30.4% are high utilizers [1]

-3.6% 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

55 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

240 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

Opioid Claims **9,461**

3.2% prescription claims filled for an opioid

0.3% higher than Medicaid FFS benchmark

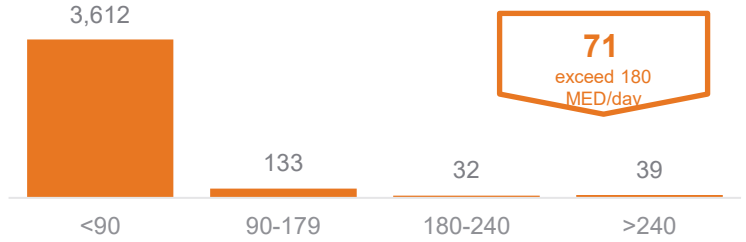
Utilizers **3,816**

31.1% are high utilizers [1]

-4.8% 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

48 opioid utilizing members with 3+ pharmacies

Shoppers: Poly Prescriber

251 Shoppers: Poly Prescriber

opioid utilizing members with 3+ prescribers

OPTUMRx®

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

Opioid Utilization

Opportunities date range: Mar - Jun 2021
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers: 4,016

3.2% 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 3.2% of all prescriptions this period, which is 0.4% higher than the benchmark
- 1,219 high opioid utilizers were identified this period, which is -3.6% lower than the benchmark

Opioid claims

9,995
TOTAL RXS

PERCENT OPIOID CLAIMS
3.2%

Opioid utilizers

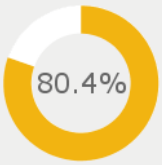
4,016
TOTAL UTILIZERS

HIGH UTILIZERS
30.4%
1,219 high utilizers

-3.6% under benchmark

High utilizers – view definition

Claim breakdown



short acting opioids

80.4% of all opioid Rxs were filled for short acting opioids. **1,234** Rxs were for medication assisted therapy (MAT) and **82** 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

79 utilizers exceed 180 MED/day

MED Scores	<90	90-179	180-240	>240
Utilizers	3,806	131	31	48

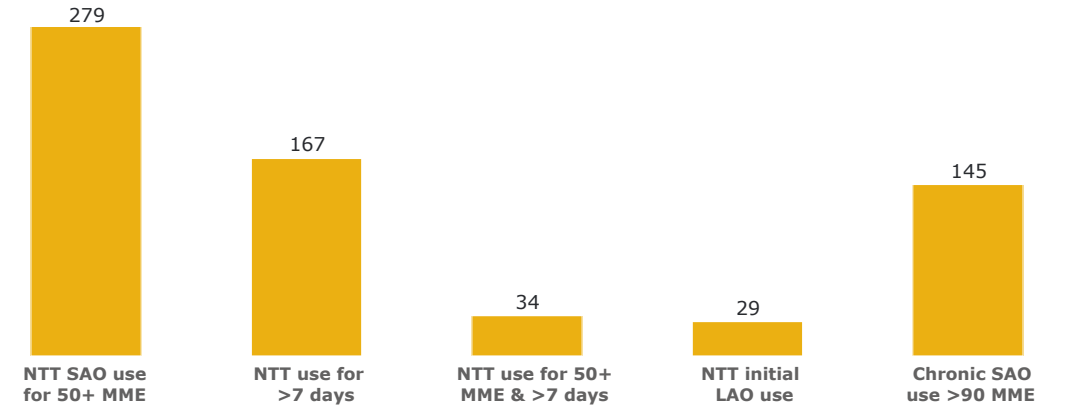
MED *– Morphine Equivalent Dose is a relative potency of an opioid to standard of a morphine; Cumulative MED is daily MED or narcotic load across all active opioid prescriptions in a members profile within a 120 day period*

Opioid Opportunity Assessment

Opportunities date range: Mar - Jun 2021
Benchmark: MEDICAID FEE FOR SERVICE

Utilizers

(new to therapy and chronic use)



7.5% of opioid Rxs	6.0% of opioid Rxs	1.6% of opioid Rxs	1.4% of opioid Rxs	11.8% of opioid Rxs

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

55 opioid utilizing members use 3 or more pharmacies and 240 opioid utilizing members use 3 or more prescribers.

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

Opioid utilizers with potentially contraindicated medication use

SKELETAL MUSCLE RELAXANTS	BENZODIAZEPINES	ANTICONVULSANTS	MEDICATION ASSISTED THERAPY	PRENATAL
703	577	667	N/A	117

Anticonvulsants –view definition

New Business

PA Drug Class Summary

Time Frame: 4/1/2021 to 6/30/2021

Drug Class	Approved	Denied	Total	Approval Rate
DERMATOLOGICALS*	101	76	177	57.06%
ANTIVIRALS*	3	15	18	16.67%

Dermatological PA Approval Review

1. Topical Acne
2. Rosacea
3. Head Lice
4. Topical Onychomycosis

PA	Drug Name	Total Reviews	Approvals	Denials
Topical Acne	Azelex 20% cream (azelaic acid)	1	1	
	Amzeeq (minocycline micronized foam 4%)	1		1
	clindamycin-benzoyl peroxide gel	21	7	14
	clindamycin-tretinoin gel	1		1
	Retin-A Micro Pump	1	1	0
	tretinoin microsphere gel	5	2	3
	adapalene cream or gel	20	5	5
	adapalene-benzoyl peroxide gel	1		1
	Epiduo Forte (adapalene-benzoyl peroxide)	1		1
	dapsone gel 5% or 7%	4	1	3
	tazarotene cream 0.1%	1	1	
Rosacea	metronidazole gel or cream	11	4	7
	azelaic acid gel 15%	2		2
	Rhofade (oxymetazoline cream 1%)	1		1
	Soolantra (ivermectin) cream 1%	1	1	
Head Lice	ivermectin cream 1%	3	2	1
	ivermectin lotion 0.5%	21	14	7
	Lindane shampoo 1%	2	1	1
	malathion lotion 0.5%	23	14	9
	Spinosad susp 0.9%	24	23	1
Topical Onychomycosis	efinaconazole solution 10% (Jublia)	4		4

Red font denotes drug is on PA/ST

Topical Acne & Rosacea Utilization

PA	Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range
Topical Acne	adapalene cream 0.1%	5	$819.58	$163.92	4	45	14 – 43
	adapalene gel 0.1%	14	$1,460.96	$104.35	8	45	13 – 43
	adapalene gel 0.3%	9	$894.72	$99.72	6	55	13 – 37
	adapalene-benzoyl gel 0.1-2.5%	3	$137.84	$44.82	1	45	19
	Epiduo Forte gel (adapalene-benzoyl) 0.3-2.5%	6	$3,264.30	$544.05	6	45	13 – 18
	dapsone gel 5% or 7.5%	7	$2,237.85	$319.69	5		14 – 34
	benzoyl peroxide gel	13	$195.90	$15.07	9		14 – 19
	benzoyl peroxide wash	6	$66.74	$13.35	3		13 – 18
	benzoyl-erythromycin gel	44	$3,493.86	$79.41	30		11 – 51
	Ery pad 2%	1	$80.79	$80.79	1	60	17
	erythromycin gel 2%	21	$1,062.08	$50.57	16	60	1 – 38
	erythromycin solution 2%	2	$74.52	$37.26	1	60	14 – 15
	clindamycin lotion, aerosol, gel	528	$30,027.50	$56.87	408		0 – 64
	clindamycin-benzoyl peroxide	29	$2,664.78	$91.89	27		10 – 47
	Onexton gel (clindamycin-benzoyl)	1	$614.24	$614.24	1	50	11
	sulfacetamide lotion 10%	1	$93.20	$93.20	1	30	12
	sulfacetamide emulsion 10-5%	1	$53.15	$53.15	1	227	42
	sulfacetamide cream 10-2%	**1**	**$379.51**	**$379.51**	**1**	**57**	**39**
	tretinoin cream	331	$32,422.59	$97.95	262		2 – 61
	tretinoin gel	52	$5,833.28	$112.18	40		1 – 46
	tretinoin microsphere gel	6	$1,777.61	$296.27	3		17 – 34
	Retin-A micro gel 0.08%	1	$884.52	$884.52	1	50	25
	tazarotene cream	5	$643.55	$128.71	3		15 – 59
	Tazorac gel	1	$468.40	$468.40	1	30	23
Rosacea	Miravaso gel (brimonidine)	1	$535.54	$535.54	1	30	41
	Soolantra cream 1% (ivermectin)	5	$2,100.96	$420.19	4	45	22 – 43
	azelaic gel 15% (Finacea gel/AER)	6	$652.36	$108.73	3	50	23 – 35
	metronidazole cream 0.75%	6	$315.85	$52.64	6	45	12 – 51
	metronidazole gel 0.75%	6	$266.17	$44.36	4	45	18 – 51
	metronidazole gel 1%	7	$786.70	$112.39	7	60	10 – 55
	metronidazole lotion 0.75%	1	$68.00	$68.00	1	59	39

Red font denotes drug is on Step Therapy

Topical Acne ST Criteria:
Trial of a generic topical acne agent (benzoyl peroxide, tretinoin, clindamycin phosphate, erythromycin, sulfacetamide sodium/sulfur, sulfacetamide sodium) in the past 120 days

Rosacea ST Criteria:
Trial of a generic topical acne agent (benzoyl peroxide, clindamycin phosphate, erythromycin, sulfacetamide sodium/sulfur, sulfacetamide sodium, tretinoin, metronidazole cream/gel/lotion) in the past 120 days.

Head Lice Utilization

PA	Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Avg Qty	Age Range
Head Lice	ivermectin lotion 0.5%	19	$4,442.62	$233.82	19	117	3 – 17
	Lindane shampoo 1%	1	$119.99	$119.99	1	60	15
	malathion lotion 0.5%	11	$2,419.00	$219.91	11	59	2 – 29
	Spinosad susp 0.9%	24	$5,892.96	$245.54	21	120	1 – 19

Red font denotes drug is on Step Therapy

Head Lice ST Criteria

Trial of a permethrin or pyrethrins-piperonyl butoxide product within the past 90 days

Antiviral PA Approval Review

Time frame: 4/1/2021 to 6/30/2021

Drug Name	Drug Name	Total Reviews	Approvals	Denials
HIV Nucleoside, Nucleotide Inhibitors	Truvada	1 (DAW 1)	1	
HCV Polymerase Inhibitors Antivirals	Epclusa (sofosbuvir-velpatasvir)	3		3
	sofosbuvir-velpatasvir	2	1	1
HCV Protease Inhibitor Antivirals	Mavyret (glecaprevir-ribrentasvir)	10	1	9
HCV Replication Complex Inhibitors	Harvoni (ledipasvir-sofosbuvir)	2		2

Red font denotes drug is on PA

Antiviral Utilization

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Truvada	10	$10,281.84	$1,028.18	8	17 – 42
sofosbuvir-velpatasvir	3	$24,021.60	$8,007.20	1	23
Mavyret	6	$77,223.60	$12,870.60	3	37 – 44

Red font denotes drug is on PA

Cholbam Utilization

Time frame: 4/1/2021 to 6/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range	Prescriber Taxonomy
Cholbam -Bile acid synthesis disorder (E78.7, E78.79) -Peroxisomal disorders (E71.5) -Zellweger spectrum disorder (E71.510)	6	$124,413.00	$20,735.50	2	1, 4	Gastroenterology, Pediatric Gastroenterology

Patient 1:

- E78.7 Disorder of bile acid and cholesterol metabolism, unspecified
- E78.9 Disorder of lipoprotein metabolism, unspecified

Patient 2:

- E78.79 Other disorders of bile acid and cholesterol metabolism
- E78.89 Other lipoprotein metabolism disorders
- E80.6 Other disorders of bilirubin metabolism (Dubin-Johnson syndrome, Rotor's syndrome)

Pancreatic Enzyme Utilization

Time frame: 4/1/2021 to 6/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Creon	74	$137,243.27	$1,854.64	36	0 – 63
Pancreaze	1	$32.01	$32.01	1	20
Pertzye	12	$17,676.20	$1,473.02	5	1 – 23
Viokace	3	$987.00	$329.00	1	45
Zenpep	23	$51,774.61	$2,251.07	10	3 – 64

Hemophilia Factor Product Utilization

Time frame: 4/1/2021 to 6/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty	Utilizers
Advate Inj	12	$458,671.68	$38,222.64	21,961 per 27.5 days	3
Benefix Inj	1	$8,884.50	$8,884.50	6,120 per 2 days	1
Hemlibre Inj	3	$184,880.28	$61,626.76	4 per 28 days	1
Humate-P	6	$38,757.82	$6,459.64	4,640 per 15 days	2
Novoseven RT Inj	1	$48,010.50	$48,010.50	20,000 per 28 days	1
Recombinate	3	$145,033.2	$48,344.40	27,780 per 28 days	1
Xyntha Solof	4	$139,984.24	$46,661.42	22,004 per 28.5 days	1
TOTAL	**30**	**$1,024,222.24**			**10**

Factor	Drug Name	Total Rx	Paid Amount	Paid/Rx	Avg Qty
FACTOR VIII ALBUMIN-FREE RECOMBINANT, hamster murine	Advate Inj 250	3	$28,553.58	$9,517.86	5,464 per 18.6 days
	Advate Inj 1000	6	$251,562.60	$41,927.10	24,090 per 29 days
	Advate 1500	3	$178,555.50	$59,518.50	34,200 per 30 days
FACTOR IX RECOMBINANT, hamster	Benefix Inj 3000	1	$8,884.50	$8,884.50	6,120 per 2 days
EMICIZUMAB-KXWH	Hemlibre Inj 150/ml	3	$184,880.28	$61,626.76	4 per 28 days
ANTIHEMOPHILIC FACTOR/VON WILLEBRAND FACTOR COMPLEX (HUMAN)	Humate-P Sol 250-600	4	$21,745.46	$5,436.36	3,903.5 per 22 days
	Humate-P Sol 500-1200	1	$5,603.86	$5,603.86	4,024 per 4 days
	Humate-P 2400	1	$11,408.50	$11,408.50	8,200 per 4 days
COAGULATION FACTOR VIIA (RECOMBINANT)	Novoseven RT Inj 1mg	1	$48,010.50	$48,010.50	20,000 per 28 days
FACTOR VIII RECOMBINANT, bovine hamster murine	Recombinate Inj	3	$145,033.20	$48,344.40	27,780 per 28 days
FACTOR VIII ALBUMIN-FREE RECOMBINANT, hamster murine	Xyntha Solof Kit 250	1	$5,375.16	$5,375.16	3,374 per 28 days
	Xyntha Solof Inj 1000	2	$94,085.40	$47,042.70	29,580 per 29 days
	Xyntha Solof Inj 2000	1	$40,523.70	$20,261.85	25,480 per 28 days
Total		**30**	**$1,024,222.24**		

Hemophilia – Member Utilization

ICD-10 Codes:

- D66 Hereditary factor VIII deficiency
- D67 Hereditary factor IX deficiency
- D68 Other coagulation defects
- D68.1 Hereditary factor XI deficiency
- D68.2 Hereditary deficiency of other clotting factors
- D68.311 Acquired hemophilia
- D68.4 Acquired coagulation factor deficiency
- M25 – M25.08 Hemarthrosis (joint bleeds)

	Mbr	Dates of Fill	Drug Name	Quantity	Total Rx	Paid Amount	Prescriber Taxonomy
1	**12 yrs** Male D68	6/23/21	Humate-P Sol 250-600 Humate-P Sol 500-1200 Humate-P Sol 2400	1,860 /4 days 4,024 /4 days 8,200 /4 days	3	$2,595.90 $5,603.86 $11,408.50 **$19,608.26**	Hematology & Oncology, Pediatric
2	**9 yrs** Male D66	4/30/21 5/6/21 5/26/21	Advate Inj 250 unit (lidocaine-prilocaine cream)	3,276 /18 days 10,920 /30 days 2,196 /18 days	3	$5,710.74 $19,011.30 $3,831.54 **$28,553.58**	Hematology & Oncology, Pediatric
3	**14 yrs** Male D66	4/27/21 4/27/21 5/26/21 5/26/21 6/22/21 6/22/21	Advate Inj 1000 unit Advate Inj 1500 unit Advate Inj 1000 unit Advate Inj 1500 unit Advate Inj 1000 unit Advate Inj 1500 unit	21,900 /30 days 34,200 /30 days 21,900 /30 days 34,200 /30 days 21,900 /30 days 34,200 /30 days	6	$38,116.50 $59,518.50 $38,116.50 $59,518.50 $38,116.50 $59,518.50 **$292,905.00**	**2021:** Student B **2020:** Student A **2017:** Hematology & Oncology-Pediatric **2016:** Pediatrics; Hematology & Oncology-Pediatric
4	**5 yrs** Male D66, D68.4 D68.311	5/5/21 6/2/21 6/30/21	Advate Inj 1000 unit (lidocaine-prilocaine cream)	26,280 /28 days	3	$45,737.70 $45,737.70 $45,737.70 **$137,213.10**	Hematology & Oncology, Pediatric
5	**4 yrs** Female D66, 68.4, D68.311	4/22/21 4/20/21 6/17/21	Humate Sol 250-600 (lidocaine-prilocaine cream)	5,290 /28 days 4,232 /28 days 4,232 /28 days	3	$7,363.60 $5,892.98 $5,892.98 **$19,149.56**	Pediatrics
6	**4 yrs** Male D66, D68	4/22/21 4/22/21 5/24/21 6/22/21	Xyntha Solof Kit 250 Xyntha Solof Inj 1000 Xyntha Solof Inj 1000 Xyntha Solof Inj 2000	3,374 /28 days 30,600 /30 days 28,560 /28 days 25,480 /28days	4	$5,375.16 $48,664.50 $45,420.90 $40,523.70 **$139,984.26**	Hematology & Oncology, Pediatric
7	**17 yrs** Male D67	6/1/21	Benefix Inj	6,120 /2 days	1	$8,884.50	Hematology & Oncology, Pediatric
8	**1 yrs** Male D68.1, D68.2	4/9/21	Novoseven RT Inj	20,000 /28 days	1	$48,010.50	Pediatrics
9	**43 yrs** Male D66	4/20/21 5/18/21 6/16/21	Recombinate Inj	25,920 /28 days 29,520 /28 days 27,900 /28days	3	$45,108.00 $51,372.00 $48,553.20 **$145,033.20**	Student in an Organized Health Care Education/ Training Program
10	**47 yrs** Male D66, M25	4/5/21 5/3/21 6/5/21	Hemlibra Inj (cyclobenzaprine, celecoxib, Nucynta, pregabalin)	4 /28 days 4 /28 days 4 /28 days	3	$61,626.76 $61,626.76 $61,626.76 **$184,880.28**	Physician Assistant, Medical

Hemophilia treatment management by other states:

- State A – all agents are available with no PA or QL
- State B – MAC rates
- State C – preferred/non-preferred; specialty rate/MAC, prescriptions written with +/-3% aggregate of prescribed dose
- State D – pegylated products on PA

Cystic Fibrosis Medication Compliance

Time frame: 1/1/2021 – 8/12/2021

- 39 members utilizing the below drugs,
- 9 members seem non-compliant

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Age Range
Pulmozyme sol 1mg/ml (dornase alfa)	183	$710,451.83	$3,882.25	38	0 – 58
Kalydeco (ivacaftor)	10	$239,066.45	$23,906.65	2	7, 16
Orkambi (lumacaftor-ivacaftor)	53	$905,544.27	$17,085.74	8	2 – 7
Symdeko (tezacaftor-ivacaftor)	3	$2,086.71	$695.57	1	11
Trikafta (elexacaftor-tezacaftor-ivacaftor)	96	$2,156,659.11	$22,465.20	16	6 – 58

Member utilization of possible non-compliance

- Cystic Fibrosis ICD-10 codes E84 to E84.9
- Pancreatitis ICD-10 codes K85 to K86.9
- Pulmozyme indications: cystic fibrosis, mucolysis, off-label – atelectasis

	Mbr	Dates of Fill	Drug Name	Total Rx	Paid Amount	Diagnosis	Prescriber Taxonomy
1	**15 yrs Male**	2/11/21 4/12/21 5/18/21	Pulmozyme Pulmozyme Pulmozyme	3	$8,712.79	No CF diagnosis	Pediatrics
2	**18 yrs Male**	1/6/21 1/26/21 2/4/21 2/22/21 3/22/21 3/29/21 4/27/21 5/3/21 5/27/21 6/8/21	Pulmozyme Trikafta Pulmozyme Trikafta Trikafta Pulmozyme Pulmozyme Trikafta Trikafta Pulmozyme	10	$5,271.75	E84, E84.8, E84.9 K86.81 No CF drugs after 6/9/21 but other drugs filled, i.e., Albuterol neb	Pulmonology, Pediatric
3	**11 yrs Female**	1/4/21 1/21/21 2/8/21 2/22/21 3/15/21 3/22/21 4/15/21	Pulmozyme Symdeko Pulmozyme Symdeko Pulmozyme Symdeko Trikafta	7	$2,917.32	E84.0, E84.8, E84.9 K86.81, K86.89 Uses Hypersal neb 7% monthly $189.80 for 8 scripts	Pulmonology, Pediatric
4	**11 yrs Male**	1/7/21 2/2/21	Pulmozyme Pulmozyme	2	$4,022.41	No CF diagnosis	Adolescent Medicine, Pediatrics
5	**8 yrs Male**	1/11/21 2/20/21	Pulmozyme Pulmozyme	2	$3,981.36	No CF diagnosis	Pulmonology, Pediatric
6	**9 yrs Male**	1/19/21 6/18/21 6/18/21 6/19/21	Pulmozyme Pulmozyme Tobramycin neb Pertzye cap 24000	2	$6.75	E84.9, K86.81 No claims 6/20/21 to 8/22/21; Active mbr	Adolescent Medicine, Pediatrics
7	**3 yrs Female**	2/16/21 5/10/21	Pulmozyme Pulmozyme	2	$6,696.92	E84.19, E84.9, K86.81, K86.89 No Rx after 5/10/21	Adolescent Medicine, Pediatrics
8	**3 yrs Male**	2/11/21 2/16/21 5/6/21	Pulmozyme Pulmozyme Pulmozyme	3	$10,043.53	E84, E84.19, E84.8, E84.9, K86.81 No Rx after 7/8/21	Pediatrics
9	**0 yrs Male**	2/16/21 3/23/21	Pulmozyme Pulmozyme	2	$6,700.62	E84.8, E84.9, K86 Active member	Pulmonology, Pediatric

Utilization for Brexafemme Comparison
Time frame: 4/1/2021 to 6/30/2021

Drug Name	Total Rx	Paid Amount	Paid/Rx	Utilizers	Diagnosis	Age Range
Brexafemme tab 150 mg (ibrexafungerp) ▪ *vulvovaginal candidiasis*	0	$142.50 AWP ~$285 AWP/Rx				
clotrimazole troche 10 mg ▪ *vulvovaginal candidiasis*	7	$231.17	$33.02	6		4 – 14
Cresemba cap 186 mg (isavuconazonium sulfate) ▪ *aspergillosis (B44 – B44.9)* ▪ *mucormycosis (B46 – B46.5)* ▪ *Off label:* esophageal candidiasis, candidiasis prophylaxis B37.1, B37.6, B37.84	1	$5,346.36	$5,346.36	1	B39.9 histoplasmosis	23
fluconazole susp 10 mg/ml ▪ *vulvovaginal candidiasis*	40	$908.75	$22.72	36		0 – 17
fluconazole susp 40 mg/ml ▪ *vulvovaginal candidiasis*	55	$2,080.31	$37.82	48		0 – 12
fluconazole tab 100 mg ▪ *vulvovaginal candidiasis*	49	$632.80	$12.91	38		5 – 60
fluconazole tab 150 mg ▪ *vulvovaginal candidiasis*	511	$5,372.94	$10.51	413		9 – 64
fluconazole tab 200 mg ▪ *vulvovaginal candidiasis*	43	$1,074.06	$24.98	35		13 – 64
itraconazole cap 100 mg	2	$31.88	$15.94	2		10, 40
itraconazole sol 10 mg/ml	3	$1,492.16	$497.39	2		3, 44
ketoconazole tab 200 mg	2	$31.74	$15.87	2		13, 14
miconazole cream 2% ▪ *vulvovaginal candidiasis*	1	$13.33	$13.33	1		18
nystatin susp ▪ *vulvovaginal candidiasis*	468	$8,458.46	$18.07	203		0 – 64
voriconazole tab 200 mg	6	$1,450.89	$241.82	1		34

INTRODUCTION

- The oral antifungals class includes agents for the treatment of many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, onychomycosis, and ringworm infections (*Micromedex 2021*).
- The agents are often used in persons living with human immunodeficiency virus (HIV) and neutropenia due to hematopoietic stem cell transplants, or after aggressive chemotherapy and radiation *(Centers for Disease Control and Prevention, National Institutes of Health, HIV Medicine Association of the Infectious Diseases Society of America [CDC/NIH/IDSA] 2021).*
- The most current treatment guidelines and therapy recommendations should be used when prescribing these agents, as resistant organisms have been reported.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis *(Prescribing information: clotrimazole 2016, nystatin suspension 2019, Oravig 2020).*
- Cresemba (isavuconazonium sulfate), Diflucan (fluconazole), Vfend (voriconazole), and Noxafil (posaconazole) are available as oral and intravenous formulations. Ketoconazole, terbinafine, and nystatin are available as oral and topical preparations. Brexafemme (ibrexafungerp), Sporanox and Tolsura (itraconazole) are only available as oral formulations (due to its formulation Tolsura exhibits greater bioavailability than conventional capsule formulations of itraconazole) *(Tolsura prescribing information 2020).* Clotrimazole and miconazole are available as oral, topical, and vaginal formulations. Only the oral formulations will be discussed in this review.
- In May 2016, the Food and Drug Administration (FDA) recommended limiting the use of ketoconazole for the treatment of skin and nail fungal infections due to the risk of severe liver injuries and adrenal gland problems and advised that it can lead to harmful drug interactions with other medications. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated *(FDA Drug Safety Communication 2016).*
- Medispan class: Antifungals; Imidazole-Related Antifungals

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ancobon (flucytosine)	✔
Brexafemme (ibrexafungerp)	--
Clotrimazole	✔
Cresemba (isavuconazonium sulfate)	--
Diflucan (fluconazole)	✔
Griseofulvin microsize	✔
Gris-PEG (griseofulvin ultramicrosize)	✔
Ketoconazole	✔
Noxafil (posaconazole)	✔ (delayed-release tablets) ✔ (suspension) -- (delayed-release suspension)
Nystatin	✔
Oravig (miconazole)	--
Sporanox (itraconazole)	✔ (both oral solution and capsule)
Terbinafine	✔
Tolsura (itraconazole)*	--
Vfend (voriconazole)	✔

* 65 mg tablet; Sporanox and its generics are available as 100 mg tablets

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Brexafemme (ibrexafungerp)	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	Noxafil (posaconazole)	nystatin	Oravig (miconazole)	terbinafine	voriconazole
Oropharyngeal candidiasis		✔							✔ a	✔ b	✔		
Oropharyngeal and esophageal candidiasis			✔				✔ b						
Esophageal candidiasis													✔ h
Non-esophageal mucous membrane gastrointestinal candidiasis										✔ c			
Prophylactically to reduce the incidence of oropharyngeal candidiasis in patients immunocompromised by conditions that include chemotherapy, radiotherapy, or steroid therapy utilized in the treatment of leukemia, solid tumors, or renal transplantation		✔											
Serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*				✔ e									
Vaginal candidiasis			✔										
Treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis	✔												
Cryptococcal meningitis			✔										
Prophylactically to decrease the incidence of candidiasis in patients undergoing bone marrow transplantation who receive cytotoxic chemotherapy and/or radiation therapy			✔										
Treatment of the following ringworm infections: tinea corporis (ringworm of the body), tinea pedis (athlete's foot), tinea cruris (ringworm of the groin and thigh), tinea barbae (barber's itch), tinea capitis (ringworm of the scalp), and tinea unguium (onychomycosis, ringworm of the					✔								

Indication	Brexafemme (ibrexafungerp)	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	Noxafil (posaconazole)	nystatin	Oravig (miconazole)	terbinafine	voriconazole
nails), caused by one or more of the following genera of fungi: *Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. interdigitalis, T. verrucosum, T. megnini, T. gallinae, T. crateriform, T. sulphureum, T. schoenleini, Microsporum audouini, M. canis, M. gypseum* and *Epidermophyton floccosum*													
Onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)							✔ f,g					✔ c	
Treatment of the following systemic infections in patients who have failed or are intolerant to other therapies: blastomycosis, coccidioidomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis								✔					
Prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-vs-host disease (GVHD) or those with hematologic malignancies with prolonged neutropenia from chemotherapy									✔ i				
Blastomycosis, pulmonary and extrapulmonary in immunocompromised and non-immunocompromised patients							✔ d						
Histoplasmosis, including chronic cavitary pulmonary disease and disseminated, nonmeningeal histoplasmosis in immunocompromised and non-immunocompromised patients							✔ d						
Aspergillosis, pulmonary and extrapulmonary, in patients who are intolerant of or who are							✔ d						

Indication	Brexafemme (ibrexafungerp)	clotrimazole	fluconazole	flucytosine	griseofulvin	isavuconazonium sulfate	itraconazole	ketoconazole	Noxafil (posaconazole)	nystatin	Oravig (miconazole)	terbinafine	voriconazole
refractory to amphotericin B therapy in immunocompromised and non-immunocompromised patients													
Invasive aspergillosis						✔							✔ h
Invasive mucormycosis						✔							
Candidemia in non-neutropenic patients and the following *Candida* infections: disseminated infections in skin and infections in abdomen, kidney, bladder wall, and wounds													✔ h
Serious fungal infections caused by *Scedosporium apiospermum* (asexual form of *Pseudallescheria boydii*) and *Fusarium* species including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy													✔ h

[a] Including oropharyngeal candidiasis refractory to itraconazole and/or fluconazole in adult and pediatric patients aged 13 years and older (oral suspension only)
[b] Oral solution/suspension only.
[c] Oral tablets only.
[d] Oral capsules only.
[e] Should be used in combination with amphotericin B for the treatment of systemic candidiasis and cryptococcosis because of the emergence of resistance to flucytosine.
[f] In non-immunocompromised patients.
[g] Tolsura is not indicated for treatment of onychomycosis.
[h] For use in patients 2 years of age or older.
[i] Delayed-release tablets indicated for adults and pediatric patients 2 years of age and older who weigh > 40 kg; oral suspension is indicated for adults and pediatric patients 13 years of age and older; Powdermix for delayed-release oral suspension is indicated for pediatric patients 2 years of age and older who weigh ≤ 40 kg; injection is indicated for adults and pediatric patients 2 years of age and older.

(Prescribing information: Ancobon 2019, Brexafemme 2021, clotrimazole 2016, Cresemba 2021, Diflucan 2020, griseofulvin suspension 2020, griseofulvin tablets 2018, Gris-PEG 2016, ketoconazole 2020, Noxafil 2021, nystatin suspension 2019, nystatin tablets 2020,Oravig 2020, Sporanox capsules 2019, Sporanox oral solution 2019, terbinafine 2021, Tolsura 2020, Vfend 2021)

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

CLINICAL EFFICACY SUMMARY

- The oral antifungal agents are FDA-approved for a variety of indications. Some head-to-head clinical trials have been conducted to evaluate the efficacy of the oral antifungal agents for the treatment of various indications.

- For the treatment of aspergillosis, open-label trials have demonstrated the effectiveness of itraconazole for the treatment of pulmonary aspergillosis in patients who are immunocompromised and/or refractory to amphotericin B *(Caillot 2003, Caillot et al 2001).* Another study demonstrated the superiority of itraconazole over standard supportive measures in chronic cavitary pulmonary aspergillosis (CCPA) *(Agarwal et al 2013).* Posaconazole has been shown to be effective in the treatment of invasive aspergillosis in patients who are refractory to ≥ 7 days of antifungal therapy or intolerant to conventional therapy *(Walsh et al 2007).* In the treatment of invasive mucormycosis, isavuconazonium sulfate was studied in a single-arm, open-label trial and was associated with an all-cause mortality rate of 38% through day 42 and an end-of-treatment success rate of 31%. Isavuconazonium sulfate was shown to be noninferior to voriconazole as treatment for invasive aspergillosis for all-cause mortality at day 42 *(McCormack 2015).* Another trial found isavuconazonium sulfate noninferior to voriconazole in all-cause mortality at day 42 in patients receiving primary treatment for invasive mold disease primarily caused by *Aspergillus* species *(Maertens et al 2016).*
- Open-label studies evaluating the use of itraconazole in the treatment of blastomycosis and histoplasmosis have demonstrated clinical response and/or success rates of 81 to 90% *(Dismukes et al 1992, Wheat et al 1995).* In a multicenter, prospective trial, a relapse-free rate of 95.3% was demonstrated at 1 year in patients treated with itraconazole for a first episode of mild to moderate disseminated histoplasmosis who had successfully completed 12 weeks of induction therapy with itraconazole *(Hecht et al 1997).*
- In a double-blind, randomized, controlled trial, fluconazole and itraconazole were compared in pediatric patients with signs of sepsis and positive blood cultures for *Candida* species. Statistically similar cure rates were observed between groups *(Mondal et al 2004*). In another randomized, controlled trial, voriconazole and amphotericin B were compared in patients with candidemia and demonstrated no significant difference between groups in rates of successful response. However, significantly more patients infected with *C. tropicalis* had a successful response to voriconazole compared to amphotericin B *(Kulberg et al 2005).*
- Fluconazole with or without flucytosine has also been compared to amphotericin B with or without flucytosine for the treatment of *Cryptococcus* species infection with somewhat conflicting results. In a multicenter, randomized, controlled trial, no significant difference in successful treatment in HIV-infected patients with cryptococcal meningitis was demonstrated with oral fluconazole vs amphotericin B, with or without flucytosine *(Saag et al 1992)*. Conversely, in a prospective, randomized controlled trial, significantly fewer treatment failures were demonstrated in patients with or without acquired immunodeficiency syndrome (AIDS) treated with amphotericin B plus flucytosine compared to oral fluconazole *(Larsen et al 1990).* A Cochrane review concluded that the most effective regimen for cryptococcal meningitis in patients with HIV is combination therapy with flucytosine and amphotericin B (*Tenforde et al 2018*).
- In the treatment of various dermatophyte infections, studies comparing ketoconazole and griseofulvin have shown conflicting results. Some studies demonstrate significantly better response to ketoconazole compared to griseofulvin *(Jolly et al 1983, Legendre and Steltz 1980)* while other studies failed to replicate this finding *(Gan et al 1987, Stratigos et al 1983, Tanz et al 1985, Tanz et al 1988).* Comparison of griseofulvin and terbinafine for the treatment of tinea corporis and tinea cruris showed significantly higher clinical and mycological cure rates for terbinafine at week 6 compared to griseofulvin and significantly higher rates of relapse with griseofulvin *(Voravutinon 1993).* A meta-analysis found that griseofulvin was more effective than terbinafine in treatment of children with tinea capitis caused by *Microsporum* species, and that terbinafine, itraconazole, and fluconazole are at least similar to griseofulvin in treatment of children with tinea capitis caused by *Trichophyton* species. The findings also suggested that terbinafine was more effective than griseofulvin in *T. tonsurans* infection *(Chen et al 2016).* Combination treatment with oral terbinafine and itraconazole for dermatophytosis was found to have higher clinical and mycological cure compared to itraconazole or terbinafine alone (90% vs 50% vs 35%, respectively). Specific clinical measures included itching, erythema, and scaling. Significant adverse effects were not observed (*Sharma et al 2020*).
- Multiple studies have been conducted evaluating the use of antifungals for oral candidiasis. A Bayesian network meta-analysis of 31 randomized controlled trials (N = 4042) found fluconazole to have better mycological cure rates compared with other agents including itraconazole, miconazole, clotrimazole, ketoconazole, and nystatin (*Fang et al 2021).* A Cochrane review meta-analysis found limited results comparing antifungals for the treatment and prevention of oropharyngeal candidiasis in HIV-positive children and adults but did find fluconazole and ketoconazole were superior to nystatin in clinical cure. Itraconazole and fluconazole were superior to clotrimazole in clinical cure. They also found that fluconazole was effective for prevention *(Pienaar et al 2010).*
- Studies evaluating the oral antifungal agents as prophylaxis against fungal infections in immunocompromised patients have compared various agents head-to-head. A multicenter, prospective, randomized trial compared fluconazole, itraconazole solution, and posaconazole in patients after remission-induction chemotherapy. Significantly fewer invasive

fungal infections occurred with posaconazole compared to fluconazole and itraconazole. Also of note, significantly fewer cases of invasive aspergillosis were observed, and significantly fewer patients experienced treatment failure with posaconazole *(Cornely et al 2007).* Similarly, a study comparing fluconazole and posaconazole in patients with GVHD after HSCT demonstrated a significantly lower incidence of aspergillosis in the posaconazole group compared to the fluconazole group. Breakthrough fungal infections occurred in more patients in the fluconazole group *(Ullmann et al 2007).* A comparison between fluconazole and voriconazole in patients undergoing hematopoietic stem cell transplantation showed no significant differences between the groups' fungal-free survival rates and the incidence of invasive fungal infections *(Wingard et al 2010).* A network meta-analysis of 54 randomized trials concluded that posaconazole is the most effective antifungal for primary prophylaxis in patients with hematological malignancy, but mortality was similar among all of the agents included in the analysis (*Lee et al 2018*).

- The efficacy and safety of voriconazole in the treatment of immunocompromised pediatric patients (aged 2 to < 18 years) with invasive aspergillosis or invasive/esophageal candidiasis were evaluated in 2 noncomparative, open-label trials *(Martin et al 2017).* Of the 53 patients enrolled in the studies, 25 were aged 2 to 12 years. For all patients, global response rates were 64% for invasive aspergillosis and 76% for invasive/esophageal candidiasis at end of treatment. Among patients aged 2 to 12 years, corresponding response rates were 40% and 89%. Treatment-related hepatic adverse events occurred in 22.6% and 22.7% of the aspergillosis and candidiasis groups, respectively; visual adverse events occurred in 16.1% and 27.3% of patients, respectively.
- Studies comparing the oral antifungal agents for the treatment of onychomycosis have shown varying results. Comparisons of itraconazole (continuous or pulse dose regimens) and terbinafine have demonstrated conflicting results. Some studies showed no difference between treatments *(Bahadir et al 2000, Degreef et al 1999, Honeyman et al 1997)* while others show significantly better results with terbinafine *(Brautigam 1998, Brautigam et al 1995, De Backer et al 1996, De Backer et al 1998, Evans et al 1999, Sigurgeirsson et al 1999, Sigurgeirsson et al 2002).* A study comparing griseofulvin microsize and terbinafine demonstrated significantly higher rates of negative cultures at 72 weeks with terbinafine compared to griseofulvin *(Hofmann et al 1995).* Similarly, 2 studies demonstrated significantly higher complete and mycological cure rates at 1 year for terbinafine compared to griseofulvin microsize *(Faergemann et al 1995, Haneke et al 1995).* A Cochrane review including 48 studies (N = 10,200) of oral antifungal agents for the treatment of onychomycosis found high-quality evidence that terbinafine and azole antifungals were superior to placebo for mycological and clinical cure. Moderate-quality evidence suggested that terbinafine resulted in higher cure rates than azoles with similar safety risks, and that azoles and griseofulvin had similar efficacy but griseofulvin was associated with more adverse events. There was low-quality evidence that terbinafine was superior to griseofulvin with respect to both safety and efficacy (*Kreijkamp-Kaspers et al 2017*). A network meta-analysis of 26 randomized controlled trials (N = 8136) found continuous regimens of terbinafine 250 mg or itraconazole 200 mg increased mycologic cure compared with topical treatments, but fluconazole and pulse regimens of itraconazole or terbinafine had similar cure rates to topical treatments (*Gupta et al 2020*).
- A Cochrane review of 15 trials (N = 1438) evaluating oral antifungals for tinea pedis suggested that terbinafine and itraconazole were superior to placebo, and terbinafine was superior to griseofulvin. No significant difference was detected between terbinafine and itraconazole, fluconazole and itraconazole, fluconazole and ketoconazole, or between griseofulvin and ketoconazole, although the trials were generally small (*Bell-Syer et al 2012*).
- In the treatment of vaginal candidiasis, oral fluconazole was found to be similar to topical antifungal agents in clinical response. These results were similar when comparing single-dose oral treatment with fluconazole and topical regimens of clotrimazole or miconazole for 1 dose *(van Heusden et al 1990, van Heusden et al 1994).*
- In two Phase 3 trials, VANISH 303 and 306, ibrexafungerp 300 mg twice daily for 1 day demonstrated a significant clinical response compared to placebo in non-pregnant females with vulvovaginal candidiasis. At follow-up, complete clinical response rates (defined as an absence of signs and symptoms without need for additional therapy) in VANISH 303 and VANISH 306 were 59.5% and 72.5%, respectively, with ibrexafungerp compared to 44% and 49.4%, respectively with placebo. The most common adverse events were diarrhea, nausea, abdominal pain, dizziness, and vomiting (*Brexafemme prescribing information 2021, US National Library of Medicine 2021, US National Library of Medicine 2020*)

CLINICAL GUIDELINES

- A variety of treatment guidelines address the role of the oral antifungals in the treatment of infectious diseases. Due to changing resistance patterns, guidelines should be frequently referenced.

- Guidelines are available with recommendations for antimicrobial treatment and prophylaxis for HIV and neutropenic patients (including cancer-related immunosuppression) for selection of an appropriate antifungal to use in specific situations *(CDC/NIH/IDSA 2021, NIH/CDC/IDSA/Pediatric Infectious Diseases Society/American Academy of Pediatrics 2021, Taplitz et al 2018a, Taplitz et al 2018b).*
- Guidelines for community acquired pneumonia (CAP), skin and soft-tissue infections (SSTI), and catheter-related infections also address the treatment of fungal causes of infection, although they are less common than bacterial infections in most patients *(Metlay et al 2019, Mermel et al 2009, Stevens et al 2014).*
- Guidelines also address the role of oral fluconazole (as well as vaginal/local antimicrobials) in the treatment of fungal vaginosis *(American College of Gynecology [ACOG] 2020, CDC 2015, Pappas et al 2016).*
- Finally, multiple guidelines address the role of these agents in the treatment of specific fungal infections as 1 agent may be preferred due to volume of literature support, coverage/susceptibility patterns, and safety. Species with specific guidelines include *Aspergillus* species *(Patterson et al 2016), Blastomyces* species *(Chapman et al 2008), Candida* species *(CDC/NIH/IDSA 2020, Pappas et al 2016),* Coccidioidomycosis *(CDC/NIH/IDSA 2020, Galgiani et al 2016), Cryptococcus* species *(CDC/NIH/IDSA 2020, Perfect et al 2010),* Histoplasmosis *(CDC/NIH/IDSA 2020, Wheat et al 2007),* and Sporotrichosis *(Kauffman et al 2007).*

SAFETY SUMMARY

- **Contraindications:**
  - Isavuconazonium sulfate: familial short QT syndrome
  - Griseofulvin: porphyria, hepatocellular failure, and women who are or may become pregnant
  - Ketoconazole: acute or chronic liver disease
  - Miconazole: hypersensitivity to milk protein concentrate
  - Itraconazole: treatment of onychomycosis in patients with evidence of ventricular dysfunction, or in women who intend to become pregnant
  - Terbinafine: chronic or active hepatic disease
  - Posaconazole delayed-release oral suspension: known or suspected hereditary fructose intolerance
  - Ibrexafungerp: pregnancy
- **Boxed Warnings:**
  - Flucytosine: use with extreme caution in patients with impaired renal function; close monitoring of hematologic, renal, and hepatic status of all patients is essential.
  - Ketoconazole should only be used to treat serious systemic fungal infections when other effective antifungal therapy is not available or tolerated, and the potential benefits are considered to outweigh the potential risks; serious hepatotoxicity including death or need for liver transplantation have occurred; coadministration of the following drugs is contraindicated: dofetilide, quinidine, pimozide, cisapride, methadone, disopyramide, dronedarone, and ranolazine due to potential QT prolongation and life-threatening ventricular dysrhythmias.
  - Itraconazole should not be administered for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as congestive heart failure (CHF) or a history of CHF; coadministration of methadone, disopyramide, dofetilide, dronedarone, quinidine, isavuconazonium sulfate, ergot alkaloids (such as dihydroergotamine, ergometrine [ergonovine], ergotamine, methylergometrine [methylergonovine]), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ivabradine, ranolazine, eplerenone, cisapride, naloxegol, lomitapide, lovastatin, simvastatin, avanafil, ticagrelor and, in subjects with renal or hepatic impairment, colchicine, fesoterodine, and solifenacin is contraindicated. Coadministration with eliglustat is contraindicated in patients who are poor or intermediate metabolizers of CYP2D6 and in those taking strong or moderate CYP2D6 inhibitors. Coadministration of the former agents with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. Increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia.
- **Warnings/Precautions:**
  - A warning for hepatoxicity is in the labeling for all of the agents in this class with the exception of Brexafemme (ibrexafungerp), flucytosine, nystatin, and Oravig (miconazole).
  - Flucytosine: monitor hematologic status and bone marrow suppression. Dose adjustments may be necessary in patients with renal impairment.

- Fluconazole, griseofulvin, isavuconazonium sulfate, terbinafine, and voriconazole: rare, sometimes fatal exfoliative skin disorders have occurred. Monitor for skin rashes and discontinue treatment if rash occurs.
- Fluconazole: administer with caution to patients with potentially proarrhythmic conditions or those with renal dysfunction. Women of childbearing potential who receive doses of 400 to 800 mg daily should use effective contraception during treatment and for 1 week after the last dose due to the potential for spontaneous abortion and congenital abnormalities with fluconazole exposure during the first trimester. Additionally, caution is advised when driving or operating heavy machinery as fluconazole may cause occasional dizziness or seizures. Reversible adrenal insufficiency has been reported with fluconazole.
- Griseofulvin: a possibility of cross-sensitivity with penicillin exists. Additionally, lupus-like syndromes or exacerbations of existing lupus have been reported. Patients should avoid exposure to intense or prolonged natural or artificial sunlight.
- Ibrexafungerp: may cause fetal harm; advise females of reproductive potential to use effective contraception during treatment.
- Isavuconazonium sulfate: serious hypersensitivity and skin reactions such as Stevens-Johnson syndrome have been reported.
- Itraconazole: if neuropathy occurs and can be attributed to itraconazole, treatment should be discontinued. If a cystic fibrosis patient does not respond to treatment with itraconazole capsules or oral solution, alternative therapy should be considered. Some immunocompromised patients may have decreased bioavailability and require higher doses. Finally, transient and permanent hearing loss have been reported.
- Ketoconazole: decrease in adrenal corticosteroid secretion can occur at doses of 400 mg and higher.
- Miconazole: monitor for hypersensitivity reactions and discontinue at the first sign of such reaction.
- Posaconazole: administer with caution to patients with potentially proarrhythmic conditions. Monitoring for electrolyte disturbances (including potassium, magnesium, and calcium) is also recommended with posaconazole. The delayed-release oral suspension contains sorbitol and can precipitate a metabolic crisis that may include hypoglycemia, hypophosphatemia, lactic acidosis, and hepatic failure in patients with hereditary fructose intolerance. Patients taking any formulation of posaconazole should be monitored for severe diarrhea or vomiting as an indicator for breakthrough fungal infection.
- Terbinafine: taste and smell disturbances have been reported. Severe neutropenia has been reported. Discontinue treatment if neutrophil count is ≤ 1000 cells/mm^3. Cases of thrombotic microangiopathy (TMA), including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome, have been reported. Discontinue treatment if clinical symptoms and laboratory measurements are consistent with TMA. Treatment should be discontinued if drug reactions such as Stevens-Johnson syndrome or similar conditions occur. Development of depressive symptoms should be monitored.
- Voriconazole: visual disturbances have been reported; galactose intolerance and skeletal disturbances may occur. Voriconazole may increase risk for QT prolongation, hepatic toxicity, and dermatologic reactions (including photosensitivity-related skin reactions). Discontinue voriconazole if severe exfoliative cutaneous reactions occur. The incidence of photosensitivity reactions and elevations of liver enzymes may be higher among pediatric patients. Signs and symptoms of adrenal dysfunction should be monitored in patients taking voriconazole and corticosteroids during and after voriconazole treatment.
- Fetal toxicity may occur with some agents, including fluconazole (use in pregnancy should be avoided unless the benefits outweigh fetal risk), griseofulvin, ibrexafungerp, isavuconazonium sulfate, itraconazole, posaconazole, and voriconazole.
- In May 2016, the FDA issued a medication safety alert warning health care professionals to avoid prescribing ketoconazole oral tablets to treat skin and nail fungal infections. According to the FDA, the risk of serious liver damage and drug interactions with this agent outweigh the benefits when treating these conditions *(FDA Drug Safety Communication 2016).*

- **Adverse Effects:**
  - A variety of adverse effects from mild to severe may occur with agents in this class. Consult individual package inserts for details.
- **Drug Interactions:**
  - Many drug interactions occur with all of the agents in the class.
  - Drugs metabolized through the cytochrome P450 system increase QT prolongation and may cause torsades de pointes.

- Consult individual package inserts for details about specific drug interactions and contraindications for concomitant use of certain medications. Agents that have contraindications related to drug interactions include isavuconazonium sulfate, fluconazole, itraconazole (boxed warning), ketoconazole (boxed warning), posaconazole, and voriconazole.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ancobon (flucytosine)	Capsules	Oral	Every 6 hours	In patients with renal or hepatic dysfunction, use with extreme caution; closely monitor hematologic, renal, and hepatic status.
Brexafemme (ibrexafungerp)	Tablets	Oral	Twice daily	May be taken with or without food. Verify pregnancy status in females of reproductive potential.
Clotrimazole	Lozenges	Oral	Three to 5 times daily	
Cresemba (isavuconazonium sulfate)	Capsules	Oral	Every 8 hours x 6 doses, then once daily	Capsules cannot be chewed, opened, or crushed.
Diflucan (fluconazole)	Tablets Suspension	Oral	Once daily	Pediatric weight-based dose equivalency is available. Dosing adjustments based on renal function are necessary. (see prescribing information)
griseofulvin microsize	Tablets Suspension	Oral	Once daily, or in divided doses	Should be taken after a meal with high fat content Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
Gris-PEG (griseofulvin ultramicrosize)	Tablets	Oral	Once daily, or in divided doses	Pediatric weight-based dosing is available. (see prescribing information) Contraindicated in women who are or may become pregnant.
Ketoconazole	Tablets	Oral	Once daily	Pediatric weight-based dosing is available. (see prescribing information)
Noxafil (posaconazole)	Suspension, Tablets (delayed-release), Powdermix for delayed-release suspension	Oral	Once to 3 times daily	The oral suspension is not substitutable with the delayed-release tablets or the Powdermix for delayed-release oral suspension. The suspension must be given with a full meal. The delayed-release tablets and delayed-release oral suspension should be taken with food. The delayed-release oral suspension is not indicated for those who weigh > 40 kg because the recommended dose cannot be achieved with this formulation. For delivery of the correct dose of the delayed-release oral suspension, only the provided notched tip syringe should be used for preparation and administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nystatin	Suspension Tablets	Oral	Three to 4 times daily	Suspension may be used in infants, children, and adults for the treatment of oral candidiasis.
Oravig (miconazole)	Tablets	Buccal	Once daily	The tablet should be placed against the upper gum just above the incisor tooth. The tablet should not be chewed, crushed, or swallowed.
Sporanox (itraconazole)	Capsules Solution	Oral	Once or twice daily	Capsules should be taken with a full meal. Solution should be taken without food. Only the oral solution should be used for oropharyngeal and esophageal candidiasis; oral solution and capsules should not be used interchangeably. Dose may need to be adjusted to clinical response due to lower bioavailability in some immunocompromised patients.
Terbinafine	Tablets	Oral	Once daily	Use in patients with renal impairment (CrCl ≤ 50 mL/min) has not been studied.
Tolsura (itraconazole)	Capsules	Oral	Once or twice daily	Capsules must be administered with food and cannot be crushed, chewed, or broken. Not interchangeable with other itraconazole products. A loading dose given 3 times daily is recommended for the first 3 days for life-threatening infections
Vfend (voriconazole)	Tablets Suspension	Oral	Every 12 hours	For Aspergillosis, Scedosporiosis, Fusariosis, and Candidemia, therapy should be initiated with IV voriconazole, then switched to the oral formulation for maintenance therapy.

See the current prescribing information for full details; CrCl, creatinine clearance.

CONCLUSION

- The oral class of antifungals includes a variety of different agents used to treat many different fungal infections, including aspergillosis, blastomycosis, histoplasmosis, candidiasis, mucormycosis, onychomycosis, ringworm infections, and others.
- Resistant organisms have been reported; thus, it is important to verify susceptibility when resistant organisms are suspected. Current resistance patterns should be monitored for the antifungal agents in order to select the most appropriate therapy. Appropriate guidelines should be referenced often.
- Some patients may require intravenous therapy that is not specifically discussed in this review. Isavuconazonium sulfate, fluconazole, voriconazole, and posaconazole are available as oral and intravenous formulations. Some of these antifungal medications are also available in topical formulations.
- Clotrimazole, nystatin, and Oravig (miconazole) are not absorbed systemically. They are not used for systemic infections, but only for the treatment of oropharyngeal candidiasis.
- Onychomycosis can be treated with Sporanox (itraconazole) or terbinafine. Tolsura (itraconazole) is not indicated for onychomycosis. Griseofulvin is no longer used for this indication.
- Brexafemme (ibrexafungerp) was approved for treatment of vulvovaginal candidiasis based on significant efficacy compared to placebo. Phase 3 data comparing this new agent to active treatment are not yet available.

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Publication Date: June 28, 2021

INTRODUCTION

- Hemophilia is an X-linked congenital bleeding disorder that affects approximately 1 in 10,000 people (*World Federation of Hemophilia [WFH] 2019*).
  - Hemophilia A is characterized by a deficiency of clotting factor VIII (FVIII), while Hemophilia B is characterized by a deficiency of factor IX (FIX), and is less common then hemophilia A (*National Hemophilia Foundation [NHF] Web site, WFH 2012*).
  - The incidence of hemophilia A is approximately 1 in 5000 male births, and it affects approximately 80 to 85% of the total hemophilia population (*NHF Web site, WFH 2012*). In 2018, the number of patients in the United States (U.S.) with hemophilia A was reported to be 13,616, while those with hemophilia B was 4141 (*WFH 2019*).
- Von Willebrand Disease (VWD) is a common genetic bleeding disorder due to missing or defective von Willebrand factor (VWF), a clotting protein, which equally affects men and women (*NHF Web site*).
  - VWD is the most common bleeding disorder, affecting up to 1% of the U.S. population (*NHF Web site*). In 2018, the number of patients in the U.S. with VWD was reported to be 11,805 (*WFH 2019*).
  - There are 3 main types of VWD classified as type 1 (VWF levels 20 to 50% of normal; 60 to 80% of cases; mild symptoms), type 2 (qualitative deficiencies of VWF; 15 to 30% of patients; mild to moderate symptoms), and type 3 (very low VWF level; 5 to 10% of cases; severe symptoms) (*NHF Web site*).
    - Type 2 VWD is categorized into 4 subtypes: type 2A, type 2B, type 2M and type 2N, depending on the presence and behavior of multimers, the molecular chains of VWF.
- Other rare factor deficiencies, including those of clotting factor I (FI, or fibrinogen), factor VII (FVII), factor X (FX), factor XI (FXI), and factor XIII (FXIII) also result in bleeding disorders (*NHF Web site*).
  - These very rare factor deficiencies, from FXIII deficiency (the rarest) occurring in an estimated 1 out of 5 million people, to FXI deficiency, occurring in about 1 out of 100,000, were all discovered and identified in the 20th century (*NHF Web site*).
- Patients with hemophilia may experience acute serious (eg, joints [hemarthrosis], muscle and soft tissue; mouth, gums, and nose; hematuria) or life-threatening (eg, central nervous system, gastrointestinal, neck and throat, severe trauma) bleeds. Hemarthrosis is the most common type of bleeding, with an overall incidence of up to 80% (*Hoots and Shapiro 2019a, NHF Web site, WFH 2012*).
  - Patients with hemophilia may also develop chronic complications including musculoskeletal complications, inhibitors (neutralizing antibodies) against FVIII or FIX, and transfusion-related infections (eg, human immunodeficiency virus [HIV], hepatitis B virus [HBV], and hepatitis C virus [HCV]) (*Hoots and Shapiro 2019a, NHF Web site, WFH 2012*).
- Hemophilia is a complex disorder with regard to its diagnosis and management. Optimal management, especially of severe disease, requires both the treatment and prevention of acute bleeding with the use of clotting factor replacement therapy (*NHF Web site, WFH 2012*).
- Anti-hemophilic agents evaluated in this review include the fibrinogen, FVIIa, FVIII, FIX, FX, FXIII, and VWF concentrates; FVIII/VWF, FIX, and anti-inhibitor coagulant complexes; the monoclonal antibody Hemlibra (emicizumab-kxwh); and desmopressin.
  - The specific Food and Drug Administration (FDA)-approved indications vary by individual product. In general, these agents are indicated for the control and prevention of bleeding episodes (ie, “on-demand” treatment), routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and/or perioperative management.
  - All factor replacement concentrates are effective in temporarily replacing the missing clotting factor to promote hemostasis. The ultimate choice is determined by the specific characteristics of each product, the individual patient, and local standards of practice (*NHF 2020, NHF Web site, WFH 2012*).
  - Due to the potential risk for pathogen transmission with human plasma-derived factor concentrates, the NHF recommends use of recombinant factor replacement agents as the treatment of choice in patients with bleeding disorders (*NHF 2014, NHF 2020, NHF Web site*). Of note, no seroconversions to HIV, HBV, or HCV have been reported with any of the plasma-derived factor products currently marketed in the U.S. (*NHF Web site*).
    - A possible exception to this recommendation is in a newly diagnosed patient, who should also consider with their health care provider to initiate treatment with a plasma-derived FVIII/VWF product (*NHF 2020*). This exception is

based on the Survey of Inhibitors in Plasma Product-Exposed Toddlers (SIPPET) trial, which demonstrated a significant difference in inhibitor development between treatment with recombinant FVIII (rFVIII) of 44.5% vs 26.8% with plasma-derived FVIII/VWF (*NHF 2016b*).

  - In hemophilia A and B, extended half-life factor replacement products (ie, FVIII concentrates Adynovate, Afstyla, Eloctate, Esperoct, and Jivi; and FIX concentrates Alprolix and Idelvion) have the advantage of less-frequent dosing and may enhance the ease of administration for some patients (*Hoots and Shapiro 2020*). The need for frequent injection represents a significant burden for patients and caregivers, in particular in small children and patients with poor venous access (*Mannucci 2015, Martinowitz et al 2015*).
- For hemophilia A, there are 2 human plasma-derived FVIII concentrates (Hemofil M and Koate/Koate-DVI) and 14 rFVIII products (Adynovate, Afstyla, Advate, Eloctate, Esperoct, Helixate FS, Jivi, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, and Xyntha/Xyntha Solofuse) currently marketed in the U.S.
  - Obizur is the only rFVIII agent approved for the treatment of acquired hemophilia A.
  - Hemlibra is a bispecific monoclonal antibody that bridges FIXa and FX to promote clotting, and provides an additional treatment option for hemophilia A. Hemlibra is the only prophylactic option for hemophilia A that can be self-administered by a subcutaneous (SC) injection.
  - Three human-plasma derived FVIII concentrates rich in VWF (Alphanate, Humate-P, and Wilate) are also approved for on-demand treatment and control of bleeding episodes in hemophilia A.
- For hemophilia B, there are 2 human plasma-derived (AlphaNine SD and Mononine) and 6 recombinant (Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, and Rixubis) FIX products available in the U.S.
  - Additionally, there is a human plasma-derived prothrombin complex concentrate (PCC), Profilnine, which contains FII, FVII, FIX, and FX in variable amounts; Profilnine is rarely used due to the risk of thromboembolism (*WFH 2012*).
- Recommended treatment options for patients with inhibitors to FVIII or FIX include the bypassing agents, factor eight inhibitor bypassing activity (FEIBA; activated prothrombin complex concentrate [aPCC]) and NovoSeven RT (rFVIIa), and the bispecific antibody, Hemlibra (indicated in hemophilia A) (*NHF 2020*). These agents are not interchangeable and the treatment choice depends on multiple factors, including inhibitor type (eg, low- or high-responding), current titer of inhibitor, bleed location, and previous response to these products.
- Vonvendi is the only recombinant VWF agent available for the treatment of bleeding episodes in patients with VWD. Three human-plasma derived FVIII concentrates rich in VWF (Alphanate, Humate-P, and Wilate) are approved for the treatment of VWD; Alphanate has the lowest purity and most variable VWF specific activity of these agents.
- NovoSeven RT (rFVIIa) is the only factor replacement agent FDA-approved for treatment of bleeding episodes in patients with Glanzmann's thrombasthenia (*Grainger et al 2018*).
- Plasma-derived FX (Coagadex) and FXIII (Corifact), and rFXIII A-subunit (Tretten) concentrates are available to treat FX, FXIII, and FXIII A-subunit deficiencies, respectfully.
- Two plasma-derived fibrinogen concentrates, Fibryga and RiaSTAP, are available to manage congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.
- Desmopressin has been used for decades to prevent or treat bleeding episodes in patients with type 1 VWD and mild hemophilia A. Although the complete mechanisms of action of desmopressin are still not fully understood, it increases levels of plasma VWF and FVIII *(Franchini and Lippi 2011)*.
- Medispan classes: Antihemophilic Products - Antihemophilic Factor, Antihemophilic Factor/von Willebrand Factor Complexes, Monoclonal Antibodies, Coagulation Factor IX, Factor IX Complex, Coagulation Factor VIIa, Antiinhibitor Coagulant Complex, Coagulation Factor X, Factor XIII Concentrate, Coagulation Factor XIII A-Subunit, Von Willebrand Factor, and Fibrinogen Concentrates; Posterior Pituitary Hormones - desmopressin.

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Factor VIII concentrates (recombinant)	
Advate	-
Adynovate	-
Afstyla	-
Eloctate	-
Esperoct	-
Helixate FS	-

Drug	Generic Availability
Jivi	-
Kogenate FS	-
Kovaltry	-
Novoeight	-
Nuwiq	-
Obizur	-
Recombinate	-
Xyntha/Xyntha Solofuse	-
Factor VIII concentrates (human)	
Hemofil M	-
Koate/Koate-DVI	-
Factor VIII/von Willebrand factor complex (human)	
Alphanate	-
Humate-P	-
Wilate	-
Bi-specific monoclonal antibody	
Hemlibra (emicizumab-kxwh)	-
Factor IX concentrates (recombinant)	
Alprolix	-
BeneFIX	-
Idelvion	-
Ixinity	-
Rebinyn	-
Rixubis	-
Factor IX concentrates (human)	
Alphanine SD	-
Mononine	-
Factor IX complex (human)	
Profilnine/Profilnine SD	-
Factor VIIA concentrate (recombinant)	
NovoSeven RT	-
Anti-inhibitor coagulant complex (human)	
FEIBA	-
Factor X concentrate (human)	
Coagadex	-
Factor XIII concentrate (human)	
Corifact	-
Factor XIII A-subunit concentrate (recombinant)	
Tretten	-
von Willebrand factor concentrate (recombinant)	
Vonvendi	-
Fibrinogen (Factor I) concentrates	
Fibryga	-
RiaSTAP	-
Desmopressin agents*	

Drug	Generic Availability
DDAVP (desmopressin acetate) injection	✔
Stimate (desmopressin acetate) nasal spray	-

*Other desmopressin agents and formulations, including DDAVP (desmopressin acetate) nasal spray and tablets, Nocdurna (desmopressin acetate) tablets, and Noctiva (desmopressin acetate) nasal spray are not indicated for treatment of hemophilia or VWD, and therefore are not included in this review.

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

INDICATIONS

Table 2. FDA-approved indications: FVIII concentrates

Indications	Human		Recombinant													
	Hemofil M	Koate/ Koate DVI	Advate	Adynovate	Afstyla	Eloctate	Esperoct	Helixate FS	Jivi*	Kogenate FS	Kovaltry	Novoeight	Nuwiq	Obizur	Recombinate	Xyntha/ Xyntha Solofuse
Hemophilia A (congenital FVIII deficiency)																
On-demand treatment and control of bleeding episodes	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔
Routine prophylaxis to reduce the frequency of bleeding episodes			✔	✔	✔	✔	✔	✔ †	✔	✔ †	✔	✔	✔			
Perioperative management		✔	✔	✔	✔	✔	✔	✓	✔	✔	✔	✔	✔		✔	✔
Hemophilia A (acquired)																
Treatment of bleeding episodes														✔ ‡		

*Limitations of use: Jivi is not indicated for use in children < 12 years of age due to a greater risk for hypersensitivity reactions; Jivi is not indicated for use in previously untreated patients (PUPs).
†And to reduce the risk of joint damage in children with no pre-existing joint damage.
‡Limitation of use: Safety and efficacy of Obizur have not been established in patients with a baseline anti-porcine FVIII inhibitor titer > 20 Bethesda Units (BU).

(*Prescribing information: Advate 2018, Adynovate 2018, Afstyla 2019, Eloctate 2019, Esperoct 2019, Helixate FS 2016, Hemofil M 2018, Koate 2018, Jivi 2018, Kogenate FS 2016, Kovaltry 2016, Novoeight 2018, Nuwiq 2017, Recombinate 2018, Xyntha/Xyntha Solofuse 2019*)

Table 3. FDA-approved indications: FVIII/VWF complexes

Indications	Human		
	Alphanate	Humate-P	Wilate
Hemophilia A (congenital FVIII deficiency)			
On-demand treatment and control of bleeding episodes	✔	✔	✔
Routine prophylaxis to reduce the frequency of bleeding episodes			✔
Perioperative management	✔		
VWD			
On-demand treatment and control of bleeding episodes		✔ *	✔
Prevention of excessive bleeding during and after surgery		✔ *	
Surgical and/or invasive procedures	✔ †		
Perioperative management			✔

*This applies to patients with severe VWD as well as patients with mild to moderate VWD where use of desmopressin is known or suspected to be inadequate.
†In patients with VWD in whom desmopressin is either ineffective or contraindicated. It is not indicated for patients with severe VWD (Type 3) undergoing major surgery.

(*Prescribing information: Alphanate 2017, Humate-P 2018, Wilate 2019*)

Table 4. FDA-approved indications: Bi-specific monoclonal antibody

Indication	**Hemlibra** (emicizumab-kxwh)
Hemophilia A (congenital FVIII deficiency)	
Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with or without FVIII inhibitors	✔

(*Hemlibra prescribing information 2018*)

Table 5. FDA-approved indications: FIX concentrates and complexes

Indications	Concentrates, human		Complex, human	Concentrates, recombinant					
	AlphaNine SD*	Mononine*	Profilnine/ Profilnine SD†	Alprolix‡	BeneFIX*	Idelvion‡	Ixinity‡	Rebinyn‡ §	Rixubis‡
Hemophilia B (FIX deficiency)									
On-demand treatment and control of bleeding episodes	✔	✔	✔	✔	✔	✔	✔	✔	✔
Routine prophylaxis to reduce the frequency of bleeding episodes				✔		✔			✔
Perioperative management				✔	✔	✔	✔	✔	✔

*Is not indicated for the treatment of other factor deficiencies, hemophilia A patients with inhibitors to FVIII, or reversal of coumarin-induced anticoagulation.
†Is not indicated for use in the treatment of FVII deficiency.
‡Is not indicated for induction of immune tolerance in patients with hemophilia B.
§Is not indicated for routine prophylaxis in the treatment of patients with hemophilia B.

(*Prescribing information: AlphaNine SD 2018, Alprolix 2019, BeneFIX 2019, Idelvion 2019, Ixinity 2018, Mononine 2018, Profilnine/Profilnine SD 2018, Rebinyn 2017, Rixubis 2019*)

Table 6. FDA-approved indications: FVIIa concentrate

Indications	Recombinant
	NovoSeven RT
Hemophilia A or B with inhibitors **Congenital FVII deficiency** **Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets** **Acquired hemophilia**	
Treatment of bleeding episodes	✔
Perioperative management	✔

(*NovoSeven prescribing information 2019*)

Table 7. FDA-approved indications: Anti-inhibitor coagulant complex

Indications	Human
	FEIBA
Hemophilia A or B with inhibitors	
On-demand treatment and control of bleeding episodes	✔ *
Routine prophylaxis to prevent or reduce the frequency of bleeding episodes	✔
Perioperative management	✔

*Is not indicated for the treatment of bleeding episodes resulting from coagulation factor deficiencies in the absence of inhibitors to FVIII or FIX.

(*FEIBA prescribing information 2020*)

Table 8. FDA-approved indications: FX concentrate

Indications	Human
	Coagadex

Hereditary FX deficiency	
On-demand treatment and control of bleeding episodes	✔
Routine prophylaxis to reduce the frequency of bleeding episodes	✔
Perioperative management of bleeding in patients with mild and moderate hereditary FX deficiency	✔ *

*Limitation of use: Perioperative management of bleeding in major surgery in patients with severe hereditary FX deficiency has not been studied.

(*Coagadex prescribing information 2018*)

Table 9. FDA-approved indications: FXIII concentrates

Indications	Human	Recombinant
	Corifact (FXIII)	Tretten (FXIII A-subunit)
Congenital FXIII deficiency		
Routine prophylactic treatment	✔	
Perioperative management of surgical bleeding	✔	
Congenital FXIII A-subunit deficiency		
Routine prophylaxis of bleeding		✔ *

*Tretten is not indicated for use in patients with congenital FXIII B-subunit deficiency.

(*Prescribing information: Corifact 2019, Tretten 2016*)

Table 10. FDA-approved indications: VWF concentrate

Indications	Recombinant
	Vonvendi
VWD	
On-demand treatment and control of bleeding episodes	✔
Perioperative management of bleeding	✔

(*Vonvendi prescribing information 2019*)

Table 11. FDA-approved indications: Fibrinogen concentrates

Indications	Human	
	Fibryga	RiaSTAP
Congenital fibrinogen deficiency		
Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia.	✔ *	✔

*In adults and adolescents; Fibryga is not indicated for dysfibrinogenemia.

(*Prescribing information: Fibryga 2017, RiaSTAP 2019*)

Table 12. FDA-approved indications: Desmopressin agents

Indications	DDAVP injection*	Stimate nasal spray
Hemophilia A (congenital FVIII deficiency)		
Patients with hemophilia A with FVIII coagulant activity levels > 5%	✔	✔
VWD		
Patients with mild to moderate classic VWD (Type 1) with FVIII levels > 5%	✔	✔

*DDAVP injection is also indicated as an antidiuretic replacement therapy in the management of central diabetes insipidus, and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region; these indications are not included within this review.

(*Prescribing information: DDAVP 2019, Stimate 2013*)

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

CLINICAL EFFICACY SUMMARY

- Overall, clinical trial data consistently support the use of the FVIIa, FVIII, FIX, FX, FXIII, FXIII A-subunit, fibrinogen, and VWF concentrates; FVIII/VWF, FIX, and anti-inhibitor coagulant complexes; the monoclonal antibody, Hemlibra; and

desmopressin agents for their respective FDA-approved indications (*Antunes et al 2014, Arkin et al 1998, Arkin et al 2000, Austin et al 2016, Berntorp et al 2009, Blanchette et al 2008, Bray et al 1994, Carcao et al 2016, Chai-Adisaksopha et al 2017, Clinicaltrials.gov Web site, Collins et al 2010, Collins et al 2014, Collins et al 2018, Curry et al 2019, Escobar et al 2016, Escobar et al 2017, FDA clinical review [Esperoct] 2019, FDA clinical review [Jivi] 2018, FDA clinical review [Nuwiq] 2015, FDA clinical review [Wilate] 2019, FDA multi-discipline review [Hemlibra] 2017, Giangrande et al 2017, Gill et al 2003, Gill et al 2011, Gill et al 2015, Gruppo et al 2019, Hampton et al 2017, Inbal et al 2012, Kavakli et al 2015, Kenet et al 2016, Key et al 1998, Klukowska et al 2016, Konkle et al 2007, Konkle et al 2015, Kruse-Jarres et al 2015, Kulkarni et al 2013, Leissinger et al 2001, Leissinger et al 2011, Lentz et al 2013 , Liesner et al 2018, Lissitchkov et al 2016, Lissitchkov et al 2017, Ljung et al 2016, Lusher et al 2004, Mahlangu et al 2014 , Mahlangu et al 2016, Mahlangu et al 2018, Manco-Johnson et al 2009, Mannucci et al 2002, Matino et al 2015, Meunier et al 2017, Négrier et al 2016, Nolan et al 2016, Oldenburg et al 2016, Oldenburg et al 2017, Philipp et al 2001, Powell et al 2013, Pruthi et al 2007, Ragni et al 2002, Reding et al 2017, Rose et al 1991, Ross et al 2018, Roth et al 2001, Santagostino et al 2015, Santagostino et al 2016, Saxena et al 2016, Scharrer et al 1999, Scharrer et al 2000, Shapiro et al 1998, Shapiro et al 2005, Sjamsoedin et al 1981, Stasyshyn et al 2017, Thompson et al 2004, Tiede et al 2016, Windyga et al 2014a, Windyga et al 2014b, Young et al 2016*).

- As these products are utilized as replacement therapy in patients with deficient levels of clotting factors required for hemostasis, clinical trial data demonstrated that adequate hemostatic responses were consistently achieved with administration of these products.
- Due to ethical concerns, there are a limited number of placebo-controlled trials evaluating the hemophilia agents in the management of hemophilia or VWD. Also, head-to-head trials are rare, and available trials evaluate a relatively small number of patients.
- Within clinical trials, the clinical efficacy of the hemophilia agents was evaluated based on a subjective rating of hemostatic response achieved with the individual agents when administered either as on-demand treatment of acute bleeds or as prophylactic therapy, including in surgical settings.

- Results from a systematic review of 6 randomized controlled trials supported the use of prophylactic therapy with clotting factor concentrates for preserving joint function in children with hemophilia A or B compared to on-demand treatment. Evidence is lacking to determine if prophylaxis decreases bleeding and related complications in patients with existing damage, and the most effective prophylactic regimen in adults with hemophilia requires further investigation (*Iorio et al 2011*).
- A systematic review of available evidence for desmopressin use in bleeding disorders examined the efficacy of desmopressin treatment across a variety of scenarios *(Leissinger et al 2014)*.
  - In a prospective trial of 169 patients with mild or moderate hemophilia A or VWD utilizing SC desmopressin in the outpatient setting, ‘good’ or ‘excellent’ hemostatic responses were achieved in 91% of all bleeding episodes.
  - For surgical hemostasis, several studies demonstrated desmopressin’s efficacy in controlling postoperative bleeding in patients with VWD. Data reported from more than 150 patients (mostly children) undergoing adenotonsillar procedures showed that desmopressin was generally safe and effective, although ~5 to 25% of patients experienced breakthrough bleeding 5 to 10 days postoperatively.
- Clinical efficacy data for newer agents FDA-approved and launched in 2017 through 2019, including Esperoct, Fibryga, Hemlibra, Jivi, and Rebinyn, and new indications for Wilate in 2019, are as follows:

Esperoct

- The efficacy of Esperoct was evaluated for routine prophylaxis, on-demand treatment and control of bleeding episodes, and perioperative management in 254 previously-treated male patients with severe hemophilia A in 3 Phase 3, prospective, multinational, open-label trials in the pathfinder clinical program (*Curry et al 2019, FDA clinical review [Esperoct] 2019, Giangrande et al 2017*).
  - Pathfinder 2 was a non-randomized trial that evaluated Esperoct for prophylaxis and on-demand treatment and control of bleeding episodes in 186 males ≥ 12 years of age. The study included a routine prophylactic treatment arm with Esperoct 50 international units (IU)/kg IV infusion every 4 days (n = 175) and an on-demand treatment arm (n = 12). Of note, 1 patient changed from on-demand treatment to prophylaxis and is counted in both groups. Bleeding episodes were treated with Esperoct 20 to 75 IU/kg (*Curry et al 2019, FDA clinical review [Esperoct] 2019, Giangrande et al 2017, Hampton et al 2017, Meunier et al 2017*).
    - Seventy (40%) patients in the prophylaxis group and 0 (0%) patients in the on-demand treatment group did not have a treatment-requiring bleeding episode during the trial.

- In the prophylaxis group, the median and mean annualized bleeding rate (ABR) for treated bleeds were 1.2 (interquartile range [IQR], 0.0 to 4.3) and 3.0 (standard deviation [SD], 4.7), respectively. A total of 58% of the bleeds were spontaneous and 42% were traumatic, and the majority of bleeds (75%) occurred in joints.
- In the on-demand treatment group, the median and mean ABR for treated bleeds were 30.9 (IQR, 18.6 to 38.5) and 31.9 (SD, 19.1), respectively. A total of 78% of the bleeds were spontaneous and 21% were traumatic, and the majority of bleeds (58%) occurred in joints.
- For on-demand treatment, 968 bleeding episodes were treated with Esperoct in 117 (67%) patients, of which 436 bleeding episodes occurred in 105 patients in the prophylaxis arm and 532 bleeding episodes occurred in 12 patients in the on-demand treatment arm. The success rates for the treatment of bleeding episodes in the on-demand and prophylaxis groups were similar at 88.4% (95% confidence interval [CI], 80.0 to 93.5) and 83.7% (95% CI, 79.0 to 87.5), respectively.
- One patient developed FVIII inhibitory antibodies after 93 Esperoct exposure days (EDs).

- Pathfinder 5 was a single-arm trial that evaluated Esperoct for prophylaxis and on-demand treatment and control of bleeding episodes in 68 males < 12 years of age. All patients were treated with Esperoct 50 to 75 IU/kg twice weekly; bleeding episodes were treated with Esperoct 20 to 75 IU/kg (*FDA clinical review [Esperoct] 2019, Meunier et al 2017*).
  - For prophylaxis, the median and mean ABR for treated bleeds were 2.0 (IQR, 0.0 to 2.8) and 3.1 (SD, 7.1), respectively.
  - For treatment of bleeding episodes, 70 bleeds (all rated as mild/moderate) were treated with Esperoct in 39 (57%) patients. The overall success rate for treatment of bleeding episodes was 79%. Most bleeds (80%) were treated with ≤ 2 Esperoct injections, with a mean dose of 123.0 IU/kg/bleed (SD, 104.9; range, 44.9 to 435.5) in patients 0 to 5 years of age and 99.0 IU/kg/bleed (SD, 54.4; range, 49.9 to 296.4) in patients 6 to 11 years of age.
  - No patients developed FVIII inhibitors.
- Pathfinder 3 was an uncontrolled single-am trial that evaluated Esperoct for perioperative treatment in 34 males ≥ 12 years of age. Esperoct was administered up to 2 hours prior to surgery and postoperatively; dose levels were individually targeted to attain a minimum FVIII activity as recommended by WFH guidelines. A total of 33 patients underwent 45 major surgeries and completed the trial (*FDA clinical review [Esperoct] 2019, Hampton et al 2017*).
  - Intraoperative hemostatic effect was rated as 'excellent' or 'good' in 43/45 (95.6%) of the surgeries, and rated as 'moderate' in 2 surgeries (4.4%).
  - The median preoperative dose was 52 IU/kg, and the median total dose was 702 IU/kg. The number of doses and duration of treatment varied by procedure.

Fibryga

- A Phase 2, multicenter, open-label, crossover trial compared the pharmacokinetics and efficacy as measured by clot strength (ie, maximum clot firmness [MCF], a surrogate marker of hemostatic efficacy) of Fibryga and RiaSTAP in 22 patients with congenital afibrinogenemia (*Ross et al 2018*).
  - Bioequivalence was demonstrated for some, but not all, pharmacokinetic endpoints. Notably, bioequivalence was not demonstrated for the primary endpoint of area under the concentration-time curve normalized to dose administered.
  - A significant increase in mean plasma MCF from baseline (all 0.00 mm) to 1 hour after administration was observed with both Fibryga (9.68 mm) and RiaSTAP (10.00 mm) ($p < 0.0001$ for both products vs placebo). The difference between active treatments was -0.32 mm (95% CI, -1.70 to 1.07), which was not statistically significant.
- A Phase 3, multicenter, open-label, single-arm trial is evaluating the use of Fibryga for on-demand treatment of acute bleeding episodes and prevention of intraoperative and postoperative bleeding in patients with congenital fibrinogen deficiency; interim results are available after the treatment of 13 patients (*Lissitchkov et al 2017*).
  - Hemostatic efficacy was assessed based on an objective 4-point rating criteria and MCF.
    - Treatment success for bleeding episodes (rating of 'excellent' or 'good') was 95.7% (90% CI, 0.81 to 1.00) as assessed by the investigators, and 100% (90% CI, 0.88 to 1.00) as assessed by an independent data monitoring and endpoint adjudication committee (IDMEAC).
    - A significant increase in MCF was demonstrated in patients with bleeding episodes, from 0.0 mm at baseline to 6.5 mm (95% CI, 5.65 to 7.40; $p < 0.0001$) at 1 hour after the first fibrinogen concentrate infusion.
    - The intraoperative and postoperative efficacy of fibrinogen concentrate (based on 4 surgeries) was demonstrated with success rates of 100% (90% CI, 0.5 to 1.0) by both the surgeon or hematologist and the IDMEAC.

Hemlibra

- The efficacy of Hemlibra for routine prophylaxis in males with hemophilia A with FVIII inhibitors was evaluated in 2 Phase 3, multicenter, open-label clinical trials, HAVEN 1 in 109 adults and adolescents, and HAVEN 2 in 23 pediatric patients (*FDA multi-discipline review [Hemlibra] 2017, Oldenburg et al 2017*)
  - In the 24-week HAVEN 1 trial, the ABR was 2.9 (95% CI, 1.7 to 5.0) in patients treated with Hemlibra 1.5 mg/kg once weekly vs 23.3 (95% CI, 12.3 to 43.9) in patients with no prophylaxis, with a statistically significant reduction of 87% in favor of Hemlibra prophylaxis ($p < 0.001$). A total of 62.9% of patients treated with Hemlibra experienced 0 bleeds (95% CI, 44.9 to 78.5) vs 5.6% (95% CI, 0.1 to 27.3) with no prophylaxis, and the median ABR was 0 and 18.8, respectively (*Oldenburg et al 2017*).
    - In an intra-patient analysis of 24 eligible patients in a non-interventional study (NIS) treated with Hemlibra prophylaxis, Hemlibra prophylaxis resulted in a statistically significant 79% ABR reduction (95% CI, 51.4 to 91.1; $p = 0.0003$) vs previous bypassing agent (BPA) prophylaxis (3.3 vs 15.7 events, respectively) (*Oldenburg et al 2017*).
  - HAVEN 2 is an unpublished, ongoing, single-arm trial in pediatric males. At the time of the interim analysis, the ABR for treated bleeds was 0.3 events (95% CI, 0.1 to 0.5) and the median ABR was 0; 87% (95% CI, 75 to 94) of patients experienced 0 bleeds (*FDA multi-discipline review [Hemlibra] 2017*).
    - In an intra-patient analysis (n = 18), Hemlibra prophylaxis resulted in a 98% reduction in bleed rate compared with previous BPA treatment prior to enrollment (0.4 vs 19.8 events, respectively). On Hemlibra prophylaxis, 14 patients (77.8%) had 0 treated bleeds.
- The efficacy of Hemlibra for routine prophylaxis in adult and adolescent males with hemophilia A without FVIII inhibitors was evaluated in 2 Phase 3, multicenter, open-label trials, HAVEN 3 (N = 152) and HAVEN 4 (N = 41) (*Clinicaltrials.gov Web site, Mahlangu et al 2018*)
  - In the 24-week HAVEN 3 trial, the ABR in patients treated with Hemlibra 1.5 mg/kg once weekly was 1.5 (95% CI, 0.9 to 2.5) vs 38.2 (95% CI, 22.9 to 63.8) in patients with no prophylaxis, with a statistically significant reduction of 96% in favor of Hemlibra prophylaxis (95% CI, 92.5 to 98.0; $p < 0.0001$). For patients treated with 3 mg/kg once every 2 weeks, the ABR was 1.3 (95% CI, 0.8 to 2.3) with a statistically significant reduction of 97% (95% CI, 93.4 to 98.3, $p < 0.0001$) vs no prophylaxis. A total of 56% (95% CI, 38.1 to 72.1) of patients treated with Hemlibra 1.5 mg/kg once weekly and 60% (95% CI, 42.1 to 76.1) of patients in treated with Hemlibra 3 mg/kg once weekly experienced 0 treated bleeds, vs 0% (95% CI, 0 to 18) with no prophylaxis (*Mahlangu et al 2018*).
    - In an intra-patient analysis of 48 patients, Hemlibra 1.5 mg/kg once weekly resulted in a statistically significant 68% reduction (95% CI, 48.6 to 80.5; $p < 0.0001$) in ABR compared with previous FVIII prophylaxis in the NIS prior to enrollment (1.5 vs 4.8 events, respectively).
  - In HAVEN 4, prophylaxis with Hemlibra 6 mg/kg every 4 weeks (after 4 weeks of 3 mg/kg once weekly) at 25.6 weeks of treatment resulted in a median ABR of 2.4 (95% CI, 1.4 to 4.3). A total of 56% (95% CI, 39.7 to 71.5) of patients experienced 0 treated bleeds (*Clinicaltrials.gov Web site*).
- An Institute for Clinical and Economic Review (ICER) and New England Comparative Effectiveness Public Advisory Council final evidence report for Hemlibra in hemophilia A included a comparative clinical effectiveness review of 5 clinical trials to evaluate the comparative safety and efficacy of prophylaxis with Hemlibra, aPCC, and rFVIIa in patients with hemophilia A with inhibitors (*ICER 2018*). The review determined that for children < 12 years of age, there was high certainty that Hemlibra provided at least a small net health benefit ("B+" rating) vs no prophylaxis; in adults and children, there was high certainty that Hemlibra provided at least a small health benefit ("B+" rating) vs BPA prophylaxis.

Jivi

- The efficacy of Jivi for on-demand treatment, perioperative management of bleeding and routine prophylaxis was evaluated in the 36-week, Phase 2/3, partially randomized, multicenter, open-label PROTECT VIII trial in 134 previously treated patients (PTPs) ≥ 12 years of age with severe hemophilia A (*FDA clinical review [Jivi] 2018, Reding et al 2017*).
  - A total of 13 patients not eligible for randomization (ie, patients who experienced > 1 bleed during the run-in period) were treated with Jivi 30 to 40 IU/kg twice weekly. In these patients, the median ABR (quartile 1 to quartile 3) in the run-in period was 17.4 (14.3 to 26.0), which improved with treatment to 4.1 (2.0 to 10.6); 15% of these patients experienced 0 bleeds.
  - The median ABR (quartile 1 to quartile 3) in 11 patients randomized to Jivi 30 to 40 IU/kg twice a week was 1.9 (0 to 5.2); 46% of patients experienced 0 bleeds.
  - The median ABR for 43 patients randomized to Jivi 45 to 60 IU/kg every 5 days was 1.9 (0 to 4.2); 44% of patients experienced 0 bleeds.
  - The median ABR for all 43 patients randomized to Jivi 60 IU/kg every 7 days was 3.9 (0.0 to 6.5) for the duration of time that they remained in the treatment arm (ie, the intent-to-treat population).

- Eleven patients left the every-7-days treatment group for more frequent dosing.
- The median ABR for 32/43 patients who remained in the every-7-day treatment arm was 0.96 (0.0 to 6.5); 37.2% of patients experienced 0 bleeds.

- A total of 388 bleeding episodes were treated with Jivi in the on-demand group (n = 20), while 317 bleeding episodes were treated in the prophylaxis groups. Approximately 90% of the bleeds were successfully treated with 1 or 2 infusions in both the on-demand and prophylaxis groups.
- For perioperative management, 17 patients successfully completed 20 major surgeries using Jivi for hemostasis. Treatment with Jivi provided 'good' or 'excellent' hemostatic control during all 20 major surgeries based on a 4-point scale ('excellent', 'good', 'moderate' or 'poor').

Rebinyn

- The efficacy of Rebinyn was evaluated in 4 Phase 3, uncontrolled, multicenter trials (paradigm 2 [pivotal trial], paradigm 3 [perioperative use], paradigm 4 [extension trial of paradigm 2 and 3], and paradigm 5 [pediatrics]).
  - Paradigm 2 was a 52-week, randomized controlled trial of 74 males ≥ 12 years of age with hemophilia B (*Collins et al 2014*). The study included 2 routine prophylactic treatment arms, with single-blind randomization to either Rebinyn 10 IU/kg once weekly or 40 IU/kg once weekly, and a 28-week open-label on-demand treatment arm.
    - The median ABRs in the Rebinyn 10 IU/kg and 40 IU/kg groups were 2.93 (IQR, 0.99 to 6.02) and 1.04 (IQR, 0.00 to 4.00), respectively. The median ABR in the on-demand treatment group was 15.58 (IQR, 9.56 to 26.47). Five (17%) patients in the Rebinyn 10 IU/kg group, 13 (45%) patients in the Rebinyn 40 IU/kg group, and 1 (7%) patient in the on-demand group did not have a treatment-requiring bleeding episode during the trial.
    - For on-demand treatment, 345 bleeding episodes were treated with Rebinyn in 55 (74%) patients, of which 202 bleeding episodes occurred in the prophylaxis arms and 143 bleeding episodes occurred in the on-demand treatment arm. Treatment efficacy was rated by investigators as 'excellent' or 'good' in 92.2% (95% CI, 86.9 to 95.4) of bleeds, and 97.4% of bleeds were successfully treated with 1 or 2 injections.
  - Paradigm 3 was an open-label trial in 13 males who underwent major surgery (*Escobar et al 2017*). Intraoperative hemostatic effect was considered successful in 100% of the surgeries, and rated as 'excellent' or 'good' in 10 and 3 of the 13 surgeries evaluated, respectively.
  - Paradigm 4 was an open-label extension trial allowing for ≥ 50 additional EDs in 71 adult and adolescent patients from the paradigm 2 or 3 trials, who continued routine or on-demand treatment with Rebinyn with the possibility of switching regimens during the trial (*Young et al 2016*).
    - A total of 134 bleeds were reported in 44 (65.7%) of 67 patients in the prophylaxis arms. The median ABRs for patients within the 10 and 40 IU/kg treatment arms were 1.36 (IQR, 0.00 to 2.23) and 1.00 (IQR, 0.00 to 2.03), respectively.
    - For on-demand treatment, 207 bleeds were reported in 49 (75%) patients, of which 134 bleeding episodes occurred in the prophylaxis arms and 73 bleeding episodes occurred in the on-demand treatment arm. The overall success rate (ie, efficacy rated as 'excellent' or 'good') for treatment of all bleeding episodes was 94.6%, and 97.1% of bleeds were successfully treated with 1 or 2 injections.
- Paradigm 5 was a 52-week, open-label, single-arm trial in 25 males 1 to 12 years of age with hemophilia B (*Carcao et al 2016*). The study included 1 routine prophylactic treatment arm with once-weekly Rebinyn 40 IU/kg; bleeding episodes were treated with Rebinyn 40 IU/kg for mild/moderate bleeds and 80 IU/kg for severe bleeds.
  - With Rebinyn 40 IU/kg once-weekly prophylaxis, the median ABR was 1.0 in the total trial population. Ten (40%) patients reported no bleeds, and no spontaneous joint bleeds were reported in target joints.
  - For on-demand treatment, 42 bleeding episodes were treated with Rebinyn in 15 (60%) patients. The overall success rate for treatment of all bleeding episodes was 92.9%, and 97.6% of the bleeding episodes were resolved with 1 or 2 injections.

Wilate

- The efficacy of Wilate for routine prophylaxis and on-demand treatment of bleeding episodes was evaluated in a 6-month, Phase 3, open-label, single-arm, multicenter clinical trial in 55 (adults, n = 50; pediatrics 12 to 15 years of age, n = 5) previously treated patients with severe hemophilia A. Patients were treated every 2 to 3 days with 20 to 40 IU/kg of Wilate, with a mean dose 32 IU/kg (*Clinicaltrials.gov Web site, FDA clinical review [Wilate] 2019*).
- For routine prophylaxis, a total of 30 (54.6%) patients experienced 0 bleeding episodes, and there were 12 (21.8%) patients with 1 bleeding episode, 4 (7.3%) with 2 bleeding episodes, 4 (7.3%) with 3 bleeding episodes, and 5 (9%) with ≥ 5 bleeding episodes.

- In adults, the ABR for spontaneous bleeds was 1.67 ± 3.11 (median, 0; range, 0 to 11.76), and the ABR for all types of bleeds was 2.39 ± 3.77 (median, 0; range 0 to 15.69).
- In pediatric patients, the ABR for spontaneous bleeds was 0 (median 0; range 0 to 0), and the ABR for all types of bleeds was 0.4 ± 0.89 (median, 0; range 0 to 2).

- Breakthrough bleeds were treated with Wilate doses adjusted to the severity of the bleed. In the per-protocol population (n = 52), 57 bleeding episodes were treated with Wilate, of which 15 (26.3%) were minor, 32 (56.1%) were moderate, 10 (17.5%) were major, and none were life-threatening. A total of 41 (71.9%) bleeds were spontaneous and 16 (28.1%) were traumatic.
  - Thirty-six (63.2%) bleeding episodes were managed with 1 injection of Wilate, 12 (21.1%) were managed with 2 injections, 7 (12.3%) were managed with 3 injections, and 2 (3.6%) required > 3 injections. The mean dose of Wilate per injection was 34 IU/kg.
  - Treatment efficacy was judged as 'excellent' for 16 (28.1%), 'good' for 32 (56.1%), and 'moderate' for 9 (15.8%) bleeding episodes. Therefore, 84.2% of all bleeding episodes were treated successfully.
    - Only 1 bleeding episode was treated in 1 patient < 16 years of age; it was treated with a single injection of Wilate 62.81 IU/kg with 'excellent' efficacy.
  - Further efficacy data in the treatment of bleeding episodes are available from a pooled analysis of 37 patients with hemophilia A from 3 additional clinical studies. Patients had ≥ 150 EDs at the time of enrollment and were treated for ≥ 50 EDs and 6 months in the studies. A total of 986 bleeding episodes were experienced by patients, of which 936 (94.9%) were treated successfully.

CLINICAL GUIDELINES

NHF Medical and Scientific Advisory Council (MASAC) recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders (MASAC #259) (*NHF 2020*)

- Inherited bleeding disorders (FVII, FVIII, FIX, FX, FXIII, FXIII A-subunit deficiencies)
  - Recombinant factor replacement products are the treatment of choice for patients with hemophilia A, hemophilia B, FVII deficiency, and FXIII A-subunit deficiency.
    - A possible exception to this recommendation is for a newly diagnosed patient with Hemophilia A, who should also consider with their healthcare provider to initiate treatment with a plasma-derived FVIII/VWF product. This exception is based on the SIPPET trial (see MASAC #243 below), which demonstrated a significant difference in inhibitor development between treatment with rFVIII vs plasma-derived FVIII/VWF ((*NHF 2016b*).
    - The risk of human viral contamination associated with recombinant FVIII is exceedingly low. Third generation recombinant products do not contain any human or animal plasma-derived proteins in the culture medium or final formulation.
  - Emicizumab-kxwh (Hemlibra) was shown in Phase 3 clinical trials to be safe and effective in adults, adolescents, children, and infants with hemophilia A with and without inhibitors. The SC administration of emicizumab-kxwh is often viewed as being easier and/or less time consuming compared to IV administration of FVIII. Dosing intervals for prophylaxis with emicizumab-kxwh are longer compared with FVIII replacement, with weekly, every 2-week, or every 4-week dosing regimens.
  - Plasma-derived FX (Coagadex) and FXIII (Corifact) concentrates are available to treat FX and FXIII deficiencies, respectfully.
  - Desmopressin may be used in some patients with mild hemophilia A.
- VWD
  - Desmopressin may be used in patients with VWD type 1 and some variations of VWD type 2.
  - Recombinant VWF concentrate (Vonvendi) is available to treat patients with type 2B and type 3 VWD; it can also be used in patients with types 1, 2A, 2M, and 2N VWD who are not responsive to DDAVP and in children < 2 years of age regardless of VWD type.
  - Plasma-derived FVIII/VWF complexes (Alphanate, Humate-P, and Wilate) may be used in patients that do not respond to desmopressin (ie, VWD type 2B, type 3), those who have become transiently unresponsive to desmopressin, and in surgical situations.
- Hemophilia A or B and inhibitors to FVIII or FIX
  - Inhibitor development is the most severe complication of treatment for patients with inherited hemophilia A or B.
    - For high-titer inhibitors, immune tolerance induction (ITI) is the best option for inhibitor eradication.

- The BPAs, NovoSeven RT and FEIBA, and Hemlibra are licensed for treatment of bleeding episodes in patients with inhibitors.
  - These products are not interchangeable. Choice of product depends on multiple factors, including type of inhibitor (low- or high-responding), current titer of inhibitor, location of the bleed, and previous response to these products.
  - Thrombotic risks exist with the use of all of these agents.
- Acquired hemophilia A
  - Patients who were not born with hemophilia may develop antibodies or inhibitors that cause destruction of factors; such inhibitors may be seen in patients with autoimmune disorders.
  - Patients may be treated with NovoSeven RT or Obizur.
    - Obizur is a recombinant porcine FVIII; often the human FVIII inhibitor does not cross-react with the porcine species of FVIII, thus allowing for measurable factor levels and cessation of bleeding.
- Fibrinogen Deficiency
  - Plasma-derived fibrinogen concentrate can be used to treat patients with congenital hypofibrinogenemia and afibrinogenemia, but not dysfibrinogenemia.
  - Cryoprecipitate is the only currently available product for dysfibrinogenemia.
  - Because it has not undergone any viral attenuation steps, cryoprecipitate should not be used to treat patients with afibrinogenemia except in life- and limb-threatening emergencies when fibrinogen concentrate is not immediately available.
- Ancillary Medications
  - Aminocaproic acid and tranexamic acid are antifibrinolytics that may be used as ancillary medications in the management of hemophilia and other bleeding disorders.
    - Aminocaproic acid can be orally administered to treat mouth bleeds. A dose of appropriate factor concentrate must be given first to form the clot, and aminocaproic acid can then be administered to preserve the clot until healing has taken place. Aminocaproic acid can also be given via intravenous (IV) infusion following oral surgery (eg, wisdom tooth extraction) or ear/nose/throat surgery (eg, tonsillectomy).
    - Tranexamic acid is approved for treatment of menorrhagia and is orally administered for 5 days during menstruation.

MASAC recommendation concerning prophylaxis (MASAC #241) (*NHF 2016a*)

- Prophylaxis should be considered optimal therapy for individuals with severe hemophilia A or B (ie, factor levels < 1%).
- Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding), with the aim of keeping the trough factor level > 1% between doses.
  - Optimal dosing and frequency should be determined for each individual.
- Recombinant factor products are the most appropriate for prophylaxis due to markedly reduced risk of blood-borne infections.
- Joint bleeds with subsequent joint destruction are a lifelong problem for these individuals; there are no clear guidelines as to when to stop prophylaxis.
  - Reasons to discontinue prophylaxis may include development of an inhibitor or patient preference with physician concurrence.

MASAC recommendation regarding the use of recombinant clotting factor products with respect to pathogen transmission (MASAC #226) (*NHF 2014*)

- Current plasma-derived concentrates employed in the treatment of hemophilia A and B, VWD, and other inherited bleeding disorders are very safe with respect to transmission of HIV, HBV, HCV, and hepatitis A virus. However, these products may be capable of transmitting non-enveloped viruses such as parvovirus B19. In addition, these products are potentially capable of transmitting prions, the agents that cause Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD), which are not eliminated by current viral inactivation and product purification techniques.
  - While vCJD has been transmitted by red blood cell transfusion, no known cases have been reported from the use of plasma-derived factor products in the past 35 years of use. However, parvovirus B19 and prions may be markers for undiscovered or unrecognized blood-borne infectious agents.
  - This possibility suggests a potentially improved safety profile for recombinant products over plasma-derived products with respect to pathogen transmission.

- MASAC fully endorses the following recommendation made in April 1998 by the Public Health Service's Advisory Committee on Blood Safety and Availability:
  - "Every effort should be made to make recombinant clotting factors available to all who would benefit from them, and all barriers to conversion from human plasma-derived concentrates to recombinant clotting factors should be removed."
- Recombinant factor products are potentially the safest factor products available with respect to pathogen transmission and should be considered the treatment of choice for hemophilia A.
  - For hemophilia A and B patients with inhibitors, there are often overriding concerns about efficacy that supersede those of potentially increased safety with respect to pathogen transmission.
  - In all patients, including those with inhibitors, efficacy must be weighed against the risk of potential pathogen transmission.

MASAC recommendation on SIPPET (Survey of Inhibitors in Plasma Product-Exposed Toddlers): results and recommendations for treatment products for PUPs with hemophilia A (MASAC #243) (*NHF 2016b*)

- Inhibitor development affects up to 30% of PUPs treated with FVIII; inhibitors may occur with both plasma-derived and rFVIII concentrates.
- SIPPET was a prospective randomized controlled trial that evaluated the frequency of inhibitor formation in PUPs treated with rFVIII vs plasma-derived FVIII/VWF complex.
  - There was a significant difference in inhibitor development between the 2 treatments; there was a cumulative incidence of 44.5% with rFVIII vs 26.8% with plasma-derived FVIII/VWF (HR, 1.87; 95% CI, 1.17 to 2.96).
  - The NHF noted differences between SIPPET and previous studies that showed minimal increase in inhibitor formation with rFVIII, including ethnicity differences, use of a third generation agent, and the fact that about half of the patients were on on-demand therapy (episodic) vs a prophylactic regimen.
- The NHF recommends newly diagnosed patients and caregivers consider the following:
  - Initiation of therapy with a plasma-derived FVIII/VWF product in all PUPs.
  - Initiation of therapy with an rFVIII product as previously recommended by MASAC.
  - Initiation of therapy with a newer rFVIII product.

WFH Guidelines for the Management of Hemophilia (*WFH 2012*)

- Principles of care
  - The primary aim of care is to prevent and treat bleeding with the deficient clotting factor.
  - Acute bleeds should be treated as quickly as possible, preferably within 2 hours.
  - Prevention of bleeding can be achieved by prophylactic factor replacement.
- Prophylactic factor replacement therapy
  - Prophylaxis prevents bleeding and joint destruction and should be the goal of therapy to preserve normal musculoskeletal function.
    - Prophylaxis does not reverse established joint damage; however, it decreases the frequency of bleeding and may slow progression of joint disease and improve quality of life.
  - The administration and dosing protocol should be individualized as much as possible based on age, venous access, bleeding phenotype, activity, and availability of clotting factor concentrates.
- Clotting factor concentrates
  - FVIII concentrates are the treatment of choice for hemophilia A.
    - Plasma-derived FVIII concentrates may contain variable amounts of VWF. It is therefore important to ascertain a product's VWF content (as measured by ristocetin cofactor activity) if it is used for the treatment of VWD.
  - FIX concentrates are the treatment of choice for hemophilia B. The WFH does not express a preference for recombinant over plasma-derived concentrates, and the choice between these classes must be made according to local criteria.
    - Allergic reactions may occur with infusions of FIX concentrates in patients with anti-FIX inhibitors; hydrocortisone may be used to treat such reactions. Changing the brand of clotting factor concentrate sometimes reduces symptoms.
  - The WFH does not express a preference for recombinant over plasma-derived concentrates, and the choice between these classes must be made according to local criteria.

        - In-process viral inactivation is the single largest contributor to the safety of plasma-derived concentrates. However, some viruses (eg, human parvovirus B19) are relatively resistant to current viral inactivation/elimination processes, and none of the current methods can inactivate prions.
    - Concentrates of lower purity may give rise to allergic reactions. Patients who experience these repeatedly with a particular product may benefit from administration of an antihistamine immediately prior to infusion or from use of a higher purity concentrate.
    - For surgery and invasive procedures, the dosage and duration of clotting factor concentrate coverage depends on the type of surgery performed.
- Other pharmacological options
    - DDAVP may be the treatment of choice for patients with mild or moderate hemophilia A when FVIII can be raised to an appropriate therapeutic level, as it avoids the expense and potential hazards of using a clotting factor concentrate.
- Inhibitors
    - "Inhibitors" in hemophilia refer to IgG antibodies that neutralize clotting factors. Inhibitors to FVIII or FIX are considered the most severe treatment-related complication in hemophilia.
        - The presence of a new inhibitor should be suspected in any patient who fails to respond clinically to clotting factors, particularly if they have been previously responsive. In this situation, the expected recovery and half-life of the transfused clotting factor are severely diminished.
        - Inhibitors are more frequently encountered in patients with severe hemophilia compared with those with moderate or mild hemophilia. The cumulative incidence (ie, lifetime risk) of inhibitor development in severe hemophilia A ranges from 20 to 30%, and is approximately 5 to 10% in moderate or mild disease.
        - In severe hemophilia, inhibitors do not change the site, frequency, or severity of bleeding, while in moderate or mild hemophilia, the inhibitor may neutralize endogenously synthesized FVIII, thereby effectively converting the patient's phenotype to severe.
        - In all cases, inhibitors render treatment with replacement factor concentrates difficult.
    - Management of bleeding in patients with inhibitors must be in consultation with a center experienced in their management.
        - Choice of treatment should be based on the titer of inhibitor, records of clinical response to product, and site and nature of bleed.
        - Porcine FVIII has been effective in halting bleeding in some patients, and alternative agents include BPAs, such as rFVIIa and aPCC. The efficacy of 2 doses of rFVIIa and 1 dose of aPCC for management of joint bleeding has been shown to be essentially equivalent.
        - Some patients respond better to one agent than the other, which highlights the need to individualize therapy.
    - In patients with severe hemophilia A, eradication of inhibitors is often possible by ITI therapy.
    - For the vast majority of patients, switching products does not lead to inhibitor development. However, in rare instances, inhibitors in PTPs have occurred with the introduction of new FVIII concentrates. In those patients, the inhibitor usually disappears after withdrawal of the new product.

NHLBI: Diagnosis, evaluation, and management of VWD (*NHLBI 2007*)

- General management
    - Treatment of individuals with VWD is aimed at cessation of bleeding or prophylaxis for surgical procedures.
    - Long-term risks and benefits of long-term prophylaxis should be considered carefully.
    - Fluid restriction to maintenance levels should be considered in individuals receiving DDAVP (especially young children and in surgical settings) to avoid the occurrence of hyponatremia and seizures.
- Treatment of minor bleeding and prophylaxis for minor surgery
    - Epistaxis and oropharyngeal, soft tissue, or minor bleeding should be treated with IV or nasal DDAVP, if appropriate based on trial testing.
    - If elevation of VWF is necessary and response to DDAVP is inadequate, VWF concentrate should be used, with dosing primarily based on von Willebrand Factor:Ristocetin Cofactor (VWF:RCo) units and secondarily on FVIII units.
    - For management of minor bleeding (eg, epistaxis, simple dental extraction, or menorrhagia), DDAVP and proper fluid restriction can be used without laboratory monitoring, unless DDAVP is used > 3 times within 72 hours.
    - For individuals with mild to moderate VWD, antifibrinolytics combined with DDAVP are generally effective for oral surgery. VWF concentrate should be available for individuals who cannot receive DDAVP or who bleed excessively despite this combined therapy.

- Topical agents, such as fibrin sealant or bovine thrombin, may be useful adjuncts for oral surgery.

- Treatment of major bleeding and prophylaxis for major surgery
  - Whenever possible, all major surgeries and bleeding events should be treated in hospitals with a 24-hour/day laboratory capability and with clinical monitoring by a team including a hematologist and a surgeon skilled in the management of bleeding disorders.
- Acquired von Willebrand syndrome (AVWS)
  - Individuals who have AVWS and who require surgery should be considered for a trial of therapy with DDAVP and/or VWF concentrate, with monitoring of VWF:RCo and FVIII levels, to evaluate for possible accelerated clearance of VWF.
  - For individuals who have AVWS and who bleed excessively despite therapy with DDAVP and VWF concentrate, treatment with high-dose IV immunoglobulin should be considered, especially in IgG isotype monoclonal gammopathy of undetermined significance.

SAFETY SUMMARY

Inhibitor development

- Some patients with hemophilia develop inhibitors, which are IgG antibodies that neutralize clotting factors such as FVIII and FIX and make it difficult to obtain sufficient factor levels to control bleeding (*WHF 2012*). Inhibitors to FVIII or FIX are considered the most severe treatment-related complication in hemophilia.
- The development of inhibitors has been reported in 20 to 30% of patients with severe hemophilia A and 1.5 to 3% in severe hemophilia B (*Hoots and Shapiro 2019b*).
  - Many influences may contribute to inhibitor development such as patient characteristics (eg, variations in factor and immune regulatory genes), the environment, and the hemophilia treatment.
- Inhibitors are more likely to occur within the first 50 EDs in patients with severe hemophilia A, but a baseline low risk remains through a patient's life (*Iorio et al 2012*). The cumulative inhibitor risk in PUPs is approximately 30%, whereas in PTPs it is 2 to 3 per 1000 patient-years.
  - An ED is defined as a 24-hour period during which a dose of concentrate has been administered, irrespective of size and frequency. PUPs are defined as having < 20 to 50 EDs, while PTPs are commonly defined as having > 75 to 150 EDs.

All hemophilia agents

- **Contraindication**
  - In general, all agents are contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to the agent or its components.
- **Warnings/precautions**
  - Common warnings and precautions with the factor replacement products include risks of thromboembolic events, development of neutralizing antibodies (inhibitors), and transmitting infectious agents in products made from human blood.
    - FEIBA, Hemlibra, and NovoSeven RT each have a boxed warning for the risk of thromboembolic events; boxed warning details are included further in the Safety Summary section.
- **Drug Interactions**
  - Risk of hypercoagulability with Hemlibra, FEIBA, NovoSeven RT, FX, and FXIII A-subunit agents may increase with concomitant use of other clotting factors.

FVIII concentrates (recombinant) *(Advate, Adynovate, Afstyla, Eloctate, Esperoct, Helixate FS, Jivi, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha/Xyntha Solofuse)*

- **Warnings/precautions**
  - Advate, Afstyla, Eloctate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Recombinate: Development of FVIII neutralizing antibodies (inhibitors) may occur; PUPs are at greatest risk.
  - Helixate FS, Kogenate FS: When clotting is normalized by treatment with FVIII, development of cardiovascular risk factors may be the same as the risk for non-hemophilic patients.
  - Jivi: Immune response to polyethylene glycol (PEG), manifested as symptoms of acute hypersensitivity and/or loss of drug effect, has been observed primarily in patients < 6 years of age.

- Obizur: Anamnestic reactions with rise in human FVIII inhibitors and/or porcine FVIII inhibitors have been reported; these anamnestic rises may result in lack of response to Obizur.

FVIII concentrates (human) (*Hemofil M, Koate/Koate DVI*)
- **Warnings/precautions**
  - Hemofil M: formation of antibodies to mouse protein; increase in pulse rate
  - Koate/Koate-DVI: Monitoring for intravascular hemolysis and decreasing hematocrit values should be performed in patients with A, B or AB blood groups who are receiving large or frequent doses.

FVIII/VWF complexes (human) (*Alphanate, Humate-P, Wilate*)
- **Warnings/precautions**
  - Alphanate, Humate-P: intravascular hemolysis
  - Alphanate: Vasomotor reactions may occur with rapid administration.

Bi-specific monoclonal antibody (*Hemlibra*)
- **Warnings/precautions**
  - **Boxed warning:** thrombotic microangiopathy (TMA) and thromboembolism. Cases of TMA and thrombotic events were reported when on average a cumulative amount of > 100 units/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving Hemlibra prophylaxis. Patients should be monitored for the development of TMA and thrombotic events if aPCC is administered. Administration of aPCC should be discontinued and dosing of Hemlibra suspended if symptoms occur.
  - Laboratory coagulation test interference.

FIX concentrates (recombinant) (*Alprolix, BeneFIX, Idelvion, Ixinity, Rebinyn, Rixubis*)
- **Contraindication**
  - Rixubus: Should not be used in patients with disseminated intravascular coagulation or signs of fibrinolysis.
- **Warnings/precautions**
  - Nephrotic syndrome has been reported following ITI therapy with FIX products in hemophilia B patients with FIX inhibitors, often with a history of allergic reactions.

FIX concentrates (human) (*AlphaNine SD, Mononine*)
- **Warnings/precautions**
  - Nephrotic syndrome has been reported following ITI therapy with FIX products in hemophilia B patients with FIX inhibitors, often with a history of allergic reactions.
  - Alphanine: In PUPs, it is possible that anaphylaxis may occur after a median exposure of 11 days.

FIX complexes (human) (*Profilnine/Profilnine SD*)
- **Warnings/precautions**
  - Natural rubber latex sensitivity

FVIIa concentrate (recombinant) (*NovoSeven RT*)
- **Warnings/precautions**
  - **Boxed warning:** Serious arterial and venous thrombotic events following administration of NovoSeven RT have been reported; patients should be monitored for signs or symptoms of activation of the coagulation system and for thrombosis.

Anti-inhibitor coagulant complex (human) (*FEIBA*)
- **Contraindications**
  - Disseminated intravascular coagulation
  - Acute thrombosis or embolism (including myocardial infarction)
- **Warnings/precautions**

- **Boxed warning**: Thromboembolic events have been reported during post-marketing surveillance, particularly following the administration of high doses and/or in patients with thrombotic risk factors. Patients should be monitored for signs and symptoms of thromboembolic events.
- The safety and efficacy of FEIBA for breakthrough bleeding in patients receiving Hemlibra has not been established. Cases of TMA were reported in a clinical trial where subjects received FEIBA as part of a treatment regimen for breakthrough bleeding following treatment with Hemlibra. The benefits and risks of FEIBA should be considered if it is considered required for patients receiving Hemlibra prophylaxis and patients should be closely monitored for signs and symptoms of TMA.
- Presence of isohemagglutinins and interference with laboratory tests: FEIBA contains blood group isohemagglutinins (anti-A and anti-B). Passive transmission of antibodies to erythrocyte antigens, eg, A, B, D, may interfere with some serological tests for red cell antibodies, such as antiglobulin test (Coombs test).

- **FX concentrate (human)** (*Coagadex*)
  - **Drug Interactions**
    - Coagadex should be used with caution in patients who are receiving other plasma products that may contain FX (eg, fresh frozen plasma, PCC [Profilnine]).
    - Based on the mechanism of action, Coagadex is likely to be counteracted by direct and indirect FXa inhibitors (eg, fondaparinux, apixaban, edoxaban, rivaroxaban).

- **FXIII A-subunit concentrate (recombinant)** (*Tretten*)
  - **Drug Interactions**
    - Tretten should not be administered with rFVIIa.

Desmopressin agents

- **Contraindications**
  - DDAVP injection: moderate to severe renal impairment (creatinine clearance [CrCl] < 50 mL/min); hyponatremia or a history of hyponatremia.
- **Warnings/precautions**
  - DDAVP injection, Stimate: hyponatremia. Very rare cases of hyponatremia have been reported from worldwide postmarketing experience in patients treated with desmopressin. Fluid restriction is recommended and careful medical supervision is required.
  - DDAVP injection, Stimate: polydipsia. Desmopressin products should be used with caution in patients with habitual or psychogenic polydipsia, who may be more likely to drink excessive amounts of fluids, putting them at greater risk of hyponatremia.
  - DDAVP injection, Stimate: Desmopressin should not be used to treat patients with Type 2B VWD since platelet aggregation may be induced.

DOSING AND ADMINISTRATION

- The dose and frequency of administration of the hemophilia agents varies among individual patients. The treatment dose and frequency should be calculated based on patient characteristics and clinical considerations such as the severity of the factor deficiency, the location and extent of bleeding, and presence of inhibitors.
  - Higher factor clearance may occur in pediatric patients with some agents; dose adjustment may be needed.
- The extended half-life FVIII and FIX agents are intended to reduce the dosing frequency and burden of prophylaxis regimens compared with the standard half-life agents.
  - All factor replacement products require IV administration and are available as single-use vials, with the exception of Xyntha Solofuse which is available as a single-use prefilled dual-chamber syringe.
- Treatment dose and frequency should be calculated based the patient's clinical condition and the product's prescribing information. See Table 13 for general dosing information.

Table 13. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Factor VIII concentrates (recombinant)				
Advate Adynovate Afstyla Eloctate Esperoct Helixate FS Jivi Kogenate FS Kovaltry Novoeight Nuwiq Obizur Recombinate Xyntha/Xyntha Solofuse	Injection	IV	Routine prophylaxis (standard half-life agents): • Advate, Helixate FS, Kogenate FS, Kovaltry, Novoeight, Nuwiq, Obizur, Recombinate, Xyntha/Xyntha Solofuse: 2 to 4 times/week Routine prophylaxis (extended half-life agents): • Adynovate: 2 times/week • Afstyla: 2 to 3 times/week • Eloctate: Every 3 to 5 days • Esperoct: Every 4 days (adolescents/adults); 2 times/week (children < 12 years of age) • Jivi: Every 5 days On-demand treatment/perioperative management: • Individualized dose and frequency	• Jivi is not indicated for use in children < 12 years of age • Obizur is indicated in adults with acquired hemophilia A.
Factor VIII concentrates (human)				
Hemofil M Koate/Koate-DVI	Injection	IV	On-demand treatment/perioperative management: • Individualized dose and frequency	
Factor VIII/von Willebrand factor complex (human)				
Alphanate Humate-P Wilate	Injection	IV	On-demand treatment/perioperative management: • Individualized dose and frequency Routine prophylaxis in hemophilia A: • Wilate: Every 2 to 3 days	• Humate-P is indicated in adults for hemophilia A. • Wilate is indicated in adolescents and adults for hemophilia A.
Bi-specific monoclonal antibody				
Hemlibra (emicizumab-kxwh)	Injection	SC	Routine prophylaxis: • Once weekly for the first 4 weeks, followed by a maintenance dose once weekly, every 2 weeks, or every 4 weeks.	• May be self-administered
Factor IX concentrates (recombinant)				
Alprolix BeneFIX Idelvion	Injection	IV	Routine prophylaxis (standard half-life agents): Rixubis: Twice weekly Routine prophylaxis (extended half-life agents):	• Ixinity is indicated in patients ≥ 12 years of age.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Ixinity Rebinyn Rixubis			• Alprolix: Every 7 or 10 days • Idelvion: Every 7 days; every 14 days in some cases On-demand treatment/perioperative management: • Individualized dose and frequency	
Factor IX concentrates (human)				
Alphanine SD Mononine	Injection	IV	On-demand treatment: • Individualized dose and frequency	
Factor IX complex (human)				
Profilnine/ Profilnine SD	Injection	IV	On-demand treatment: • Individualized dose and frequency	
Factor VIIA concentrate (recombinant)				
NovoSeven RT	Injection	IV	On-demand treatment/perioperative management: • Individualized dose and frequency	• NovoSeven RT is indicated in adults with acquired hemophilia.
Anti-inhibitor coagulant complex (human)				
FEIBA	Injection	IV	Routine prophylaxis: • Every other day On-demand treatment/perioperative management: • Every 6 to 12 hours	
Factor X concentrate (human)				
Coagadex	Injection	IV	Routine prophylaxis: • 2 times/week On-demand treatment/perioperative management: • Individualized dose and frequency	
Factor XIII concentrate (human)				
Corifact	Injection	IV	Routine prophylaxis: • Every 28 days Perioperative management: • Individualized dose and frequency	
Factor XIII A-subunit concentrate (recombinant)				
Tretten	Injection	IV	Routine prophylaxis: • Once monthly	
von Willebrand factor concentrate (recombinant)				
Vonvendi	Injection	IV	On-demand treatment/perioperative management: • Individualized dose and frequency	• Vonvendi is indicated in patients ≥ 18 years of age.
Fibrinogen Concentrates				
Fibryga RiaSTAP	Injection	IV	On-demand treatment: • Individualized dose and frequency	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Desmopressin agents				
DDAVP (desmopressin acetate)	Injection	IV	On-demand treatment: • Weight-based IV infusion over 15 to 30 minutes Perioperative management: • 30 minutes prior to the scheduled procedure	
Stimate (desmopressin acetate)	Nasal spray	Nasal insufflation	On-demand treatment: • One spray in each nostril (or a single spray in one nostril in patients < 50 kg) Perioperative management: • 2 hours prior to the scheduled procedure	• Spray pump requires priming.

*Hemophilia agents may be used in pediatric patients unless otherwise noted.

See the current prescribing information for full details.

CONCLUSION

- Hemophilia A and B, VWD, and other rare bleeding disorders due to less prevalent factor deficiencies, are complex disorders with regard to diagnosis and management. In general, optimal management, especially of severe disease, requires both the treatment and prevention of acute bleeding with the use of clotting factor replacement therapy.
- Factor replacement concentrates are all generally effective in temporarily replacing the missing clotting factor to promote hemostasis. The ultimate choice is determined by the specific characteristics of each product, the individual patient, and local standards of practice.
  - Due to the potential risk for pathogen transmission with human plasma-derived factor concentrates, recombinant factor replacement agents are generally recommended as the treatment of choice in patients with bleeding disorders.
  - In hemophilia A and B, extended half-life factor replacement products are intended to reduce the dosing frequency and burden of prophylaxis regimens compared with standard factor products with shorter half-lives.
- Hemlibra is a first-in-class bispecific monoclonal antibody with a unique mechanism of action that provides a safe and effective option for routine prophylaxis in patients with hemophilia A with or without FVIII inhibitors.
  - Hemlibra is the only prophylactic option in patients with hemophilia A that can be self-administered by a once-weekly SC injection, with a once-every-4-weeks dosing regimen for eligible patients.
- Certain desmopressin formulations, including the DDAVP injection and Stimate nasal spray, may be used in some patients with mild hemophilia A, VWD type 1 and some variations of VWD type 2.

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Publication Date: April 1, 2020