South Dakota Department of Social Services

Medicaid P&T Committee Meeting

June 23, 2017

DEPARTMENT OF SOCIAL SERVICES
MEDICAL SERVICES
700 Governors Drive
Pierre, South Dakota 57501-2291
(605) 773-3495
FAX (605) 773-5246

SOUTH DAKOTA
MEDICAID P&T COMMITTEE MEETING
AGENDA

June 23, 2017
1:00 – 3:00 PM

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

Call to order

Approval of minutes of previous meeting

PA Update

Review of top 15 therapeutic categories/top 50 drugs

Review of Specialty Drugs

Review of Insulin Products – Deidra Van Gilder, PharmD, SDSU

Old business
- **Opioid utilization and strategies for management**
- **Review of Eucrisa**

New business
- **Review of Dupixent**
- **Review of Codeine and Tramadol Utilization**
- **Review of Xrylix Kit**
- **Review of Xorvolex**
- **Review of Zipsor**
- **Review of Cambia**

Oral presentations and comments by manufacturers' representatives

Next meeting date/adjournment

Minutes of the March 31, 2017
Pharmacy & Therapeutics (P&T) Committee Meeting
South Dakota Department of Social Services, Division of Medical Services

Members Present

Dana Darger, Mikal Holland, Bill Ladwig, Michelle Baack, Kelley Oehlke, Richard Holm, Lenny Petrik, James Engelbrecht, Timothy Soundy

DSS Staff Present

Mike Jockheck

Administrative Business

The meeting was called to order by Darger at 1:00 P.M. The minutes of the December meeting were presented. Petrik made a motion to approve, Oehlke seconded the motion. The motion was approved unanimously.

Prior Authorization Update (PA) and Statistics

The committee reviewed the PA activity for January 2017. There were a total of 3,545 Pas processed in the month of January, with 97.32% of those requests responded to in less than eight hours. There were 2,782 requests (78%) received electronically and 763 requests (22%) received by fax.

Analysis of the Top 15 Therapeutic Classes and Drug Spend

The committee reviewed the top 15 therapeutic classes by total cost of claims from 10/01/16 – 12/31/16. The top five classes were antipsychotic agents, insulins, respiratory and CNS stimulants, amphetamines, and anticonvulsants, misc. The top 15 therapeutic classes make up 40.75% of total claims. The committee also reviewed the top 50 drugs based on total claims cost and number of claims. The top 50 drugs by claims cost make up 14.08% of total claims. Baack asked for a breakdown of all products included in the insulin class. Darger asked for a presentation on insulin, including the new biosimilar insulins. Possible presenters will be researched.

Opioid Strategies for Management Review

At the December meeting the Committee was asked to provide insight on ways to manage opioid utilization. Holm discussed opioid prescribing statistics. The South Dakota Board of Medicine's white paper on responsible opioid prescribing was discussed. An overview of several state Medicaid morphine milligram equivalents (MME) prior authorization requirements were reviewed. Baack asked that a report on MMEs/day be provided, excluding patients with a terminal or cancer diagnosis. Ladwig suggested that patients taking more than 90 MME/day be identified. It was also requested that the MME report be broken down into smaller groupings, to determine

current opioid utilization. Holland suggested a review of providers. Soundy discussed ways to identify patients with acute pain. Baack asked the committee if patients on chronic opioids should also be required to have naloxone available. Further discussion of opioid utilization management will be added to the agenda for future meetings. There was no public comment.

Methadone Second Review
A PA form was developed and presented to the committee at the December meeting. The committee asked that the form be re-reviewed in March. Darger discussed methadone use in neuropathic pain and for renally impaired patients. Soundy made a motion to accept the form as presented. Englebrecht seconded. The motion was unanimously approved. There was no public comment.

Over-the-counter (OTC) Iron
The State requested the committee's insight whether OTC iron should be a covered product. A review of several state Medicaid's OTC iron policies were reviewed. Baack suggested that iron be covered for children. Holm made a motion to cover OTC iron products for children aged 2 and under. Englebrecht seconded. The motion passed unanimously. There was no public comment.

Nuplazid Second Review
At the December meeting the committee requested a PA form be developed and presented for review. The committee asked that the form be amended to state that the medication be prescribed by, or in consultation with, a neurologist or psychiatrist. Oehlke made a motion to approve the form as amended. Baack seconded. The motion passed unanimously. There was no public comment.

Specialty Medication Review
Utilization of medications over $5,000 for CY2016 was presented to the committee. Engelbrecht recommended that this report be included in each pack and that biosimilars be included. There was no public comment.

Emflaza Review
Emflaza information was presented for review. Panna Patel, representative from Marathon Pharmaceuticals, spoke regarding prolonged ambulation and less instances of weight gain. The committee requested that information be brought back to regarding Emflaza versus prednisone in clinical trials, if available. Englebrecht made a motion to approve the prior authorization criteria (diagnosis of Duchenne muscular dystrophy and age greater than 5 years) as presented. Holland seconded. The motion passed unanimously.

Diclegis Review
Diclegis prior authorization criteria was presented for review at the request of two OB/GYN providers. The committee discussed if prior therapy with ondansetron should be required. There was no public comment. Baack made a motion that the PA requirements be amended and that the requirement for a trial of ondansetron be removed and the diagnosis of hyperemesis gravidarum be required. Soundy seconded. The motion passed unanimously.

Eucrisa Review
Eucrisa information was presented for review. Adil Anwar, representative from Pfizer Pharmaceuticals, spoke regarding the indications and duration of therapy. Baack asked for additional information regarding pimecrolimus and tacrolimus creams/ointments. The committee would like a comparison in cost, indication and place in therapy between Eucrisa and other available agents. Engelbrecht requested additional information about what other payors are doing with drugs indicated for atopic dermatitis. This information will be revisited at the June meeting.

Onzetra Review
Onzetra information was presented for review. There was no public comment. Baack made a motion to add prior authorization criteria to this drug (requesting a trial of all other triptans). Soundy seconded. The motion passed unanimously.

Keveyis Review
No action was taken. There was no public comment

The next meetings are scheduled for 06/23/2017, and 09/29/2017. Holland motioned to adjourn. Ladwig seconded. The meeting adjourned at 2:45 P.M.

health information designs

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2017 – April 30, 2017

Time Ratio

Total PAs	Response Under 8 Hours	Response Over 8 Hours	% Under 8 Hours	% Over 8 Hours
3,071	3,050	21	99.32%	0.68%

By Form Type

Form Type	Description	Approve	Deny
ADP	Antidepressant	62	233
AFX	Amrix and Fexmid	1	1
AMB	Ambien CR	5	6
ANF	Anti-Infectives (antibiotics)	0	1
ANT	Antihistamines	4	37
APS	Antipsychotic	244	721
ARB	ARBS	2	3
AUB	Aubagio	0	1
COA	Oral Anticoagulants	10	31
CON	Chronic Constipation Medication	17	9
DAW	Dispense As Written	11	9
GIA	Gastrointestinal Agents	2	0
GLP	GLP-1 Agonists	21	4
GRA	Gralise	1	1
GRH	Growth Hormone	6	7
GSM	Genitourinary SMR	6	36
HEP	Hepatitis Meds	0	4
HLM	Head Lice Medication	35	11
HOR	Horizant	0	1
LID	Lidoderm	1	82
LYR	Lyrica	22	211
MAX	Max Units Override	59	511
NAR	Name Brand Narcotics	3	0
NUC	Opioids	3	11
ONF	Onfi	7	2
OPH	Ophthalmic Antihistamines	0	21
PPI	Proton Pump Inhibitors	34	97
SMR	Skeletal Muscle Relaxants	1	4
STE	Nasal Steroids	6	65
STI	Stimulants	2	16
SUB	Suboxone/Subutex	7	24
TIM	Targeted Immune Modulators	6	18
TOP	Topical Acne Agents	10	68
TRP	Triptans	9	57
ULT	Ultram ER	0	2
UNK	Unknown (online)	0	146
VUS	Vusion	0	1
XIF	Xifaxan	1	21
Totals		**598**	**2473**

health information designs

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2017 – April 30, 2017

By Request Type

04/01/17 – 04/30/17	# of Requests	Electronic Requests		Faxed Requests	
		#	%	#	%
Prior Authorizations					
Antidepressant	295	204	69%	91	31%
Amrix and Fexmid	2	2	100%	0	0%
Ambien CR	11	5	45%	6	55%
Anti-Infectives (antibiotics)	1	1	100%	0	0%
Antihistamines	41	30	73%	11	27%
Antipsychotic	965	650	67%	315	33%
ARBS	5	0	0%	5	100%
Aubagio	1	0	0%	1	100%
Oral Anticoagulants	41	29	71%	12	29%
Chronic Constipation Medications	26	0	0%	26	100%
Dispense As Written	20	0	0%	20	100%
Gastrointestinal Agents	2	0	0%	2	100%
GLP-1 Agonists	25	0	0%	25	100%
Gralise	2	2	100%	0	0%
Growth Hormone	13	5	38%	8	62%
Genitourinary SMR	42	29	69%	13	31%
Hepatitis Meds	4	0	0%	4	100%
Head Lice Medication	46	0	0%	46	100%
Horizant	1	1	100%	0	0%
Lidoderm	83	72	87%	11	13%
Lyrica	233	169	73%	64	27%
Max Units Override	570	460	81%	110	19%
Name Brand Narcotics	3	0	0%	3	100%
Opioids	14	7	50%	7	50%
Onfi	9	0	0%	9	100%
Ophthalmic Antihistamines	21	16	76%	5	24%
Proton Pump Inhibitors	131	98	75%	33	25%
Skeletal Muscle Relaxants	5	4	80%	1	20%
Nasal Steroids	71	54	76%	17	24%
Stimulants	18	14	78%	4	22%
Suboxone/Subutex	31	20	65%	11	35%
Targeted Immune Modulators	24	14	58%	10	42%
Topical Acne Agents	78	61	78%	17	22%
Triptans	66	50	76%	16	24%
Ultram ER	2	1	50%	1	50%
UNKNOWN(online)	146	146	100%		
Vusion	1	1	100%	0	0%
Xifaxan	22	21	95%	1	5%
Prior Authorization Totals	**3071**	**2166**	**71%**	**905**	**29%**

health information designs

South Dakota Medicaid
Monthly Prior Authorization Report
April 1, 2017 – April 30, 2017

Electronic PAs (Unique)

04/01/17 – 04/30/17	# Unique Approved	# Unique Denied	# Unique Incomplete	Unique Total	Approval %	Total Transactions
Prior Authorizations:						
Antidepressant	4	187	0	191	2.10%	204
Amrix and Fexmid	1	1	0	2	50.00%	2
Ambien CR	0	5	0	5	0.00%	5
Anti-Infectives(anti-biotic)	0	1	0	1	0.00%	1
Antihistamines	0	30	0	30	0.00%	30
Antipsychotic	7	530	0	537	1.30%	650
Oral Anticoagulants	0	23	0	23	0.00%	29
Gralise	1	1	0	2	50.00%	2
Growth Hormone	0	5	0	5	0.00%	5
Genitourinary SMR	1	23	0	24	4.20%	29
Horizant	0	1	0	1	0.00%	1
Lidoderm	0	60	0	60	0.00%	72
Lyrica	1	154	0	155	0.60%	169
Max Units Override	0	442	0	442	0.00%	460
Opioids	0	7	0	7	0.00%	7
Ophthalmic Antihistamines	0	16	0	16	0.00%	16
Proton Pump Inhibitors	14	74	0	88	15.90%	98
Skeletal Muscle Relaxants	0	4	0	4	0.00%	4
Nasal Steroids	0	49	0	49	0.00%	54
Stimulants	0	13	0	13	0.00%	14
Suboxone/Subutex	0	17	0	17	0.00%	20
Targeted Immune Modulators	0	14	0	14	0.00%	14
Topical Acne Agents	2	58	0	60	3.30%	61
Triptans	2	48	0	50	4.00%	50
Ultram ER	0	1	0	1	0.00%	1
UNKNOWN(online)	0	139	0	139	0.00%	146
Vusion	0	1	0	1	0.00%	1
Xifaxan	0	18	0	18	0.00%	21
TOTALS	33	1922	0	1955	1.70%	2166

TOP 50 DRUGS BASED ON NUMBER OF CLAIMS FROM 01/01/2017 - 03/31/2017

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AMOXICILLIN	PENICILLINS	9,155	$ 77,291.78	$ 8.44	4.15%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	4,689	$ 79,590.14	$ 16.97	2.13%
AZITHROMYCIN	MACROLIDES	4,298	$ 65,118.17	$ 15.15	1.95%
METHYLPHENIDATE ER	RESPIRATORY AND CNS STIMULANTS	3,991	$ 821,824.05	$ 205.92	1.81%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,913	$ 36,235.63	$ 9.26	1.78%
FLUOXETINE HCL	ANTIDEPRESSANTS	3,830	$ 42,768.44	$ 11.17	1.74%
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	3,516	$ 24,266.26	$ 6.90	1.60%
VYVANSE	AMPHETAMINES	3,495	$ 899,537.54	$ 257.38	1.59%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	3,436	$ 62,661.36	$ 18.24	1.56%
SERTRALINE HCL	ANTIDEPRESSANTS	3,429	$ 25,291.29	$ 7.38	1.56%
MONTELUKAST SODIUM	LEUKOTRIENE MODIFIERS	3,293	$ 51,470.38	$ 15.63	1.49%
LEVOTHYROXINE SODIUM	THYROID AGENTS	3,239	$ 50,458.22	$ 15.58	1.47%
TRAZODONE HCL	ANTIDEPRESSANTS	2,763	$ 16,994.66	$ 6.15	1.25%
GABAPENTIN	ANTICONVULSANTS, MISCELLANEOUS	2,575	$ 38,385.47	$ 14.91	1.17%
TRAMADOL HCL	OPIATE AGONISTS	2,453	$ 19,819.19	$ 8.08	1.11%
LISINOPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	2,377	$ 12,707.40	$ 5.35	1.08%
TAMIFLU	NEURAMINIDASE INHIBITORS	2,316	$ 510,172.02	$ 220.28	1.05%
AMOXICILLIN-CLAVULANATE POTASS	PENICILLINS	2,208	$ 42,824.60	$ 19.40	1.00%
DEXTROAMPHETAMINE-AMPHET ER	AMPHETAMINES	2,128	$ 250,451.16	$ 117.69	0.97%
GUANFACINE HCL ER	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	2,117	$ 54,352.75	$ 25.67	0.96%
CEFDINIR	CEPHALOSPORINS	2,079	$ 77,558.42	$ 37.31	0.94%
LORATADINE	SECOND GENERATION ANTIHISTAMINES	2,033	$ 11,670.94	$ 5.74	0.92%
CLONIDINE HCL	CENTRAL ALPHA-AGONISTS	1,956	$ 12,638.87	$ 6.46	0.89%
VENTOLIN HFA	BETA-ADRENERGIC AGONISTS	1,940	$ 111,835.09	$ 57.65	0.88%
FLUTICASONE PROPIONATE	CORTICOSTEROIDS (EENT)	1,923	$ 17,764.36	$ 9.24	0.87%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	1,900	$ 14,106.34	$ 7.42	0.86%
PREDNISONE	ADRENALS	1,846	$ 13,634.10	$ 7.39	0.84%
POLYETHYLENE GLYCOL 3350	CATHARTICS AND LAXATIVES	1,782	$ 46,247.14	$ 25.95	0.81%
CEPHALEXIN	CEPHALOSPORINS	1,706	$ 25,934.49	$ 15.20	0.77%
PROAIR HFA	BETA-ADRENERGIC AGONISTS	1,668	$ 102,164.81	$ 61.25	0.76%
METFORMIN HCL	BIGUANIDES	1,642	$ 11,346.55	$ 6.91	0.74%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	1,610	$ 11,670.68	$ 7.25	0.73%
ONDANSETRON ODT	5-HT3 RECEPTOR ANTAGONISTS	1,580	$ 20,938.55	$ 13.25	0.72%
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	1,580	$ 40,707.72	$ 25.76	0.72%
ARIPIPRAZOLE	ANTIPSYCHOTIC AGENTS	1,509	$ 112,728.40	$ 74.70	0.68%
ESCITALOPRAM OXALATE	ANTIDEPRESSANTS	1,475	$ 14,148.26	$ 9.59	0.67%
VITAMIN D2	VITAMIN D	1,459	$ 8,758.95	$ 6.00	0.66%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,441	$ 16,647.31	$ 11.55	0.65%
CITALOPRAM HBR	ANTIDEPRESSANTS	1,412	$ 8,147.36	$ 5.77	0.64%
QUETIAPINE FUMARATE	ANTIPSYCHOTIC AGENTS	1,392	$ 16,755.86	$ 12.04	0.63%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	1,390	$ 140,446.97	$ 101.04	0.63%
LAMOTRIGINE	ANTICONVULSANTS, MISCELLANEOUS	1,359	$ 18,411.70	$ 13.55	0.62%
ATORVASTATIN CALCIUM	HMG-COA REDUCTASE INHIBITORS	1,344	$ 13,524.05	$ 10.06	0.61%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC,SEDATIV/HYP)	1,342	$ 9,059.99	$ 6.75	0.61%
TRIAMCINOLONE ACETONIDE	ANTI-INFLAMMATORY AGENTS (SKIN, MUCOUS)	1,304	$ 15,439.90	$ 11.84	0.59%
CYCLOBENZAPRINE HCL	CENTRALLY ACTING SKELETAL MUSCLE RELAXNT	1,289	$ 7,986.83	$ 6.20	0.58%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,270	$ 260,866.24	$ 205.41	0.58%
PREDNISOLONE SODIUM PHOSPHATE	ADRENALS	1,228	$ 11,272.16	$ 9.18	0.56%
VENLAFAXINE HCL ER	ANTIDEPRESSANTS	1,209	$ 23,593.95	$ 19.52	0.55%
LEVETIRACETAM	ANTICONVULSANTS, MISCELLANEOUS	1,201	$ 23,295.08	$ 19.40	0.54%
TOTAL TOP 50		116,090	$ 4,401,521.58	$ 37.91	52.67%

Total Rx Claims From 01/01/2017 - 03/31/2017	220,418

TOP 50 DRUGS BASED ON TOTAL CLAIMS COST FROM 01/01/2017 - 03/31/2017

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
VYVANSE	AMPHETAMINES	3,495	$ 899,537.54	$ 257.38	1.59%
METHYLPHENIDATE ER	RESPIRATORY AND CNS STIMULANTS	3,991	$ 821,824.05	$ 205.92	1.81%
TAMIFLU	NEURAMINIDASE INHIBITORS	2,316	$ 510,172.02	$ 220.28	1.05%
LATUDA	ANTIPSYCHOTIC AGENTS	423	$ 441,515.25	$ 1,043.77	0.19%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	962	$ 423,231.58	$ 439.95	0.44%
HUMIRA PEN	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	65	$ 353,676.29	$ 5,441.17	0.03%
INVEGA SUSTENNA	ANTIPSYCHOTIC AGENTS	166	$ 312,477.50	$ 1,882.39	0.08%
LYRICA	ANTICONVULSANTS, MISCELLANEOUS	679	$ 310,251.10	$ 456.92	0.31%
NOVOLOG FLEXPEN	INSULINS	484	$ 272,342.41	$ 562.69	0.22%
DEXMETHYLPHENIDATE HCL ER	RESPIRATORY AND CNS STIMULANTS	1,270	$ 260,866.24	$ 205.41	0.58%
DEXTROAMPHETAMINE-AMPHET ER	AMPHETAMINES	2,128	$ 250,451.16	$ 117.69	0.97%
ONFI	BENZODIAZEPINES (ANTICONVULSANTS)	238	$ 249,867.60	$ 1,049.86	0.11%
GATTEX	GI DRUGS, MISCELLANEOUS	7	$ 236,005.01	$ 33,715.00	0.00%
ENBREL	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	57	$ 235,917.68	$ 4,138.91	0.03%
ADVATE	HEMOSTATICS	8	$ 235,086.29	$ 29,385.79	0.00%
LANTUS SOLOSTAR	INSULINS	521	$ 217,305.29	$ 417.09	0.24%
ORKAMBI	CYSTIC FIBROSIS (CFTR) POTENTIATORS	11	$ 210,580.96	$ 19,143.72	0.00%
ADVAIR DISKUS	CORTICOSTEROIDS (RESPIRATORY TRACT)	564	$ 209,349.30	$ 371.19	0.26%
PULMOZYME	MUCOLYTIC AGENTS	56	$ 201,895.27	$ 3,605.27	0.03%
FLOVENT HFA	CORTICOSTEROIDS (RESPIRATORY TRACT)	874	$ 197,098.77	$ 225.51	0.40%
NOVOLOG	INSULINS	403	$ 189,216.01	$ 469.52	0.18%
PREVACID	PROTON-PUMP INHIBITORS	366	$ 176,893.13	$ 483.31	0.17%
RECOMBINATE	HEMOSTATICS	7	$ 161,093.80	$ 23,013.40	0.00%
LEVEMIR FLEXTOUCH	INSULINS	307	$ 149,668.56	$ 487.52	0.14%
BUDESONIDE	CORTICOSTEROIDS (RESPIRATORY TRACT)	477	$ 149,054.72	$ 312.48	0.22%
HUMIRA	DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	31	$ 140,582.44	$ 4,534.92	0.01%
OSELTAMIVIR PHOSPHATE	NEURAMINIDASE INHIBITORS	1,390	$ 140,446.97	$ 101.04	0.63%
VIMPAT	ANTICONVULSANTS, MISCELLANEOUS	169	$ 129,031.03	$ 763.50	0.08%
COPAXONE	IMMUNOMODULATORY AGENTS	21	$ 126,423.30	$ 6,020.16	0.01%
GENOTROPIN	PITUITARY	37	$ 117,936.95	$ 3,187.49	0.02%
ARIPIPRAZOLE	ANTIPSYCHOTIC AGENTS	1,509	$ 112,728.40	$ 74.70	0.68%
VENTOLIN HFA	BETA-ADRENERGIC AGONISTS	1,940	$ 111,835.09	$ 57.65	0.88%
EPCLUSA	HCV ANTIVIRALS	4	$ 104,070.32	$ 26,017.58	0.00%
IMBRUVICA	ANTINEOPLASTIC AGENTS	9	$ 102,536.42	$ 11,392.94	0.00%
PROAIR HFA	BETA-ADRENERGIC AGONISTS	1,668	$ 102,164.81	$ 61.25	0.76%
JANUVIA	DIPEPTIDYL PEPTIDASE-4(DPP-4) INHIBITORS	272	$ 102,025.18	$ 375.09	0.12%
IBRANCE	ANTINEOPLASTIC AGENTS	9	$ 99,899.93	$ 11,099.99	0.00%
OXYCONTIN	OPIATE AGONISTS	280	$ 98,683.69	$ 352.44	0.13%
PROMACTA	HEMATOPOIETIC AGENTS	9	$ 98,167.74	$ 10,907.53	0.00%
XIFAXAN	ANTIBACTERIALS, MISCELLANEOUS	54	$ 94,552.09	$ 1,750.96	0.02%
ARISTADA	ANTIPSYCHOTIC AGENTS	45	$ 93,661.98	$ 2,081.38	0.02%
NORDITROPIN FLEXPRO	PITUITARY	39	$ 92,528.95	$ 2,372.54	0.02%
BANZEL	ANTICONVULSANTS, MISCELLANEOUS	50	$ 91,307.80	$ 1,826.16	0.02%
LANTUS	INSULINS	228	$ 91,144.89	$ 399.76	0.10%
SPIRIVA	ANTIMUSCARINICS/ANTISPASMODICS	238	$ 90,441.81	$ 380.01	0.11%
SYMBICORT	CORTICOSTEROIDS (RESPIRATORY TRACT)	278	$ 84,655.87	$ 304.52	0.13%
CREON	DIGESTANTS	72	$ 82,557.92	$ 1,146.64	0.03%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	4,689	$ 79,590.14	$ 16.97	2.13%
REXULTI	ANTIPSYCHOTIC AGENTS	87	$ 79,259.93	$ 911.03	0.04%
ADVAIR HFA	CORTICOSTEROIDS (RESPIRATORY TRACT)	228	$ 79,163.57	$ 347.21	0.10%
TOTAL TOP 25		33,231	$ 10,220,774.75	$ 307.57	15.08%

Total Rx Claims From 01/01/2017 - 03/31/2017	220,418

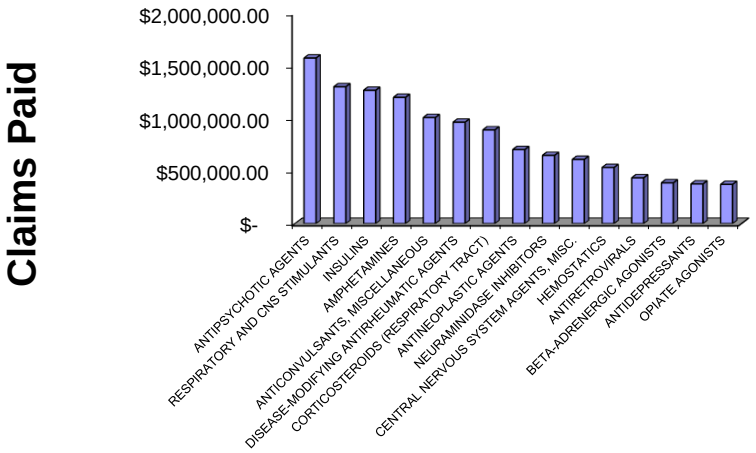
SOUTH DAKOTA MEDICAID
Cost Management Analysis

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 01/01/2017 - 03/31/2017

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	7,029	$ 1,575,906.71	$ 224.20	3.19%
RESPIRATORY AND CNS STIMULANTS	7,291	$ 1,303,804.26	$ 178.82	3.31%
INSULINS	2,632	$ 1,270,227.35	$ 482.61	1.19%
AMPHETAMINES	6,745	$ 1,202,723.47	$ 178.31	3.06%
ANTICONVULSANTS, MISCELLANEOUS	10,055	$ 1,011,195.19	$ 100.57	4.56%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	250	$ 967,094.64	$ 3,868.38	0.11%
CORTICOSTEROIDS (RESPIRATORY TRACT)	3,152	$ 893,927.58	$ 283.61	1.43%
ANTINEOPLASTIC AGENTS	482	$ 705,608.11	$ 1,463.92	0.22%
NEURAMINIDASE INHIBITORS	3,706	$ 650,618.99	$ 175.56	1.68%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	3,160	$ 612,570.29	$ 193.85	1.43%
HEMOSTATICS	27	$ 535,315.15	$ 19,826.49	0.01%
ANTIRETROVIRALS	279	$ 436,515.54	$ 1,564.57	0.13%
BETA-ADRENERGIC AGONISTS	7,992	$ 388,878.62	$ 48.66	3.63%
ANTIDEPRESSANTS	20,479	$ 378,351.23	$ 18.48	9.29%
OPIATE AGONISTS	11,188	$ 374,203.46	$ 33.45	5.08%
TOTAL TOP 15	84,467	$ 12,306,940.59	$ 145.70	38.32%

Total Rx Claims From 01/01/2017 - 03/31/2017	220,418

Top 15 Therapeutic Classes
Based on Total Cost of Claims



SD Medicaid Specialty Medications		
01/01/2017 - 4/30/2017		
Description	**Rx Num**	**Total Remb Amt**
ACTEMRA 162 MG/0.9 ML SYRINGE	13	$40,726.60
ADEMPAS 2.5 MG TABLET	1	$9,606.52
ADVATE 1,801-2,400 UNITS VIAL	4	$240,970.00
ADVATE 401-800 UNITS VIAL	6	$66,088.06
AFINITOR 2.5 MG TABLET	1	$5,507.53
AFINITOR 7.5 MG TABLET	4	$52,893.51
AFINITOR DISPERZ 2 MG TABLET	2	$25,577.32
ALPROLIX 1,000 UNIT NOMINAL	4	$87,027.37
AMPYRA ER 10 MG TABLET	7	$15,783.46
AUBAGIO 14 MG TABLET	10	$60,792.54
CATHFLO ACTIVASE 2 MG VIAL	1	$152.14
CIMZIA 200 MG/ML STARTER KIT	1	$11,526.45
CIMZIA 200 MG/ML SYRINGE KIT	7	$38,248.35
COPAXONE 20 MG/ML SYRINGE	2	$14,856.22
COPAXONE 40 MG/ML SYRINGE	24	$143,216.26
COSENTYX 300 MG DOSE-2 SYRINGE	1	$17,993.14
EPCLUSA 400 MG-100 MG TABLET	5	$130,087.90
GATTEX 5 MG 30-VIAL KIT	8	$271,402.96
GENOTROPIN 12 MG CARTRIDGE	7	$32,677.94
GENOTROPIN 5 MG CARTRIDGE	32	$83,515.33
GENOTROPIN MINIQUICK 0.6 MG	4	$8,612.12
GENOTROPIN MINIQUICK 2 MG	4	$28,665.96
GILENYA 0.5 MG CAPSULE	7	$50,977.06
GLEEVEC 400 MG TABLET	4	$42,275.68
HIZENTRA 2 GRAM/10 ML VIAL	6	$5,638.96
HIZENTRA 4 GRAM/20 ML VIAL	6	$19,657.10
HUMATROPE 12 MG CARTRIDGE	2	$8,549.38
HUMATROPE 24 MG CARTRIDGE	3	$2,633.29
HUMATROPE 6 MG CARTRIDGE	2	$1,923.13
IBRANCE 125 MG CAPSULE	9	$99,361.61
IBRANCE 75 MG CAPSULE	3	$34,349.46
ICLUSIG 15 MG TABLET	1	$34,580.46
IMATINIB MESYLATE 400 MG TAB	1	$9,133.99
IMATINIB MESYLATE 400 MG TAB	7	$61,660.90
IMBRUVICA 140 MG CAPSULE	10	$114,128.96
KALYDECO 150 MG TABLET	3	$74,855.88
KINERET 100 MG/0.67 ML SYRINGE	8	$30,839.22
KUVAN 100 MG POWDER PACKET	1	$2,092.39
KUVAN 100 MG TABLET	4	$25,418.04
LETAIRIS 10 MG TABLET	1	$8,827.02
LYNPARZA 50 MG CAPSULE	4	$38,945.76
NINLARO 4 MG CAPSULE	1	$9,419.19
NORDITROPIN FLEXPRO 10 MG/1.5	22	$51,833.11

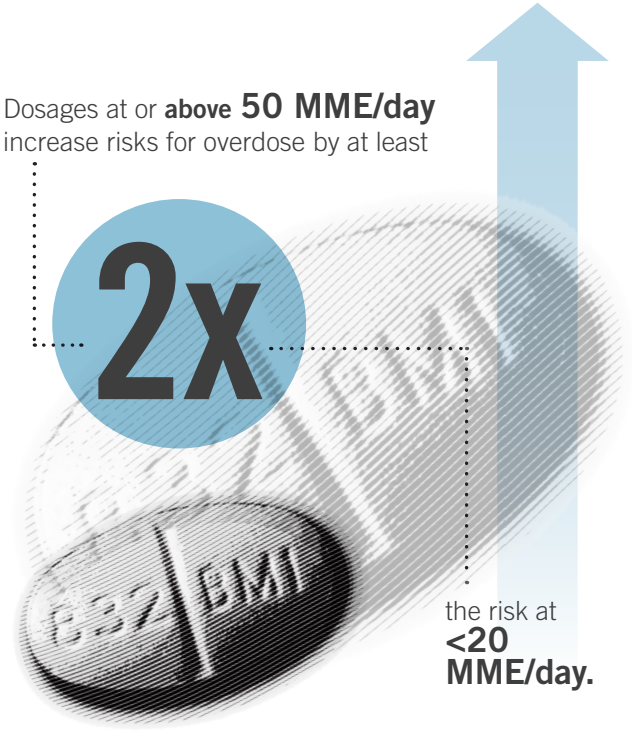
SD Medicaid Specialty Medications		
01/01/2017 - 4/30/2017		
Description	**Rx Num**	**Total Remb Amt**
NORDITROPIN FLEXPRO 15 MG/1.5	14	$33,082.11
NORDITROPIN FLEXPRO 30 MG/3 ML	4	$20,897.40
NORDITROPIN FLEXPRO 5 MG/1.5	10	$11,878.44
NOVOEIGHT 2,000 UNIT VIAL	1	$61,325.51
NUTROPIN AQ NUSPIN 10 INJECTOR	15	$38,410.27
NUTROPIN AQ NUSPIN 20 INJECTOR	5	$35,871.54
OMNITROPE 10 MG/1.5 ML CRTG	3	$16,364.59
ORENCIA 125 MG/ML SYRINGE	12	$47,541.56
ORENCIA CLICKJECT 125 MG/ML	3	$8,486.97
ORKAMBI 100 MG-125 MG TABLET	5	$85,756.42
ORKAMBI 200 MG-125 MG TABLET	8	$166,432.72
OTEZLA 28 DAY STARTER PACK	1	$2,888.76
OTEZLA 30 MG TABLET	3	$8,478.63
PRALUENT 75 MG/ML PEN	4	$4,681.52
PROMACTA 25 MG TABLET	12	$131,902.89
REBIF 44 MCG/0.5 ML SYRINGE	8	$54,680.40
RECOMBINATE 1,241-1,800 UNIT V	3	$117,908.89
RECOMBINATE 220-400 UNIT VIAL	1	$10,248.78
RECOMBINATE 401-800 UNIT VIAL	3	$30,041.81
RECOMBINATE 801-1,240 UNIT VL	1	$41,232.51
REMODULIN 1 MG/ML VIAL	3	$7,398.45
REPATHA 140 MG/ML SURECLICK	14	$16,343.88
REVLIMID 10 MG CAPSULE	4	$68,555.91
REVLIMID 15 MG CAPSULE	1	$13,097.82
SABRIL 500 MG POWDER PACKET	2	$15,164.92
SIMPONI 50 MG/0.5 ML PEN INJEC	4	$16,628.14
STELARA 45 MG/0.5 ML SYRINGE	2	$18,247.31
STELARA 90 MG/ML SYRINGE	1	$19,917.70
SUTENT 37.5 MG CAPSULE	2	$30,051.44
TECFIDERA DR 240 MG CAPSULE	13	$90,848.51
TETRABENAZINE 12.5 MG TABLET	3	$22,127.91
TETRABENAZINE 12.5 MG TABLET	4	$16,455.56
TETRABENAZINE 25 MG TABLET	5	$37,007.34
TOBI PODHALER 28 MG INHALE CAP	4	$39,217.34
TRACLEER 125 MG TABLET	4	$40,745.96
TRACLEER 62.5 MG TABLET	4	$20,876.72
TYKERB 250 MG TABLET	2	$10,989.10
VOTRIENT 200 MG TABLET	4	$41,120.85
XALKORI 250 MG CAPSULE	6	$93,014.34
XELJANZ 5 MG TABLET	5	$19,835.90
XELJANZ XR 11 MG TABLET	6	$23,457.97
XENAZINE 12.5 MG TABLET	4	$40,298.65
XENAZINE 25 MG TABLET	3	$17,870.95

SD Medicaid Specialty Medications		
01/01/2017 - 4/30/2017		
Description	**Rx Num**	**Total Remb Amt**
XOLAIR 150 MG VIAL	24	$70,684.62
ZENPEP DR 10,000 UNITS CAPSULE	13	$13,098.91
ZENPEP DR 15,000 UNITS CAPSULE	5	$2,087.69
ZENPEP DR 20,000 UNITS CAPSULE	8	$8,892.19
ZENPEP DR 40,000 UNITS CAPSULE	5	$33,329.14
ZENPEP DR 5,000 UNITS CAPSULE	1	$142.65
ZYTIGA 250 MG TABLET	4	$37,638.30

CALCULATING TOTAL DAILY DOSE OF OPIOIDS FOR SAFER DOSAGE

Higher Dosage, Higher Risk.

Higher dosages of opioids are associated with higher risk of overdose and death—even relatively low dosages (20-50 morphine milligram equivalents (MME) per day) increase risk. Higher dosages haven't been shown to reduce pain over the long term. One randomized trial found no difference in pain or function between a more liberal opioid dose escalation strategy (with average final dosage 52 MME) and maintenance of current dosage (average final dosage 40 MME).



WHY IS IT IMPORTANT TO CALCULATE THE TOTAL DAILY DOSAGE OF OPIOIDS?

Patients prescribed higher opioid dosages are at higher risk of overdose death.

In a national sample of Veterans Health Administration (VHA) patients with chronic pain receiving opioids from 2004–2009, **patients who died** of opioid overdose were prescribed an average of **98 MME/day**, while **other patients** were prescribed an average of **48 MME/day**.

Calculating the total daily dose of opioids helps identify patients who may benefit from closer monitoring, reduction or tapering of opioids, prescribing of naloxone, or other measures to reduce risk of overdose.

HOW MUCH IS 50 OR 90 MME/DAY FOR COMMONLY PRESCRIBED OPIOIDS?

50 MME/day:

- 50 mg of hydrocodone (10 tablets of hydrocodone/acetaminophen 5/300)
- 33 mg of oxycodone (~2 tablets of oxycodone sustained-release 15 mg)
- 12 mg of methadone (<3 tablets of methadone 5 mg)

90 MME/day:

- 90 mg of hydrocodone (9 tablets of hydrocodone/acetaminophen 10/325)
- 60 mg of oxycodone (~2 tablets of oxycodone sustained-release 30 mg)
- ~20 mg of methadone (4 tablets of methadone 5 mg)

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline.html

Drug/Class Name Topical Immunomodulators

Date 05/24/2017

Drug Name(s):

- Elidel 1% cream
- Protopic/Tacrolimus 0.03% ointment
- Protopic/Tacrolimus 0.1% ointment
- Eucrisa 2% ointment

FDA-Approved Indications:

- Elidel: indicated as second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other treatments or when other treatments are not advisable.
- Protopic: (0.03% for ages 2 and older, 0.1% for ages 16 and older) indicated as second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children, who have failed to respond adequately to other treatments or when other treatments are not advisable.
- Eucrisa: indicated for treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Black Box Warning (TCIs):

- Long-term safety of topical calcineurin inhibitors has not been established. Although a causal relationship has not been established, rare cases of malignancy (skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.

Noted in PI (TCIs):

- If signs/symptoms of atopic dermatitis do not improve within 6 weeks, patients should be re-examined by their healthcare provider
- Continuous long-term use of calcineurin inhibitors should be avoided

Literature Review:

- Topical corticosteroids are first-line treatment
- Topical calcineurin inhibitors (TCIs) may be considered for use when:
    - Recalcitrance to steroids
    - Sensitive areas (face, anogenital, skin folds, etc)
    - Steroid-induced atrophy
    - Long-term uninterrupted topical steroid use
- There are a number of studies where TCIs have been used for long periods of time.
    - For continuous use, studies have shown these agents are safe and effective when used as a steroid sparing agent
    - For non-continuous use, studies have shown safety when these agents are used between 1 – 5 years
- Currently, Eucrisa is not included in atopic dermatitis treatment guideline recommendations

Drug/Class Name Topical Immunomodulators

Date 05/24/2017

Cost Comparison:

- Elidel 1% cream, 60gm $559
- Tacrolimus 0.03% ointment, 60gm - $475 (Brand $525)
- Tacrolimus 0.1% ointment, 60gm - $475 (Brand $525)
- Eucrisa 2% ointment, 60g - $626

Summary of criteria:

- Requires diagnosis of atopic dermatitis, age checks (specific to product), some require prior use of a topical steroid or documentation of use on an area where steroids are not indicated

References:

- Clinical Pharmacology [online database]. Tampa, FL: Elsevier/Gold Standard, Inc.; 2015. Available at www.clinicalpharmacology.com. Accessed on April 13, 2017.
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- Elidel Prescribing Information. Bridgewater, NJ. Valeant Pharmaceuticals North America LLC. August 2014.
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- Eucrisa Prescribing Information. Palo Alto, CA. Anacor Pharmaceuticals, Inc.. December 2016
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol. 2014 Jul;71(1):116-32.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

This is an update to the FDA Drug Safety Communications:

- FDA evaluating the potential risks of using codeine cough-and-cold medicines in children issued on July 1, 2015, and
- FDA evaluating the risks of using the pain medicine tramadol in children aged 17 and younger issued on September 21, 2015.

Safety Announcement

[4-20-2017] The Food and Drug Administration (FDA) is restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. We are also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

As a result, we are requiring several changes to the labels of all prescription medicines containing these drugs. These new actions further limit the use of these medicines beyond our 2013 restriction of codeine use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. We are now adding:

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened *Warning* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions

in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

Caregivers and patients should always read the label on prescription bottles to find out if a medicine contains codeine or tramadol. You can also ask your child's health care provider or a pharmacist. Watch closely for signs of breathing problems in a child of any age who is taking these medicines or in infants exposed to codeine or tramadol through breastmilk. These signs include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness. If you notice any of these signs, stop giving the medicine and seek medical attention immediately by going to an emergency room or calling 911.

Health care professionals should be aware that tramadol and single-ingredient codeine medicines are FDA-approved only for use in adults. Consider recommending over-the-counter (OTC) or other FDA-approved prescription medicines for cough and pain management in children younger than 12 years and in adolescents younger than 18 years, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection, not serious, and usually will get better on its own so treatment may not be necessary.

Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.

In early 2013, FDA added a *Boxed Warning* to the codeine drug label cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids. We also issued Drug Safety Communications in July 2015 and September 2015 warning about the risk of serious breathing problems in some children who metabolized codeine and tramadol much faster to their active form than usual (called ultra-rapid metabolism), causing potentially dangerously high levels in their bodies too quickly. At that time, we said we would continue to evaluate this safety issue. As part of that safety review, the codeine-related safety issues were discussed at an FDA Advisory Committee meeting in December 2015.

Our review of several decades of adverse event reports submitted to FDA* from January 1969 to May 2015 identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. This includes only reports submitted to FDA, so there may be additional cases about which we are unaware. We also identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016 (see Data Summary). The majority of serious side effects with both codeine and tramadol

occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In our review of the medical literature[1-19] for data regarding codeine use during breastfeeding, we found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature[4,5,23,24] for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

We will continue to monitor this safety issue. We are considering additional regulatory action for the OTC codeine products that are available in some states. OTC codeine products are available in combination with other medicines for cough and cold symptoms. We are also considering an FDA Advisory Committee meeting to discuss the role of prescription opioid cough-and-cold medicines, including codeine, to treat cough in children.

We urge patients and health care professionals to report side effects involving codeine- and tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

List of Prescription Codeine and Tramadol Pain and Cough Medicines

Medicines Containing Codeine	Medicines Containing Tramadol
Codeine Sulfate	Conzip
Butalbital, Acetaminopen, Caffeine, and Codeine phosphate	Ultracet
Fiorinal with codeine	Ultram
Soma Compound with codeine	Ultram ER
Tylenol with codeine	Generic products containing tramadol
Promethazine with codeine (cough)	
Prometh VC with codeine (cough)	
Triacin-C (cough)	
Tuxarin ER (cough)	
Tuzistra-XR (cough)	
Generic products containing codeine	
Medicines Containing Dihydrocodeine	
Synalgos-DC	

Facts about Codeine and Tramadol

- Codeine

- An opioid pain reliever used to treat mild to moderate pain. It is usually combined with other medicines, such as acetaminophen, in prescription pain medicines.
- Single-ingredient codeine is approved for pain management in adults only.
- Also used to reduce coughing. It is frequently combined with promethazine in prescription cough-and-cold medicines and with other cold remedies in over-the-counter (OTC) preparations.
- Common side effects include drowsiness, lightheadedness, dizziness, feeling tired, shortness of breath, nausea, vomiting, stomach pain, constipation, itching, or rash.
- In 2014, nearly 1.9 million patients 18 years of age and younger received a dispensed prescription for codeine-containing products from U.S. outpatient retail pharmacies. Of the total pediatric patients, nearly 1.4 million patients received codeine-containing analgesic products, and 483,000 patients received codeine-containing cough-and-cold products.[20]

- Tramadol
  - An opioid pain reliever FDA-approved only in adults to treat moderate to moderately severe pain.
  - Available as a single ingredient under the brand names Ultram, Ultram ER, Conzip and also as generics.
  - Also available in combination with acetaminophen under the brand name Ultracet and as generics.
  - Common side effects include headache, dizziness, drowsiness, feeling tired, constipation, diarrhea, nausea, vomiting, stomach pain, itching, or flushing.
  - In 2014, nearly 167,000 patients younger than 18 years of age received a dispensed prescription for tramadol-containing products from U.S. outpatient retail pharmacies. [21]

Additional Information for Caregivers and Patients

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain:
  - Codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years due to the risk of serious side effects, including slowed or difficult breathing and death.
  - Codeine is not recommended to treat cough or pain and tramadol is not recommended to treat pain in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease that may increase the risk of breathing problems.
  - Tramadol should not be used to treat pain in children up to 18 years of age after surgery to remove their tonsils and/or adenoids. The drug label for codeine already warns against use in children up to 18 years of age after surgery to remove their tonsils and/or adenoids.

    - Breastfeeding is not recommended during treatment with codeine or tramadol because the medicine passes through breast milk and can harm the baby.
- Talk to your health care provider or a pharmacist to find out if a medicine your child is taking contains codeine or tramadol.
- Always read the label on prescription bottles to find out if a medicine contains codeine or tramadol, or ask your child's health care provider or a pharmacist.
- If patients of any age are known to be CYP2D6 ultra-rapid metabolizers, which means their bodies convert codeine or tramadol into their active forms faster and more completely than usual, they should not use codeine or tramadol.
- If a child has taken codeine or tramadol and you notice any signs of slow or shallow breathing, difficult or noisy breathing, confusion, or unusual sleepiness in a child of any age, seek medical attention immediately by taking the child to an emergency room or calling 911.
- Report any side effects from codeine- or tramadol- containing medicines to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- FDA is warning about several safety issues with prescription medicines containing codeine used for pain or cough and tramadol used for pain and requiring the following changes to the drug labels:
    - FDA's strongest warning, called a *Contraindication*, alerting that codeine and tramadol should not be used to treat pain in children younger than 12 years, and codeine should not be used to relieve cough in these children.
    - A new *Contraindication* to the tramadol label to restrict its use in children younger than 18 years to treat pain after a tonsillectomy and/or adenoidectomy. The label of codeine-containing products already carry this Contraindication.
    - A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or compromised respiratory function, that may increase the risk of serious breathing problems.
    - Strengthening the *Warning* to patients that breastfeeding is not recommended during treatment with codeine or tramadol due to the potential for serious adverse reactions in a breastfed infant, such as excess sedation, respiratory depression, and death.
- All tramadol-containing products and single-ingredient codeine drugs are FDA-approved for use only in adults.
- If you have determined that a codeine-or tramadol-containing product is appropriate for an adolescent patient, counsel parents and caregivers on how to recognize the signs of opioid toxicity, and advise them to stop giving the adolescent codeine or tramadol and seek medical attention immediately if their adolescent is exhibiting these signs.

- Report adverse events involving codeine- or tramadol- containing medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

Codeine

A search of the FDA Adverse Event Reporting System (FAERS) database from January 1969 to May 2015 identified 64 worldwide cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years. Fifty cases were reported in children younger than 12 years. Respiratory depression occurred after the children received a range of one to 18 doses, with a median of five doses. The most frequently reported codeine-containing medicines in the cases were acetaminophen with codeine used for pain, and promethazine with codeine (with or without phenylephrine) used for cough and cold.

Of the 24 cases reporting death, 21 occurred in children younger than 12 years. The reasons for codeine-containing medicine use in these cases included post-tonsillectomy and/or adenoidectomy pain management, other post-operative pain, general pain, sore or strep throat pain, and cough and cold.

Ten of the 64 cases mentioned the status of cytochrome P450 isoenzyme 2D6 (CYP2D6) genotype. Seven of these patients were ultra-rapid metabolizers, five of whom died. Ultra-rapid metabolizers of substrates of CYP2D6 convert codeine in their bodies too quickly into potentially dangerously high levels of morphine, the active form of codeine, contributing to life-threatening or fatal respiratory depression. The three other patients were extensive metabolizers, with one death.

Fifteen of the 64 cases reported codeine or morphine blood levels; the remaining 49 cases did not. In 13 cases, the blood levels were above the therapeutic range, and in two cases the blood levels were within the therapeutic range. One patient who had blood levels in the therapeutic range died following pain management post-tonsillectomy and adenoidectomy.

Tramadol

A search of the FAERS database from January 1969 to March 2016 identified nine cases worldwide of respiratory depression in children younger than 18 years of age, including three deaths. With the exception of a 15-year-old treated for multiple days with tramadol, respiratory depression occurred within the first 24 hours of drug administration.

The three fatalities occurred outside the U.S. in children younger than 6 years. Elevated serum tramadol concentrations were noted in all three. The reasons for tramadol treatment in these children were to treat pain after tonsillectomy, pain after clubfoot surgery, and to manage fever. All three cases involved tramadol oral drops, a formulation not available in the U.S.

The one case in which CYP2D6 ultra-rapid metabolizer status was reported occurred in a 5-year-old child from France who was prescribed a single tramadol dose in the evening post-adenotonsillectomy and returned to the healthcare facility the next morning with opioid intoxication; he was resuscitated.[22] A urine sample showed increased metabolite concentrations. Genotyping of CYP2D6 was conducted, and three functional alleles were found that were consistent with ultra-rapid metabolism.

One non-fatal U.S. case involved a 6-year-old who was prescribed tramadol for neuropathy of the hands and feet. After the third dose, the patient experienced respiratory depression and was unresponsive. The patient fully recovered after receiving two doses of naloxone.

Four other non-fatal cases reported in teenagers using tramadol for musculoskeletal pain or sciatica described unresponsiveness or somnolence after one or a few doses of tramadol; all required medical intervention. Two of these were U.S. cases.

Breastfeeding Mothers

Codeine and its active metabolite, morphine, are present in breast milk. A search of the medical literature[1-19] for relevant data regarding codeine use during lactation revealed numerous reports of respiratory depression and sedation, including one infant death, especially in mothers who have the CYP2D6 ultra-rapid metabolizer genotype.

In the case of the infant death, the mother was found to be a CYP2D6 ultra-rapid metabolizer, which potentially led to higher levels of morphine secreted into the breast milk leading to the infant's death. In other studies comparing drowsiness in breastfed babies whose mothers took codeine/acetaminophen compared to acetaminophen alone, the frequency of somnolence was higher in the codeine/acetaminophen-exposed group. Some of the mothers of those babies were CYP2D6 ultra-rapid metabolizers.[15,16]

Mothers who are ultra-rapid metabolizers of codeine achieve higher-than-expected serum levels of morphine, potentially leading to higher levels of morphine in breast milk that can be dangerous to their breastfed infants. In women with normal codeine metabolism, the amount of codeine secreted into breast milk is low and dose-dependent.

According to *Drugs in Pregnancy and Lactation*[5], both tramadol and its pharmacologic active metabolite (O-desmethyltramadol) are excreted into human milk. The mean absolute bioavailability of a 100-mg dose is 75%. Thus, ingestion of the recommended dose may produce drug amounts in breast milk that could exceed those reported above. The effect of this exposure on a nursing infant is unknown.

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Related Information

FDA statement from Douglas Throckmorton, M.D., Deputy Center Director for Regulatory Programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers

Consumer Update: Codeine and Tramadol Can Cause Breathing Problems for Children

Use of Codeine and Tramadol Products in Breastfeeding Women – Questions and Answers

Codeine Information

Tramadol Information

Opioid Medications

What's on the Label (high resolution) (PDF - 546KB)

The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective

Think It Through: Managing the Benefits and Risks of Medicines

Advisory Committees: Critical to the FDA's Product Review Process

CY 2016 Utilization of Tramadol and Codeine

Drug	Number of Claims	Cost	Unique # of Patients
Tramadol – All patients	11,442	$106,775	2982
Tramadol < 12	12	$64	10
Tramadol < 18	236	$1478	164

Drug	Number of Claims	Cost	Unique Patients
Codeine – All patients	5001	$64,361	3182
Codeine < 12	880	$9070	758
Codeine < 18	1556	$16,810	1314

*Just codeine products; not including hydrocodone.

Drug/Class Name Xrylix Kit (diclofenac 1.5% topical solution/xrylix sheets)

Date 05/24/2017

Drug Name(s):

- Xrylix Kit

FDA-Approved Indications:

- Indicated for the treatment of signs and symptoms of osteoarthritis of the knee(s)

Dosage and Administration:

- 40 drops per knee, 4 times a day

Dosage Form and Strengths:

- Diclofenac 1.5% topical solution with Xrylix sheets

Contraindications:

- Should not be used in patients who have experienced asthma, urticaria or allergic-type reactions after taking aspirin or other NSAIDs
- Should not be used in the setting of a coronary artery bypass graft (CABG) surgery

Warnings and Precautions:

- Increased risk of cardiovascular thrombotic events, myocardial infarction and stroke, which can be fatal
- Can cause serious gastrointestinal adverse events including bleeding, ulceration and perforation of the stomach, small intestine or large intestine, which can be fatal
- Borderline elevations or greater elevations of transaminases occurred in about 15% of oral diclofenac-treated patients
- NSAIDs, including diclofenac, can lead to new onset or worsening of preexisting hypertension, either of which may contribute to the increased incidence of CV events
- Fluid retention and edema have been observed in some patients treated with NSAIDs
- Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury
- Anaphylactoid reactions may occur in patients without prior exposure to diclofenac
- NSAIDs can cause serious skin adverse events such as exfoliative dermatitis, Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which can be fatal
- Patients with asthma may have aspirin-sensitive asthma; use with caution in patients with preexisting asthma

Adverse Reactions:

- Application site reactions: dry skin, contact dermatitis
- Dyspepsia, abdominal pain, diarrhea
- Pharyngitis

Drug/Class Name Xrylix Kit (diclofenac 1.5% topical solution/xrylix sheets)

Date 05/24/2017

Drug Interactions:

- Aspirin
- Anticoagulants
- ACE inhibitors
- Diuretics
- Lithium
- Methotrexate
- Cyclosporine
- Oral NSAIDs

Cost:

- $5,062 (contains 30 sheets)

References:

- Xrylix Prescribing Information. San Fernando, CA. PureTek Corporation. March 2016.

Drug/Class Name Zorvolex, Zipsor and Cambia (diclofenac products)

Date 05/24/2017

Drug Name(s):

- Zorvolex capsules
- Zipsor capsules
- Cambia powder for oral solution

FDA-Approved Indications:

- Zorvolex: management of mild to moderate acute pain and management of osteoarthritis pain
- Zipsor: relief of mild to moderate acute pain
- Cambia: acute treatment of migraine attacks with or without aura in adults 18 years of age or older

Dosage and Administration:

- Zorvolex: acute pain, 18-35mg 3 times a day; osteoarthritis pain, 35mg 3 times a day
- Zipsor: 25mg 4 times a day
- Cambia: 50mg, mixed with 1 to 2 ounces of water as a single dose

Dosage Form and Strengths:

- Zorvolex (diclofenac) capsules, 18mg and 35mg
- Zipsor (diclofenac potassium) capsules, 25mg
- Cambia (diclofenac potassium) powder packets, 50mg

Contraindications:

- History of asthma, urticarial or other allergic-type reactions after taking aspirin or other NSAIDs
- Should not be used in the setting of a coronary artery bypass graft (CABG) surgery

Warnings and Precautions:

- Serious and potentially fatal cardiovascular thrombotic events, myocardial infarction and stroke can occur with NSAID treatment
- Serious gastrointestinal adverse events, including bleeding, ulceration and perforation
- Hepatotoxicity
- Hypertension – patients taking some antihypertensive medications may have impaired response to those therapies when taking NSAIDs
- Heart failure and edema
- Renal toxicity
- Anaphylactic reactions
- Exacerbation of asthma related to aspirin sensitivity
- Serious skin reactions
- Premature closure of fetal ductus arteriosus
- Hematologic toxicity

Drug/Class Name Zorvolex, Zipsor and Cambia (diclofenac products)

Date 05/24/2017

Adverse Reactions:

- Edema, nausea, headache, dizziness, vomiting, constipation, pruritus, diarrhea, flatulence, pain in extremity, abdominal pain, sinusitis, alanine aminotransferase increased, blood creatinine increased, hypertension and dyspepsia

Drug Interactions:

- Drugs that interfere with hemostasis (warfarin, aspirin, etc)
- ACE inhibitors, ARBs or beta-blockers
- Diuretics
- Digoxin

Cost:

- Zorvolex – both strengths, $3.82/capsule
- Zipsor - $8.42/capsule
- Cambia - $55.99/packet ($504 for a box of 9 packets)
- Diclofenac potassium – 50mg, $0.49/tablet

References:

- Zorvolex Prescribing Information. Philadelphia, PA. Iroko Pharmaceuticals, LLC. May 2016.
- Zipsor Prescribing Information. Newark, CA. Depomed, Inc. December 2012.
- Cambia Prescribing Information. Newark, CA. Depomed, Inc. May, 2016.