

# South Dakota Department of Social Services

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Medicaid P&T Committee Meeting  
September 9, 2011

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

STATE OF SOUTH DAKOTA  
OFFICE OF THE GOVERNOR  
EXECUTIVE ORDER 2005-09

WHEREAS, The state of South Dakota recognizes that outpatient prescription drugs are an essential component of patient care; and,

WHEREAS, The state of South Dakota provides prescription drug coverage as a health benefit for its citizens who qualify for the Medical Assistance Program under the provisions of SDCL 28-6; and,

WHEREAS, The population of the Medical Assistance Program continues to increase each year; and,

WHEREAS, The state of South Dakota recognizes efforts must be made to establish a plan that will provide for the effective continuation of the prescription drug coverage benefit; and,

WHEREAS, The state of South Dakota recognizes there is a need to address the high costs of prescription drugs, the increased expenditures for those prescription drugs, and the need to find ways to control the costs of prescription drugs while ensuring the needs of recipients are being met; and,

WHEREAS, The state of South Dakota recognizes that requiring a prior authorization program for coverage of a drug can be an effective tool for helping to ensure beneficiaries have access to medically necessary medications in a clinically appropriate and cost-effective manner; and,

WHEREAS, Requiring a prior authorization program for coverage of a drug can help control prescription drug costs while protecting the consumer's needs;

IT IS, THEREFORE, BY EXECUTIVE ORDER, directed that the South Dakota Medicaid Pharmaceutical and Therapeutics (P & T) Committee be established and authorized to function in compliance with the following sections of this order.

General Provisions

Section 1. The name of the committee is the South Dakota Medicaid Pharmaceutical and Therapeutics (P & T) Committee.

Section 2. The governor of the state of South Dakota may appoint as many members as he deems necessary to accomplish the goals of this committee.

Section 3. The South Dakota Medicaid P & T Committee shall work with the Department of Social Services in addressing the high costs of prescription drugs, the increased expenditures for those prescription drugs, and the need to find ways to control the costs of prescription drugs while ensuring the needs of recipients are being met.

Section 4. The South Dakota Medicaid P & T Committee shall provide expertise and direction to the Department of Social Services in matters relating to the drugs being used by our recipient population including, but not limited to: establishing a prior authorization program, instituting quantity limits, establishing restrictions on early refills, mandating the use of generic drugs, amending the co-pay requirements, investigating state buying pools, considering the coverage of certain over-the-counter medications, developing a preferred drug list, and working with a pharmacy benefit manager to establish a prior authorization program for certain selected drugs.

Section 5. The South Dakota Medicaid P & T Committee shall make recommendations to the Department of Social Services in the development and maintenance of a list of drugs that will require prior authorization before being dispensed for any medically accepted indication.

Section 6. The South Dakota Medicaid P & T Committee shall ensure that interested parties have an opportunity to present public testimony with information or evidence supporting inclusion of a product for prior authorization.

Section 7. The South Dakota Medicaid P & T Committee shall analyze and consider the recommendations of interested parties and the potential impact of a decision to require prior authorization of a drug for individuals covered by the Medical Assistance Program under the provisions of SDCL Chapter 28-6.

Section 8. The South Dakota Medicaid P & T Committee shall develop its recommendations of drugs to be placed on the prior authorization program by considering the clinical efficacy, safety, and cost-effectiveness of a product.

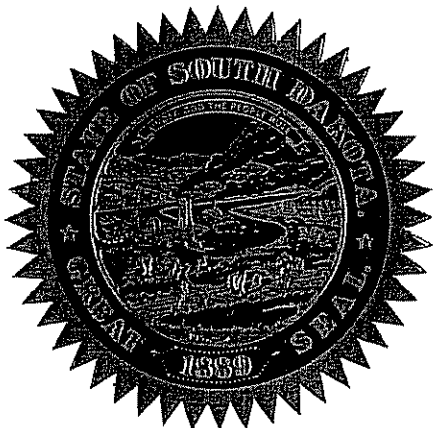
Section 9. The South Dakota Medicaid P & T Committee shall be administered by the South Dakota Department of Social Services.

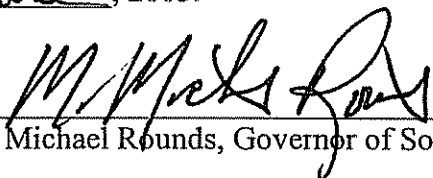
Section 10. The South Dakota Medicaid P & T Committee shall meet on a semiannual basis, or more often at the discretion of the Secretary of the Department of Social Services.


Section 11. Each member of the South Dakota Medicaid P & T Committee may receive per diem compensation and allowable reimbursement for expenses pursuant to SDCL 4-7-10.4.

Section 12. Executive Order 2003-05 is hereby rescinded.

Dated in Pierre, South Dakota, this 8<sup>th</sup> day of June, 2005.



  
M. Michael Rounds, Governor of South Dakota

ATTEST:  
  
Chris Nelson, Secretary of State



**DEPARTMENT OF SOCIAL SERVICES**

MEDICAL SERVICES  
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Pierre, South Dakota 57501-2291  
(605) 773-3495  
FAX (605) 773-5246

**SOUTH DAKOTA  
MEDICAID P&T COMMITTEE MEETING  
AGENDA**

**Friday, September 9, 2011  
1:00 – 3:00 PM**

**DDN Locations:**

**Sioux Falls**

**University Center  
Room UC282S  
2205 Career Avenue**

**Pierre**

**Capitol Building  
DDN Room B  
500 E Capitol**

**Rapid City**

**Dept of Health  
909 E. St. Patrick St. #7**

**Call to Order**

**Approval of Minutes of Previous Meeting**

**Prior Authorization Update**

**Review of Top 15 Therapeutic Categories/Top 25 Drugs**

**Old Business**

**Ophthalmic Antihistamines-form/criteria  
Less Sedating Antihistamines  
Colcrys  
Medications used to treat RLS  
Nexiclon**

**New Business**

**Medications used to treat Hepatitis C  
Topical acne agents  
Gralise  
Dificid**

**Oral Presentations and Comments by Manufacturers' Representatives**

**Next Meeting Date/Adjournment**

**Minutes of the June 10, 2011  
Pharmacy & Therapeutics (P&T) Committee Meeting  
SD Department of Social Services, Medical Services Division**

**Members present**

Bill Ladwig, R.Ph.; Debra Farver, PharmD.; James Engelbrecht, M.D.

**Members absent**

Timothy Soundy, M.D.; Dana Darger, R.Ph.; Willis Sutliff, M.D.; Rick Holm, M.D.

**DSS staff present**

Mike Jockheck, R.Ph.; Larry Iversen, Director of Medical Services

**HID staff present**

Candace Rieth, Pharm.D.

**Administrative Business**

The P&T meeting was called to order by B. Ladwig at approximately 1:00pm. The minutes of the March 4, 2011 meeting were presented. D. Farver made a motion to approve. B. Ladwig seconded the motion. The motion was approved unanimously.

**Prior Authorization Update and Statistics**

C. Rieth presented an overview of the prior authorization (PA) activity for March 2011. There were a total of 2,304 PAs processed in the month of March, with 99.61% of those requests responded to in less than 8 hours. There were 1,283 (95%) requests received electronically and 70 (5%) requests received by fax.

**Analysis of the Top 15 Therapeutic Classes**

C. Rieth reviewed the Top 15 Therapeutic Classes by total cost of claims from 01/01/2011 – 03/31/2011. The top five classes were antipsychotics, cerebral stimulants, amphetamines, adrenals, and antidepressants. The top 15 therapeutic classes make up 41.78% of total claims. C. Rieth also reviewed the top 25 drugs based on total claims cost and number of claims. The top 25 drugs by claims cost make up 17.31% of total claims.

**Triptan Review**

The P&T committee voted in March to place triptans on prior authorization, grandfathering recipients stable on therapy. C. Rieth presented clinical information, claims data, and a prior authorization form for triptans. M. Gniel, representing Merck, spoke regarding Maxalt. D. Farver made a motion to approve the triptan prior authorization form. J. Engelbrecht seconded the motion. The motion was approved unanimously.

**Multiple Sclerosis Agents Review**

The P&T committee voted in March to place agents used to treat multiple sclerosis on prior authorization, grandfathering recipients stable on therapy. C. Rieth presented clinical information, data and prior authorization forms for specific agents used to treat multiple sclerosis. C. Jones, representing Acorda, spoke regarding Ampyra. J. Porter and R. Troxell, representing Novartis, spoke regarding Gilenya. The committee addressed each prior authorization form individually. Changes suggested for Ampyra prior authorization form included wording from specialist to physiatrist/neurologist and to remove the timed 25 foot walk requirement. J. Engelbrecht made a motion to approve the form with changes. D. Farver seconded the motion. The motion was approved unanimously. A motion was made by D. Farver to approve the Extavia prior authorization form with criteria including diagnosis and neurologist involved in therapy. J. Engelbrecht seconded the motion. The motion was approved unanimously. Changes suggested for Gilenya prior authorization form included criteria for coverage; neurologist involved in therapy and diagnosis of relapsing multiple sclerosis. D. Farver made a

motion to approve the Gilenya prior authorization form with changes. J. Engelbrecht seconded the motion. The motion was approved unanimously. A motion was made by D. Farver to approve the Novantrone prior authorization form with criteria including diagnosis and neurologist involved in therapy. J. Engelbrecht seconded the motion. The motion was approved unanimously. A motion was made by J. Engelbrecht to approve the Tysabri prior authorization form with criteria including diagnosis, neurologist or gastroenterologist involved in therapy and age of 18 or above. D. Farver seconded the motion. The motion was approved unanimously.

### **Ophthalmic Antihistamines**

The committee placed ophthalmic antihistamines on prior authorization at the March meeting. C. Rieth presented clinical information and data for ophthalmic antihistamines. There was no public comment. A recommendation was made to bring the form back to the September meeting for review.

### **Less Sedating Antihistamines**

The committee asked that less sedating antihistamines be reviewed with recent changes in the class; Allegra gaining OTC status. A recommendation was made to table this topic until the September meeting.

### **PAH Review**

A recommendation was made to table this topic.

### **Topical Ketoconazole Agents**

C. Rieth presented clinical information and claims data for topical ketoconazole agents. There was no public comment. A motion was made by D. Farver to place these agents on prior authorization with a failure of ketoconazole cream or shampoo. J. Engelbrecht seconded the motion. The motion was approved unanimously.

### **Colcryst Review**

A recommendation was made to review this topic in the future and include colchicine data.

### **Horizant Review**

C. Rieth presented clinical information for Horizant. B. Streng, representing GSK, spoke regarding Horizant. A recommendation was made to review this topic at the September meeting and include gabapentin, Requip and Mirapex data.

### **Nexiclon Review**

C. Rieth presented clinical information for Nexiclon. There was no public comment. J. Engelbrecht made a motion to place Nexiclon on prior authorization with failure of clonidine as the criteria for coverage. D. Farver seconded the motion. The motion passed unanimously. A prior authorization form will be brought to the September meeting for committee approval.

The next meeting date is scheduled for September 9, 2011. The location will be updated on the website as soon as possible. A motion was made by D. Farver at 2:25pm to adjourn the SD Medicaid P&T meeting. B. Ladwig seconded the motion. Motion passed unanimously and the meeting was adjourned.



**South Dakota Medicaid  
Monthly Prior Authorization Report  
June 1, 2011 – June 30, 2011**

**Time Ratio**

Total PAs	Response Under 8 Hours	Response Over 8 Hours	% Under 8 Hours	% Over 8 Hours
1,838	1,779	56	96.95%	3.05%

**By Form Type**

Form Type	Description	Approve	Deny
ADP	Antidepressant	64	134
ALT	Altabax	0	7
AMB	Ambien CR	5	18
ANT	Antihistamines	34	72
APS	Antipsychotic	9	13
ARB	ARBS	12	9
CYA	Cyanocobalamin	1	1
DAW	Dispense As Written	25	49
GRH	Growth Hormone	6	11
HLM	Head Lice Medication	24	40
MAX	Max Units Override	53	933
NAR	Name Brand Narcotics	7	18
NUC	Opioids	3	25
PPI	Proton Pump Inhibitors	54	135
STI	Stimulants	7	32
SUB	Suboxone/Subutex	3	4
TIM	Targeted Immune Modulators	6	5
ULT	Ultram ER	2	8
VUS	Vusion	1	3
XEN	Xenical	0	2
<b>Totals</b>		316	1519

**South Dakota Medicaid  
Monthly Prior Authorization Report  
June 1, 2011 – June 30, 2011**

**By Request Type**

06/01/11 - 06/30/11	# of Requests	Electronic Requests		Faxed Requests	
		#	%	#	%
<b>Prior Authorizations:</b>					
Altabax	7	6	86%	1	14%
Ambien CR	23	17	74%	6	26%
Antihistamines	106	93	88%	13	12%
Antipsychotic	22	16	73%	6	27%
ARBS	21	16	76%	5	24%
Cyanocobalamin	2	1	50%	1	50%
Dispense As Written	74	45	61%	29	39%
Growth Hormone	17	10	59%	7	41%
Head Lice Medication	64	32	50%	32	50%
Max Units Override	986	915	93%	71	7%
Name Brand Narcotics	25	16	64%	9	36%
Opioids	28	21	75%	7	25%
Proton Pump Inhibitors	189	158	84%	31	16%
Stimulants	39	31	79%	8	21%
Suboxone/Subutex	7	4	57%	3	43%
Targeted Immune Modulators	11	5	45%	6	55%
Ultram ER	10	7	70%	3	30%
Vusion	4	2	50%	2	50%
Xenical	2	0	0%	2	100%
<b>Prior Authorization Totals</b>	<b>1,637</b>	<b>1,395</b>	<b>85%</b>	<b>242</b>	<b>15%</b>



**South Dakota Medicaid  
Monthly Prior Authorization Report  
June 1, 2011 – June 30, 2011**

**Electronic PAs (unique)**

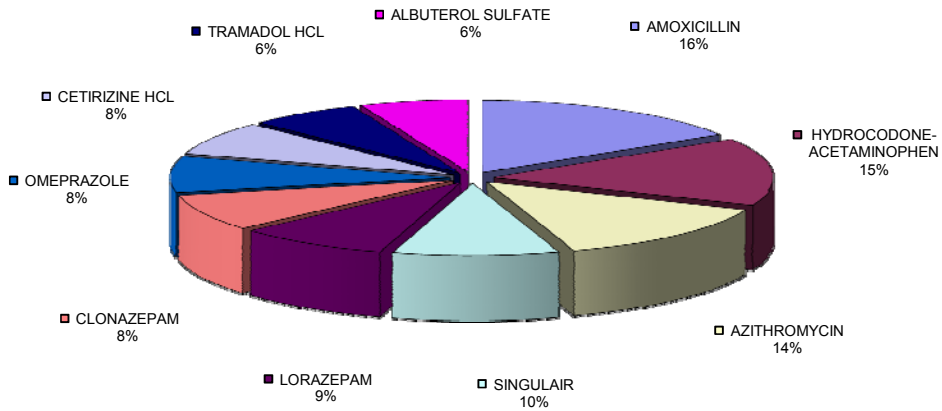
6/01/11 - 6/30/11	# Unique Approved	# Unique Denied	# Unique Incomplete	Unique Total	Approval %	Total Transactions
<b>Prior Authorizations:</b>						
Antidepressant	41	123	0	164	25.00%	164
Altabax	0	6	0	6	0.00%	6
Ambien CR	1	16	0	17	5.90%	17
Antihistamines	22	64	0	86	25.60%	93
Antipsychotic	3	13	0	16	18.80%	16
ARBS	8	8	0	16	50.00%	16
Cyanocobalamin	0	1	0	1	0.00%	1
Dispense As Written	0	42	0	42	0.00%	45
Growth Hormone	0	10	0	10	0.00%	10
Head Lice Medication	0	32	0	32	0.00%	32
Max Units Override	0	836	0	836	0.00%	904
Name Brand Narcotics	0	15	0	15	0.00%	16
Opioids	0	21	0	21	0.00%	21
Proton Pump Inhibitors	27	119	0	146	18.50%	158
Stimulants	0	29	0	29	0.00%	31
Suboxone/Subutex	0	4	0	4	0.00%	4
Targeted Immune Modulators	1	4	0	5	20.00%	5
Ultram ER	0	7	0	7	0.00%	7
Vusion	0	2	0	2	0.00%	2
<b>Prior Authorization Totals:</b>	103	1352	0	1455	7.10%	1559

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 04/01/2011 - 06/30/2011

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
AMOXICILLIN	PENICILLINS	6,371	\$ 64,439.40	\$ 10.11	3.21%
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	5,999	\$ 68,758.15	\$ 11.46	3.02%
AZITHROMYCIN	MACROLIDES	5,382	\$ 94,543.57	\$ 17.57	2.71%
SINGLAIR	LEUKOTRIENE MODIFIERS	3,794	\$ 495,747.86	\$ 130.67	1.91%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	3,490	\$ 30,986.23	\$ 8.88	1.76%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,233	\$ 28,820.04	\$ 8.91	1.63%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,191	\$ 54,576.11	\$ 17.10	1.61%
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	2,975	\$ 60,477.50	\$ 20.33	1.50%
TRAMADOL HCL	OPIATE AGONISTS	2,560	\$ 29,097.86	\$ 11.37	1.29%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	2,460	\$ 45,663.84	\$ 18.56	1.24%
CONCERTA	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	2,415	\$ 456,555.73	\$ 189.05	1.22%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,339	\$ 20,216.46	\$ 8.64	1.18%
SERTRALINE HCL	ANTIDEPRESSANTS	2,214	\$ 19,231.19	\$ 8.69	1.11%
LEVOTHYROXINE SODIUM	THYROID AGENTS	2,213	\$ 20,135.54	\$ 9.10	1.11%
LORATADINE	SECOND GENERATION ANTIHISTAMINES	2,090	\$ 16,500.14	\$ 7.89	1.05%
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	2,049	\$ 59,358.43	\$ 28.97	1.03%
VYVANSE	AMPHETAMINES	2,033	\$ 290,489.42	\$ 142.89	1.02%
CEFDINIR	CEPHALOSPORINS	1,977	\$ 75,266.05	\$ 38.07	1.00%
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	1,937	\$ 17,729.92	\$ 9.15	0.98%
TRAZODONE HCL	ANTIDEPRESSANTS	1,936	\$ 14,201.99	\$ 7.34	0.97%
CITALOPRAM HBR	ANTIDEPRESSANTS	1,862	\$ 12,327.00	\$ 6.62	0.94%
CEPHALEXIN	CEPHALOSPORINS	1,860	\$ 23,017.65	\$ 12.38	0.94%
LISINAPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	1,855	\$ 12,502.98	\$ 6.74	0.93%
VENTOLIN HFA	BETA-ADRENERGIC AGONISTS	1,853	\$ 72,219.40	\$ 38.97	0.93%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,694	\$ 28,448.39	\$ 16.79	0.85%
TOTAL TOP 25		69,782	\$ 2,111,310.85	\$ 30.26	35.14%

Total Rx Claims From 04/01/2011 - 06/30/2011	198,566
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Top 10 Drugs  
Based on Number of Claims

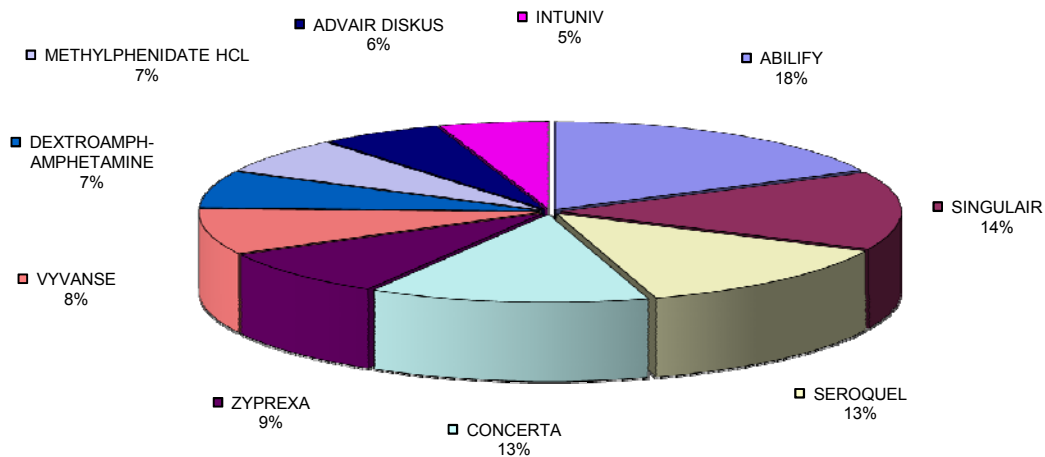


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 04/01/2011 - 06/30/2011

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ABILIFY	ANTIPSYCHOTIC AGENTS	1,329	\$ 609,598.47	\$ 458.69	0.67%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,794	\$ 495,747.86	\$ 130.67	1.91%
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,407	\$ 457,577.80	\$ 325.22	0.71%
CONCERTA	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	2,415	\$ 456,555.73	\$ 189.05	1.22%
ZYPREXA	ANTIPSYCHOTIC AGENTS	413	\$ 299,411.77	\$ 724.97	0.21%
VYVANSE	AMPHETAMINES	2,033	\$ 290,489.42	\$ 142.89	1.02%
DEXTROAMPH-AMPHETAMINE	AMPHETAMINES	1,354	\$ 231,741.18	\$ 171.15	0.68%
METHYLPHENIDATE HCL	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,626	\$ 231,370.99	\$ 142.29	0.82%
ADVAIR DISKUS	ADRENALS	974	\$ 199,510.52	\$ 204.84	0.49%
INTUNIV	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,163	\$ 178,321.69	\$ 153.33	0.59%
ADDERALL XR	AMPHETAMINES	727	\$ 166,229.65	\$ 228.65	0.37%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	971	\$ 165,865.90	\$ 170.82	0.49%
FOCALIN XR	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	967	\$ 162,023.63	\$ 167.55	0.49%
PULMOZYME	ENZYMES	61	\$ 153,155.53	\$ 2,510.75	0.03%
LANSOPRAZOLE	PROTON-PUMP INHIBITORS	1,450	\$ 149,855.97	\$ 103.35	0.73%
OXYCONTIN	OPIATE AGONISTS	432	\$ 148,895.42	\$ 344.67	0.22%
GEODON	ANTIPSYCHOTIC AGENTS	329	\$ 129,824.10	\$ 394.60	0.17%
CYMBALTA	ANTIDEPRESSANTS	754	\$ 128,762.91	\$ 170.77	0.38%
FLOVENT HFA	ADRENALS	881	\$ 115,094.40	\$ 130.64	0.44%
GENOTROPIN	PITUITARY	61	\$ 111,263.17	\$ 1,823.99	0.03%
XOPENEX	BETA-ADRENERGIC AGONISTS	628	\$ 107,311.38	\$ 170.88	0.32%
NOVOLOG	INSULINS	488	\$ 105,534.41	\$ 216.26	0.25%
VENLAFAXINE HCL ER	ANTIDEPRESSANTS	723	\$ 103,149.36	\$ 142.67	0.36%
NEXIUM	PROTON-PUMP INHIBITORS	487	\$ 101,275.93	\$ 207.96	0.25%
LEXAPRO	ANTIDEPRESSANTS	970	\$ 100,101.44	\$ 103.20	0.49%
TOTAL TOP 25		26,437	\$ 5,398,668.63	\$ 204.21	13.31%

Total Rx Claims From 04/01/2011 - 06/30/2011	198,566
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Top 10 Drugs  
Based on Total Claims Cost



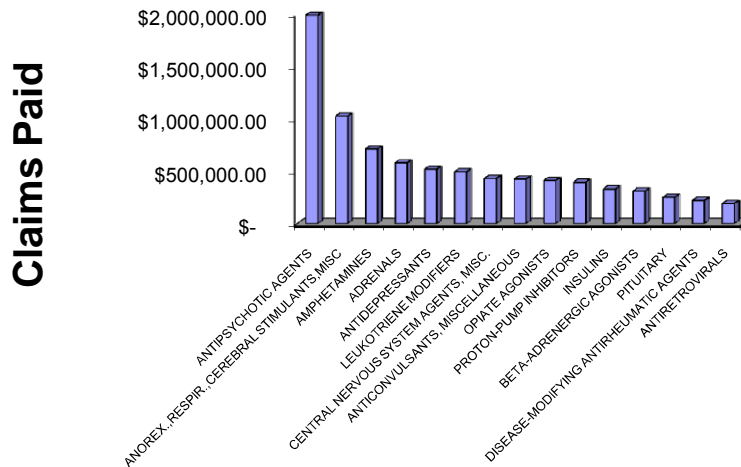
**SOUTH DAKOTA MEDICAID  
Cost Management Analysis**

**TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 04/01/2011 - 06/30/2011**

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	6,574	\$ 1,992,178.95	\$ 303.04	3.31%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,141	\$ 1,027,028.87	\$ 167.24	3.09%
AMPHETAMINES	4,767	\$ 713,341.41	\$ 149.64	2.40%
ADRENALS	6,148	\$ 582,729.55	\$ 94.78	3.10%
ANTIDEPRESSANTS	14,767	\$ 522,718.94	\$ 35.40	7.44%
LEUKOTRIENE MODIFIERS	3,806	\$ 496,701.71	\$ 130.50	1.92%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	2,193	\$ 433,000.77	\$ 197.45	1.10%
ANTICONVULSANTS, MISCELLANEOUS	6,999	\$ 425,732.13	\$ 60.83	3.52%
OPIATE AGONISTS	13,681	\$ 412,562.31	\$ 30.16	6.89%
PROTON-PUMP INHIBITORS	6,008	\$ 395,434.84	\$ 65.82	3.03%
INSULINS	1,769	\$ 332,212.49	\$ 187.80	0.89%
BETA-ADRENERGIC AGONISTS	6,667	\$ 312,666.06	\$ 46.90	3.36%
PITUITARY	549	\$ 252,482.99	\$ 459.90	0.28%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	136	\$ 222,168.85	\$ 1,633.59	0.07%
ANTIRETROVIRALS	235	\$ 193,667.05	\$ 824.12	0.12%
<b>TOTAL TOP 15</b>	<b>80,440</b>	<b>\$ 8,314,626.92</b>	<b>\$ 103.36</b>	<b>40.51%</b>

Total Rx Claims From 04/01/2011 - 06/30/2011	198,566
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**Top 15 Therapeutic Classes  
Based on Total Cost of Claims**





Antihistamine Utilization			
04/01/10 - 03/31/11			
Label Name	Rx Num	Total Reimb Amt	Avg Cost per Script
ALAVERT 10 MG ODT	58	\$722.72	\$12.46
ALL DAY ALLERGY 1 MG/ML SYRUP	6	\$78.90	\$13.15
ALL DAY ALLERGY 10 MG CHEW TAB	33	\$436.48	\$13.23
ALL DAY ALLERGY 10 MG TABLET	203	\$1,711.60	\$8.43
ALL DAY ALLERGY 5 MG CHEW TAB	41	\$1,380.79	\$33.68
ALLEGRA 30 MG/5 ML SUSPENSION	128	\$6,296.22	\$49.19
ALLEGRA ODT 30 MG TABLET	24	\$2,474.11	\$103.09
ALLERGY RELIEF 10 MG ODT	25	\$349.01	\$13.96
ALLERGY RELIEF 10 MG TABLET	68	\$497.15	\$7.31
ALLERGY RELIEF 5 MG/5 ML SOLN	16	\$191.08	\$11.94
ALLERGY RELIEF SYRUP	70	\$794.84	\$11.35
CETIRIZINE HCL 1 MG/1 ML SOLN	52	\$457.64	\$8.80
CETIRIZINE HCL 1 MG/ML SYRUP	3240	\$37,769.16	\$11.66
CETIRIZINE HCL 10 MG CHEW TAB	487	\$40,004.07	\$82.14
CETIRIZINE HCL 10 MG TABLET	6757	\$57,090.84	\$8.45
CETIRIZINE HCL 5 MG CHEW TAB	1175	\$103,693.57	\$88.25
CETIRIZINE HCL 5 MG TABLET	202	\$2,187.14	\$10.83
CHILD ALL DAY ALLERGY 1 MG/ML	183	\$2,119.22	\$11.58
CHILD CLEAR-ATADINE 10 MG TAB	6	\$100.50	\$16.75
CHILD'S CLARITIN 5 MG TAB CHEW	310	\$9,288.66	\$29.96
CLARINEX 0.5 MG/ML (2.5 MG/5)	206	\$9,644.00	\$46.82
CLARINEX 2.5 MG REDITABS	7	\$853.81	\$121.97
CLARINEX 5 MG REDITABS	42	\$4,838.82	\$115.21
CLARINEX 5 MG TABLET	139	\$15,419.93	\$110.93
CLARITIN 10 MG REDITABS	55	\$907.25	\$16.50
CLARITIN 10 MG TABLET	2	\$13.24	\$6.62
CLARITIN 5 MG REDITABS	10	\$229.22	\$22.92
CLARITIN 5 MG/5 ML SYRUP	43	\$501.15	\$11.65
CLEAR-ATADINE 10 MG TABLET	86	\$570.11	\$6.63
FEXOFENADINE HCL 180 MG TABLET	1109	\$37,522.69	\$33.83
FEXOFENADINE HCL 30 MG TABLET	165	\$4,164.38	\$25.24
FEXOFENADINE HCL 60 MG TABLET	248	\$7,064.71	\$28.49
LEVOCETIRIZINE 5 MG TABLET	67	\$4,664.65	\$69.62
LORATADINE 10 MG TABLET	7675	\$56,605.23	\$7.38
LORATADINE 5 MG/5 ML SYRUP	985	\$11,411.28	\$11.59
LORATADINE ALLERGY 5 MG/5 ML	7	\$85.33	\$12.19
NON-DROWSY ALLERGY 10 MG TAB	10	\$77.80	\$7.78
PV ALLERGY RELIEF 10 MG ODT	17	\$156.74	\$9.22
PV CETIRIZINE HCL 1 MG/ML SOLN	16	\$125.33	\$7.83
PV LORATADINE 5 MG/5 ML SYRUP	1	\$7.99	\$7.99
QC ALL DAY ALLERGY 1 MG/ML SOL	8	\$62.07	\$7.76
QC ALLERGY RELIEF 10 MG ODT	3	\$27.46	\$9.15
QC LORATADINE 10 MG TABLET	56	\$374.93	\$6.70
SB LORATADINE 10 MG TABLET	15	\$116.70	\$7.78

<b>Antihistamine Utilization</b>			
<b>04/01/10 - 03/31/11</b>			
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>	<b>Avg Cost per Script</b>
SM ALL DAY ALLERGY 1 MG/ML SYR	360	\$4,178.11	\$11.61
SM ALL DAY ALLERGY 10 MG TAB	105	\$895.94	\$8.53
SM ALLERGY RELIEF 10 MG ODT	23	\$286.05	\$12.44
SM LORATADINE 10 MG TABLET	197	\$1,526.84	\$7.75
SM LORATADINE 5 MG/5 ML SYRUP	162	\$1,930.01	\$11.91
XYZAL 2.5 MG/5 ML SOLUTION	98	\$7,381.70	\$75.32
XYZAL 5 MG TABLET	334	\$28,120.14	\$84.19
<b>7,869 recipients (74.01% 18 and younger)</b>	<b>25335</b>	<b>\$467,407.31</b>	



**ANTI-HISTAMINE PRIOR AUTHORIZATION**  
SD DEPARTMENT OF SOCIAL SERVICES  
MEDICAL SERVICES DIVISION

Fax Completed Form to:  
**866-254-0761**  
For questions regarding this  
Prior authorization, call  
**866-705-5391**

SD Medicaid requires that patients receiving anti-histamines must use **Loratadine\*** as first line.

- **Loratadine OTC and cetirizine may be prescribed WITHOUT prior authorization.** Loratadine and cetirizine are covered by Medicaid when prescribed by a physician.
- **Prior authorization is NOT required for patients < 13 years of age.**
- **Patients must use loratadine and cetirizine for a minimum of 14 days for the trial to be considered a failure.** Patient preference does not constitute failure.
- **Patients are encouraged to try and fail generic loratadine and cetirizine prior to receiving a leukotriene modifier or intranasal steroid to treat allergic rhinitis.**

**Part I: RECIPIENT INFORMATION (To be completed by physician's representative or pharmacy):**

RECIPIENT NAME:	RECIPIENT MEDICAID ID NUMBER:
Recipient Date of birth:        /        /	

**Part II: PHYSICIAN INFORMATION (To be completed by physician's representative or pharmacy):**

PHYSICIAN NAME:	PHYSICIAN DEA NUMBER:	
CITY:	PHONE: (    )	FAX: (    )

**Part III: TO BE COMPLETED BY PHYSICIAN:**

<b>REQUESTED DRUG (PLEASE CHECK):</b> <input type="checkbox"/> Allegra <input type="checkbox"/> Allegra-D <input type="checkbox"/> Claritin Rx <input type="checkbox"/> Clarinex <input type="checkbox"/> Clarinex -D <input type="checkbox"/> Claritin-D Rx <input type="checkbox"/> Zyrtec <input type="checkbox"/> Zyrtec-D <input type="checkbox"/> Fexofenadine <input type="checkbox"/> Xyzal	<b>Requested Dosage:</b> (must be completed)  <b>Diagnosis for this request:</b>
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**Qualifications for coverage:**

<input type="checkbox"/> Failed loratadine	Was trial for at least 14 days? <input type="checkbox"/> YES <input type="checkbox"/> NO	Dose:
<input type="checkbox"/> Failed cetirizine		Frequency:
Adverse Reaction (attach FDA Medwatch form) to loratadine or cetirizine or contraindicated: (provide description below)		

Physician Signature: \_\_\_\_\_

Date: \_\_\_\_\_

**Part IV: PHARMACY INFORMATION**

PHARMACY NAME:	SD MEDICAID PROVIDER NUMBER:
Phone: (    ):	FAX: (    )
Drug:	NDC#:

**Part V: FOR OFFICIAL USE ONLY**

Date:                                /                                /	Initials: _____
Approved - Effective dates of PA:    From:                                /                                /	To:                                /                                /
Denied: (Reasons)	

**South Dakota Medicaid  
P&T Meeting  
Colcris® Review**

**I. Overview**

Colcris tablets are indicated for prophylaxis and treatment of acute gout flares and the treatment of familial Mediterranean fever (FMF) in adults and children 4 years or older.

**II. Dosage and Administration**

- **Prophylaxis of Gout Flares:** The recommended dosage of Colcris for prophylaxis of gout flares for adults and adolescents older than 16 years of age is 0.6mg once or twice daily. The maximum recommended dose for prophylaxis of gout flares is 1.2mg/day.
- **Treatment of Gout Flares:** The recommended dose of Colcris for treatment of a gout flare is 1.2mg at the first sign of the flare followed by 0.6mg one hour later. Higher doses have not been found to be more effective. The maximum recommended dose for treatment of gout flares is 1.8mg over a 1 hour period. Colcris may be administered for treatment of a gout flare during prophylaxis at doses not to exceed 1.2mg at the first sign of the flare followed by 0.6mg one hour later. Wait 12 hours and then resume prophylactic dose.
- **FMF:** The recommended dosage of Colcris for FMF in adults is 1.2mg to 2.4mg daily. Colcris should be increased as needed to control disease and as tolerated in increments of 0.3mg/day to a maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in decrements of 0.3mg/day. The total daily Colcris dose may be administered in one to two divided doses. The recommended dosage of Colcris for FMF in pediatric patients 4 years of age and older is based on age. The following daily doses may be given as a single or divided dose twice daily:
  - Children 4-6 years: 0.3mg to 1.8mg daily**
  - Children 6-12 years: 0.9mg to 1.8mg daily**
  - Adolescents older than 12 years: 1.2mg to 2.4mg daily**

**III. Pharmacology/Pharmacokinetics**

**Gout:**

The exact mechanism of action of colchicine, an anti-inflammatory agent, in gout is not completely known, but it involves a reduction in lactic acid production by leukocytes, which results in a decrease in uric acid deposition and a reduction in phagocytosis, with abatement of the inflammatory response.

Colchicine is not an analgesic, though it relieves pain in acute attacks of gout. It is not a uricosuric agent and will not prevent progression of gout to chronic gouty arthritis. It does have a prophylactic, suppressive effect that helps to reduce the incidence of acute

attacks and to relieve the residual pain and mild discomfort that patients with gout occasionally feel.

**FMF:**

The mechanism by which colchicine exerts its beneficial effect in patients with FMF has not been fully elucidated; however, recent data suggest that colchicines may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1 beta. Additionally, colchicine disrupts cytoskeletal functions through inhibition of beta-tubulin polymerization into microtubules, and, consequently, prevents the activation, degranulation, and migration of neutrophils.

**Mean (% Coefficient of Variation) Pharmacokinetic Parameters in Healthy Adults**

<b>C<sub>max</sub></b> (colchicines ng/mL)	<b>T<sub>max</sub></b> (h)	<b>Vd/F</b> (L)	<b>CL/F</b> (L/hr)	<b>t<sub>1/2</sub></b> (h)
<b>Colcrlys 0.6mg Single Dose (n=13)</b>				
2.5 (28.7)	1.5 (1.0 – 3.0)	341.5 (54.4)	54.1 (31.0)	-
<b>Colcrlys 0.6mg BID x 10 days (n=13)</b>				
3.6 (23.7)	1.3 (0.5 – 3.0)	1150 (18.7)	30.3 (19)	26.6 (16.3)

**IV. Contraindications**

Patients with renal or hepatic impairment should not be given Colcrlys in conjunction with P-gp or strong CYP3A4 inhibitors. In these patients, life-threatening and fatal colchicines toxicity has been reported with colchicine taken in therapeutic doses.

**V. Warnings/Precautions**

- **Fatal overdoses** have been reported with colchicine in adults and children.
- **Blood dyscrasias:** Myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, and aplastic anemia have been reported.
- **Monitor for toxicity** and if present consider temporary interruption or discontinuation of colchicine.
- **Drug interaction P-gp and/or CYP3A4 inhibitors:** Co-administration of colchicine with P-gp and/or strong CYP3A4 inhibitors has resulted in life-threatening interactions and death.
- **Neuromuscular toxicity:** Myotoxicity including rhabdomyolysis may occur, especially in combination with other drugs known to cause this effect.

**VI. Drug Interactions**

Co-administration of P-gp and/or CYP3A4 inhibitors (*e.g.*, clarithromycin or cyclosporine) has been demonstrated to alter the concentration of colchicine. The potential for drug-drug interactions must be considered prior to and during therapy.

## VII. Adverse Reactions

**Prophylaxis of Gout Flares:** The most common adverse reaction in clinical trials for the prophylaxis of gout was diarrhea.

**Treatment of Gout Flares:** The most common adverse reactions reported in the clinical trial for gout were diarrhea (23%) and pharyngolaryngeal pain (3%).

**FMF:** The most common adverse reactions (up to 20%) are abdominal pain, diarrhea, nausea, and vomiting. These effects are usually mild, transient, and reversible upon lowering the dose.

## VIII. Utilization

<b>SD Medicaid Colcrlys and Colchicine Utilization</b>			
<b>06/01/10 - 05/31/11</b>			
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>	<b>Average cost/script</b>
COLCHICINE 0.6 MG TABLET	54	\$601.64	\$11.14
COLCRYS 0.6 MG TABLET	24	\$5,629.71	\$234.57
PROBENECID-COLCHICINE	10	\$245.60	\$24.56
<b>TOTAL 25 recipients</b>	<b>88</b>	<b>\$6,476.95</b>	

## References

1. Colcrys<sup>®</sup> [prescribing information]. Philadelphia, PA: Mutual Pharmaceutical Company, Inc.; September 2010.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
3. Clinical Pharmacology, 2011 Gold Standard.

**South Dakota Medicaid  
P&T Meeting  
Horizant<sup>®</sup> Review**

**I. Overview**

On April 6, 2011, the FDA approved Horizant (gabapentin enacarbil) extended release tablets, a once-daily treatment for moderate-to-severe restless legs syndrome (RLS). RLS is a disorder in which there is an urge or need to move the legs to stop unpleasant sensations.

**II. Dosage and Administration**

The recommended dose of Horizant is 600mg once daily taken with food at about 5pm. A dose of 1,200mg once daily provided no additional benefit compared with the 600mg dose, but caused an increase in adverse reactions.

**III. Pharmacology/Pharmacokinetic**

Gabapentin enacarbil is a prodrug of gabapentin and its therapeutic effects in RLS are attributable to gabapentin. The precise mechanism by which gabapentin is efficacious in RLS is unknown.

- **Absorption:** Mean bioavailability of gabapentin for Horizant in the fed state is about 75%. Bioavailability under fasting conditions has been estimated to be 42% to 65%. The T<sub>max</sub> of gabapentin after administration of 600mg of Horizant was 5.0 hours in fasted subjects and 7.3 hours in fed subjects. Steady state is reached in 2 days with daily administration.
- **Distribution:** Plasma protein binding of gabapentin has been reported to be <3%. The apparent volume of distribution of gabapentin in subjects receiving Horizant is 76L.
- **Metabolism:** After oral administration, gabapentin enacarbil undergoes extensive first-pass hydrolysis by non-specific carboxylesterases primarily in enterocytes and to a lesser extent in the liver, to form gabapentin, carbon dioxide, acetaldehyde, and isobutyric acid.
- **Elimination:** Following hydrolysis of gabapentin enacarbil, the released gabapentin is excreted unchanged by the kidney. Renal clearance ranged from 5 to 7 L/hr. The elimination half-life of gabapentin ranges from 5.1 to 6.0 hours and is unaltered by dose.

**IV. Warnings/Precautions**

- **Driving impairment:** Warn patients not to drive until they have gained sufficient experience with HORIZANT to assess whether it will impair their ability to drive.
- **Somnolence/sedation and dizziness:** May impair the patient's ability to operate complex machinery.

- Horizant is not interchangeable with other gabapentin products.
- **Suicidal thoughts or behaviors:** Monitor for suicidal thoughts or behaviors.

## V. Adverse Reactions

Most common adverse reactions ( $\geq 10\%$  and at least 2 times the rate of placebo) were somnolence/sedation and dizziness.

## References

1. Horizant<sup>®</sup> [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; April 2011.
2. Wolters Kluwer Health, Inc. Drug Facts and Comparisons. St. Louis, MO. 2010.
3. Clinical Pharmacology, 2011 Gold Standard.

<b>Agents Used to Treat Restless Leg Syndrome (dx code 333.94)</b>			
<b>06/01/10 - 05/31/11</b>			
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>	<b>Average Cost per Script</b>
CARBIDOPA-LEVO ER 50-200 TAB	11	\$213.95	\$19.45
CARBIDOPA-LEVODOPA 25-100 TAB	46	\$818.06	\$17.78
GABAPENTIN 100 MG CAPSULE	46	\$492.10	\$10.70
GABAPENTIN 300 MG CAPSULE	110	\$1,744.65	\$15.86
GABAPENTIN 400 MG CAPSULE	10	\$143.35	\$14.34
GABAPENTIN 600 MG TABLET	76	\$2,124.32	\$27.95
GABAPENTIN 800 MG TABLET	5	\$86.34	\$17.27
MIRAPEX 0.125 MG TABLET	3	\$238.67	\$79.56
MIRAPEX 0.25 MG TABLET	11	\$1,387.05	\$126.10
MIRAPEX 0.5 MG TABLET	1	\$87.29	\$87.29
MIRAPEX 0.75 MG TABLET	6	\$297.22	\$49.54
MIRAPEX ER 1.5 MG TABLET	2	\$547.54	\$273.77
PRAMIPEXOLE 0.125 MG TABLET	40	\$1,783.52	\$44.59
PRAMIPEXOLE 0.25 MG TABLET	107	\$6,173.66	\$57.70
PRAMIPEXOLE 0.5 MG TABLET	54	\$3,211.97	\$59.48
PRAMIPEXOLE 0.75 MG TABLET	4	\$105.40	\$26.35
PRAMIPEXOLE 1 MG TABLET	20	\$1,466.00	\$73.30
REQUIP 1 MG TABLET	1	\$25.22	\$25.22
REQUIP 2 MG TABLET	12	\$2,121.84	\$176.82
ROPINIROLE HCL 0.25 MG TABLET	26	\$513.72	\$19.76
ROPINIROLE HCL 0.5 MG TABLET	90	\$2,213.19	\$24.59
ROPINIROLE HCL 1 MG TABLET	102	\$2,083.60	\$20.43
ROPINIROLE HCL 2 MG TABLET	45	\$922.60	\$20.50
ROPINIROLE HCL 3 MG TABLET	19	\$549.98	\$28.95
ROPINIROLE HCL 4 MG TABLET	22	\$477.24	\$21.69
ROPINIROLE HCL 5 MG TABLET	12	\$397.80	\$33.15
<b>TOTAL 121 recipients</b>	<b>881</b>	<b>\$30,226.28</b>	<b>\$34.31</b>
<b>Horizant approximately \$121.04 per month</b>			

**South Dakota Medicaid  
P&T Meeting  
Nexiclon XR® Review**

**I. Indication**

Nexiclon XR is indicated in the treatment of hypertension.

**II. Dosage and Administration**

The dose of Nexiclon XR should be initiated at 0.17mg once daily. Initial dose is recommended to be administered at bedtime.

Further increments of 0.09mg once daily may be made at weekly intervals if necessary until the desired response is achieved. The therapeutic doses most commonly employed have ranged from 0.17mg to 0.52mg once daily. Doses higher than 0.52mg per day were not evaluated and are not recommended.

**III. Pharmacology**

Clonidine stimulates alpha-adrenoreceptors in the brain system. This action results in reduced sympathetic outflow from the central nervous system and in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure.

**IV. Pharmacokinetics**

Following single doses of Nexiclon XR 0.17mg, clonidine mean peak plasma concentrations of 0.49ng/mL occurred at 7.8 hours. The plasma half-life of clonidine was 13.7 hours. The half-life may increase up to 41 hours in patients with severe impairment of renal function. Following oral administration of clonidine, about 40-60% of the absorbed dose is recovered in the urine as unchanged drug in 24 hours. About 50% of the absorbed dose is metabolized in the liver.

**V. Warnings/Precautions**

- **Withdrawal** – Instruct patients not to discontinue therapy without consulting their physician. Sudden cessation of clonidine treatment has resulted in symptoms such as nervousness, agitation, headache and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma. When discontinuing therapy, reduce the dose gradually over 2 to 4 days to avoid withdrawal symptoms.
- **General Precautions** – In patients who have developed localized sensitization or an allergic reaction to a clonidine transdermal system, substitution of oral clonidine therapy may be associated with the development of a generalized skin

rash. Monitor carefully and up-titrate slowly in patients with severe coronary insufficiency, conduction disturbances, recent myocardial infarction, cerebrovascular disease, or chronic renal failure. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of a possible sedative effect of clonidine. The sedative effect may be increased by concomitant use of alcohol, barbiturates, or other sedating drugs.

- **Perioperative Use** – Nexiclon XR may be administered up to 28 hours prior to surgery and resumed the following day. Blood pressure should be carefully monitored during surgery and additional measures to control blood pressure should be available if required.

## **VI. Adverse Reactions**

Most adverse reactions are mild and tend to diminish with continued therapy. The most frequent (which also appear to be dose-related) are dry mouth (approximately 40%); drowsiness (approximately 33%); dizziness (approximately 16%); constipation and sedation (approximately 10% each).

## **VII. Drug Interactions**

No drug interaction studies have been conducted with Nexiclon XR. The following have been reported with other oral formulations of clonidine.

- Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs. If a patient receiving clonidine is also taking tricyclic antidepressants, the hypotensive effect of clonidine may be reduced, necessitating an increase in the clonidine dose.
- Monitor heart rate in patients receiving clonidine concomitantly with agents known to affect sinus node function or AV nodal conduction, e.g., digitalis, calcium channel blockers, and beta-blockers. Sinus bradycardia resulting in hospitalization and pacemaker insertion has been reported in association with the use of clonidine concomitantly with diltiazem or verapamil.
- Amitriptyline in combination with clonidine enhances the manifestation of corneal lesions in rats.
- Based on *in vitro* studies, high concentrations of alcohol may increase the rate of release of Nexiclon XR.

## References

1. Nexiclon XR [prescribing information]. Cupertino, CA: NextWave Pharmaceuticals, Inc; October 2010.

**South Dakota Department of Social Services  
P&T Meeting  
Interferons® Review**

**I. Overview**

Interferons are naturally occurring proteins that are made and secreted by cells of the immune system. Interferons modulate the response of the immune system to viruses, bacteria, cancer, and other foreign substances that invade the body. Interferons do not directly kill viral or cancerous cells; they boost the immune system response and reduce the growth of cancer cells by regulating the action of several genes that control the secretion of numerous cellular proteins that affect growth.

The interferons are primarily used for the treatment of chronic hepatitis B and hepatitis C. The hepatitis B virus (HBV) is a DNA virus that is transmitted through exposure with infected blood and body fluids, and is a leading cause of death from liver disease. The hepatitis C virus (HCV) is a RNA virus that is also transmitted through exposure with infected blood.

Interferons included in this review

Generic Name	Formulation	Example Brand Name
Interferon alfa-2b	injection	Intron A
Interferon alfacon-1	injection	Infergen
Interferon alfa-n3	injection	Alferon N
Peginterferon alfa-2a	injection	Pegasys
Peginterferon alfa-2b	injection	PegIntron

**II. Treatment Guidelines**

Clinical Guideline	Recommendation
American Association for the Study of Liver Diseases (AASLD): <b>Chronic Hepatitis B: An Update (2009)</b>	<p><u>General Information</u></p> <ul style="list-style-type: none"> <li>The aims of treatment of chronic hepatitis B are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma.</li> <li>Parameters used to assess treatment response include normalization of serum ALT, decrease in serum HBV DNA level, loss of hepatitis B e antigen (HBeAg) with or without detection of anti-HBe, and improvement in liver histology.</li> <li>Responses to antiviral therapy of chronic hepatitis B are categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on therapy or sustained off therapy.</li> <li>Seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B in the United States. While interferons are administered for predefined durations, the nucleoside/nucleotide analogues (NAs) are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of the interferons.</li> </ul> <p><u>General Treatment Recommendations</u></p> <ul style="list-style-type: none"> <li>Patients with HBeAg-positive chronic hepatitis B with ALT &gt;2</li> </ul>

Clinical Guideline	Recommendation
	<p>times normal or moderate/severe hepatitis on biopsy and HBV DNA &gt;20,000 IU/mL should be considered for treatment.</p> <ul style="list-style-type: none"> <li>○ Treatment should be delayed for 3 to 6 months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs.</li> <li>○ Patients with icteric ALT flares should be promptly treated.</li> <li>○ Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa or entecavir are preferred.</li> <li>○ Clinical trials suggest that the efficacy of peginterferon alfa is similar to or slightly better than standard interferon alfa.</li> </ul> <ul style="list-style-type: none"> <li>● Patients with HBeAg-positive chronic hepatitis B and ALT persistently normal or minimally elevated (&lt;2 times normal) generally should not be initiated on treatment.</li> <li>● Children with elevated ALT &gt;2 times normal should be considered for treatment if ALT levels remain elevated at this level for longer than 6 months. (Treatment may be initiated with interferon alfa or lamivudine.</li> <li>● Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA &gt;20,000 IU/mL and elevated ALT&gt;2 times normal) should be considered for treatment. <ul style="list-style-type: none"> <li>○ Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000-20,000 IU/mL) and borderline normal or minimally elevated ALT levels.</li> <li>○ Treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on biopsy.</li> <li>○ Treatment may be initiated with any of the 7 approved antiviral medications, but peginterferon alfa, tenofovir or entecavir are preferred in view of the need for long-term treatment.</li> </ul> </li> <li>● Patients who failed to respond to prior interferon alfa (standard or pegylated) therapy may be retreated with nucleoside/nucleotide analogues (NA).</li> <li>● Patients who failed to achieve primary response as evidenced by &lt;2 log decrease in serum HBV DNA level after at least 6 months of NA therapy should be switched to an alternative treatment or receive additional treatment.</li> <li>● In patients with inactive HBsAg carrier state, antiviral treatment is not indicated, but these patients should be monitored.</li> </ul> <p><u>Patients Who Develop Breakthrough Infection While Receiving NA Therapy</u></p> <ul style="list-style-type: none"> <li>● All patients with virologic breakthrough should be considered for rescue therapy.</li> <li>● For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares.</li> </ul> <p><u>Treatment of Patients with Lamivudine (or telbivudine)-resistant HBV</u></p> <ul style="list-style-type: none"> <li>● If adefovir is used, lamivudine (or telbivudine) should be</li> </ul>

Clinical Guideline	Recommendation
	<p>continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance.</p> <ul style="list-style-type: none"> <li>• If tenofovir is used, continuation of lamivudine (or telbivudine) is recommended to decrease the risk of subsequent antiviral resistance.</li> <li>• If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine- (or telbivudine-) resistant mutations will increase the risk of entecavir resistance. Entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time.</li> </ul> <p><u>Treatment of Patients with Adefovir-resistant HBV</u></p> <ul style="list-style-type: none"> <li>• In patients with no prior exposure to other NA, lamivudine, telbivudine or entecavir may be added. Alternatively, adefovir may be stopped and tenofovir plus lamivudine or emtricitabine may be used.</li> <li>• In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, adefovir may be stopped and tenofovir plus lamivudine, emtricitabine or entecavir may be used but the durability of response to this combination is unknown.</li> </ul> <p><u>Treatment of Patients with Entecavir-resistant HBV</u></p> <ul style="list-style-type: none"> <li>• Adefovir or tenofovir can be used as it has been shown to have activity against entecavir-resistant HBV in <i>in vitro</i> studies, but clinical data are lacking.</li> </ul> <p><u>Treatment of Patients with Compensated Cirrhosis</u></p> <ul style="list-style-type: none"> <li>• Treatment should be considered for patients with ALT &gt;2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (&gt;2,000 IU/mL).</li> <li>• Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with interferon alfa-related flares of hepatitis. In view of the need for long-term therapy, tenofovir or entecavir is preferred.</li> </ul> <p><u>Treatment of Patients with Decompensated Cirrhosis</u></p> <ul style="list-style-type: none"> <li>• Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance.</li> <li>• Lamivudine or telbivudine may be used as initial treatment in combination with adefovir or tenofovir to reduce the risk of drug resistance.</li> <li>• Entecavir or tenofovir alone would be an appropriate treatment in this setting but clinical data documenting their safety and efficacy in patients with decompensated cirrhosis are lacking.</li> <li>• Treatment should be coordinated with a transplant center.</li> <li>• Interferon alfa or peginterferon alfa should not be used in patients with decompensated cirrhosis.</li> </ul> <p><u>Treatment Duration</u></p> <ul style="list-style-type: none"> <li>• The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard interferon alfa and 48 weeks for peginterferon alfa.</li> <li>• The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peginterferon alfa.</li> <li>• Treatment with NAs should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV (for patients with HBeAg-positive chronic hepatitis B). For</li> </ul>

Clinical Guideline	Recommendation
	<p>patients with HBeAg negative chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance. For patients with compensated cirrhosis, treatment should be received long-term. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least 6 months of consolidation therapy and in HBeAg-negative patients if they have confirmed HBsAg clearance. For patients with decompensated cirrhosis and recurrent hepatitis B post–liver transplantation, life-long treatment is recommended.</p> <p><u>Recommendations for Treatment of Patients with HBV/HIV Coinfection</u></p> <ul style="list-style-type: none"> <li>• Patients who meet criteria for chronic hepatitis B should be treated.</li> <li>• Patients who are not on HAART and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as peginterferon alfa or adefovir. Although telbivudine does not target HIV, it should not be used in this circumstance.</li> <li>• Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred.</li> <li>• Patients who are already on effective HAART that does not include a drug active against HBV may be treated with peginterferon alfa or adefovir.</li> <li>• In patients with lamivudine resistance, tenofovir should be added.</li> </ul> <p><u>Recommendations for Treatment of Hepatitis B Carriers Who Require Immunosuppressive or Cytotoxic Therapy</u></p> <ul style="list-style-type: none"> <li>• Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy.</li> <li>• Patients with baseline HBV DNA &lt;2,000 IU/mL level should continue treatment for 6 months after completion of chemotherapy or immunosuppressive therapy.</li> <li>• Patients with high baseline HBV DNA (&gt;2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients.</li> <li>• Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (&lt;12 months) and baseline serum HBV DNA is not detectable.</li> <li>• Tenofovir or entecavir is preferred if longer duration of treatment is anticipated.</li> <li>• Interferon alfa should be avoided in view of the bone marrow suppressive effect.</li> </ul> <p><u>Recommendations for Treatment of Patients with Acute Symptomatic Hepatitis B</u></p> <ul style="list-style-type: none"> <li>• Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B.</li> <li>• Lamivudine or telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is preferred.</li> <li>• Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation.</li> </ul>

Clinical Guideline	Recommendation
<p>American Association for the Study of Liver Diseases (AASLD): <b>Diagnosis, Management, and Treatment of Hepatitis C: An Update (2009)</b></p>	<ul style="list-style-type: none"> <li>• Interferon alfa therapy is contraindicated.</li> </ul> <p>General Information</p> <ul style="list-style-type: none"> <li>• The goal of therapy is to prevent complications and death from HCV infection. Treatment responses are defined by a surrogate virological parameter rather than a clinical endpoint. Short-term outcomes can be measured biochemically (normalization of serum ALT levels), virologically (absence of HCV RNA from serum by a sensitive PCRbased assay), and histologically (point improvement in necroinflammatory score with no worsening in fibrosis score).</li> <li>• Several types of virological responses may occur, labeled according to their timing relative to treatment. The most important is the sustained virological response (SVR), defined as the absence of HCV RNA from serum by a sensitive PCR assay 24 weeks following discontinuation of therapy (virological cure). Undetectable virus at the end of either a 24-week or 48-week course of therapy is referred to as an end-of treatment response (ETR). An ETR does not accurately predict that an SVR will be achieved, but is necessary for it to occur.</li> <li>• The currently recommended therapy of chronic HCV infection is the combination of a pegylated interferon alfa and ribavirin.</li> <li>• Treatment decisions should be individualized based on the severity of liver disease, the potential for serious side effects, the likelihood of treatment response, the presence of comorbid conditions, and the patient’s readiness for treatment.</li> </ul> <p><u>Genotype 1 and Genotype 4 HCV Infection</u></p> <ul style="list-style-type: none"> <li>• Treatment with peginterferon plus ribavirin should be planned for 48 weeks.</li> <li>• Treatment may be discontinued in patients who do not achieve an early virological response (EVR; &gt;2 log reduction in HCV RNA at week 12 of treatment).</li> <li>• Patients who do not achieve a complete EVR (undetectable HCV RNA at week 12 of treatment) should be re-tested at week 24, and if HCV RNA remains positive, treatment should be discontinued.</li> <li>• For patients with genotype 1 infection who have delayed virus clearance (HCV RNA test becomes negative between weeks 12 and 24); consideration should be given to extending therapy to 72 weeks.</li> </ul> <p><u>Genotype 2 or Genotype 3 HCV Infection</u></p> <ul style="list-style-type: none"> <li>• Treatment with peginterferon plus ribavirin should be administered for 24 weeks.</li> </ul> <p><u>Retreatment</u></p> <ul style="list-style-type: none"> <li>• Retreatment with peginterferon plus ribavirin in patients who did not achieve an SVR after a prior full course of peginterferon plus ribavirin not recommended, even if a different type of peginterferon is administered.</li> <li>• Retreatment with peginterferon plus ribavirin can be considered for non-responders or relapsers who have previously been treated with non-pegylated interferon with or without ribavirin, or with peginterferon monotherapy, particularly if they have bridging fibrosis or cirrhosis.</li> <li>• Maintenance therapy is not recommended for patients with bridging fibrosis or cirrhosis who have failed a prior course of peginterferon and ribavirin.</li> </ul>

Clinical Guideline	Recommendation
	<p><u>Treatment of Persons with Normal Serum Aminotransferase Values</u></p> <ul style="list-style-type: none"> <li>Regardless of the serum alanine aminotransferase level, the decision to initiate therapy with pegylated interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential for serious side effects, the likelihood of response, and the presence of comorbid conditions.</li> <li>The treatment regimen for HCV-infected persons with normal aminotransferase levels should be the same as that used for persons with elevated serum aminotransferase levels.</li> </ul> <p><u>Treatment of Children</u></p> <ul style="list-style-type: none"> <li>Children aged 2-17 years who are infected with HCV should be considered appropriate candidates for treatment using the same criteria as that used for adults.</li> <li>Children should be treated with pegylated interferon alfa-2b, 60mcg/m<sup>2</sup> weekly in combination with ribavirin, 15 mg/kg daily for a duration of 48 weeks.</li> </ul> <p><u>Treatment of HIV-infected Persons</u></p> <ul style="list-style-type: none"> <li>Hepatitis C should be treated in the HIV/HCV co-infected patient in whom the likelihood of serious liver disease and a treatment response are judged to outweigh the risk of morbidity from the adverse effects of therapy.</li> <li>Initial treatment of hepatitis C in most HIV-infected patients should be peginterferon alfa plus ribavirin for 48 weeks at doses recommended for HCV mono-infected patients.</li> <li>When possible, patients receiving zidovudine (AZT) and especially didanosine (ddI) should be switched to an equivalent antiretroviral agent before beginning therapy with ribavirin.</li> <li>HIV-infected patients with decompensated liver disease (CTP Class B or C) should not be treated with peginterferon alfa and ribavirin and may be candidates for liver transplantation.</li> </ul>

### III. Indications

Indication	Interferon alfa-2b	Interferon alfacon-1	Interferon alfa-n3	Peginterferon alfa-2a	Peginterferon alfa-2b
AIDS-related Kaposi's sarcoma	√				
Chronic hepatitis B	√			√	
Chronic hepatitis C	√	√		√	√
Condylomata acuminata	√		√		
Follicular lymphoma	√				
Hairy cell leukemia	√				
Malignant melanoma	√				

### IV. Pharmacokinetics

Generic Name	Bioavailability (%)	Metabolism	Excretion (%)	Half-Life (hours)
Interferon alfa-2b	>90	Kidney-extensive	Not reported	2-3
Interferon alfacon-1	83-100	Not reported	Renal	1.3-3.4
Interferon alfa-n3	Not reported	Kidney-extensive	Not reported	4.43-6.76
Peginterferon alfa-2a	>60	Liver	Renal	60-90
Peginterferon alfa-2b	Not reported	Liver	Renal	22-60

## V. Drug Interactions

Precipitant Drug	Object Drug	Description
Interferon alfa-2b	Myelosuppressive agents (e.g., zidovudine)	There may be synergistic adverse reactions. Patients have had a higher incidence of neutropenia than that expected with zidovudine alone. Carefully monitor WBC count in myelosuppressed patients or those receiving myelosuppressive agents.
Interferon alfa-2b	Theophyllines	Concomitant use significantly reduces theophylline clearance, resulting in 100% increase in serum theophylline levels.
Interferon alfacon-1	Myelosuppressive agents	Use caution when administering with other agents known to cause myelosuppression.
Interferon alfacon-1	Drugs metabolized by cytochrome P450	Use caution when administering to patients who are receiving agents metabolized via cytochrome P450, and monitor closely for changes in therapeutic and/or toxic levels of these concomitant drugs.
Peginterferon alfa-2a	Methadone	Concomitant treatment with peginterferon alfa-2a once weekly for 4 weeks was associated with methadone levels that were 10% to 15% higher than at baseline.
Peginterferon alfa-2a	NRTIs (e.g., didanosine, zidovudine, stavudine)	Coadministration may increase toxicities, such as hematologic toxicities. Cases of hepatic decomposition were observed.
Peginterferon alfa-2a	Theophylline	Coadministration with peginterferon alfa-2a was associated with an inhibition of CYP1A2 and a 25% increase in theophylline AUC. Monitor theophylline levels and adjust dose as needed.
Peginterferon alfa-2b	CYP2C8/9 substrates (e.g., phenytoin, warfarin)	Plasma concentrations of these substrates may be reduced, decreasing the pharmacologic effects. Evaluate the response of the patient and adjust the dose of the substrate as needed.
Peginterferon alfa-2b	CYP2D6 substrates (e.g., flecainide)	Plasma concentrations of these substrates may be reduced, decreasing the pharmacologic effects. Evaluate the response of the patient and adjust the dose of the substrate as needed.
Peginterferon alfa-2b	Methadone	Methadone plasma concentrations may be elevated, increasing the pharmacologic effects and adverse reactions. Monitor patients for signs and symptoms of increased narcotic effect and adjust the methadone dose as needed.
Peginterferon alfa-2b with or without ribavirin	NRTIs	Closely monitor for treatment-associated toxicities (e.g., hepatic decompensation, anemia) especially in cirrhotic HIV/HCV coinfecting patients. Discontinue the NRTI as medically appropriate. Reduce the dose or discontinue interferon, ribavirin, or both if toxicities develop.
Peginterferon alfa-2b with ribavirin	Didanosine	Coadministration of ribavirin and didanosine is not recommended. Reports of fatal hepatic failure, as well as peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported.
Peginterferon alfa-2b with ribavirin	Pyrimidine nucleoside analogs (e.g., lamivudine, stavudine, zidovudine)	Severe neutropenia and severe anemia may develop in HIV/HCV coinfecting patients. Closely monitor the patient.

## VI. Adverse Reactions

Adverse Events	Interferon alfa-2b	Interferon alfacon-1	Interferon alfa-n3	Peginterferon alfa-2a	Peginterferon alfa-2b
<b>Cardiovascular</b>					
Bradycardia	<5				
Chest pain	<1-28	5-13	10		6-8
Flushing		4-13			4-6
Hypertension	<5-9	2-5			
Hypotension	<5		6		
Palpitations	<5	2-5			
Tachycardia	<5				
<b>Central Nervous System</b>					
Agitation/irritability	1-22	4-6		19-33	2-8
Amnesia	1-14	2-10			
Anxiety	1-9	9-19			28-47
Concentration impaired	<1-14			8-10	10-17
Confusion	1-12	4-5			
Depression	3-40	18-26	2	18-20	29-31
Drowsiness	1-33	4-7		3-5	
Dizziness	7-23	18-25	9	14-16	12-21
Fatigue	8-96	2-71	6-65	56-65	52-66
Headache	21-62	78-82	10-31	43-54	56-62
Insomnia	<1-12	24-39	2-10	19-30	23-40
Lethargy	8-96	2-71	6-65	56-65	52-66
Malaise	8-96	2-71	6-65	56-65	52-66
Paresthesia	1-21	9-13			
Somnolence	1-33	4-7		3-5	
Taste/smell disturbances		3-5			
<b>Dermatological</b>					
Alopecia	8-38	10-14		18-28	22-36
Diaphoresis/sweating	1-21	11-13	2	6	6-11
Dry skin	<1-10	2-6		4-10	11-24
Eczema				1-5	
Injection site reaction	<5	5-23	10-12	22-23	47-75
Pruritus		10-14	2	12-19	12-29
Rash	1-25	10-13		5-8	6-24
<b>Endocrine and Metabolic</b>					
Hyperthyroidism	<5				
Hypothyroidism	<5			3-4	5
Weight decrease	<1-13	2-5		4-16	11-29
<b>Gastrointestinal</b>					
Abdominal cramping	1-23	24-41		8-15	13-15
Abdominal discomfort	1-23	24-41		8-15	13-15
Abdominal pain	1-23	24-41		8-15	13-15
Anorexia	1-69	14-24	68	16-24	20-32
Constipation	<1-14	5-9			1-5
Diarrhea	2-45	24-29	2-6	11-16	18-22
Dry/painful mouth	1-28			4-6	6-12
Dyspepsia/heartburn	2-8	10-21	3	<1-6	6-9
Flatulence	<5	5-8	3		
Nausea	17-66	30-40	4-48	24-25	26-43
Taste alterations	<1-24				<1-9

Adverse Events	Interferon alfa-2b	Interferon alfacon-1	Interferon alfa-n3	Peginterferon alfa-2a	Peginterferon alfa-2b
Vomiting	2-32	11-12	29	24-25	7-14
<b>Hematological</b>					
Hematocrit decreased			7	17-52	
Hemoglobin decreased			7	17-52	
Leukopenia	<5	15-28			<1-6
Neutropenia	<5-14			21-40	6-26
Platelets increased or decreased			3	33-52	
Thrombocytopenia	<5-10	18-19		5-8	5-7
<b>Laboratory Test Abnormalities</b>					
Albuminuria	<5				
Alkaline phosphatase increased			8		
ALT/AST increased	<5-63		3		
Anemia	<5	2-6		2-14	12
Bilirubin increased or decreased	<5		4		10-14
BUN increased	<5				
LDH increased	<5				
Proteinuria	<5				
Uric acid increased					33-38
<b>Musculoskeletal</b>					
Arthralgia	3-19	43-51	5-10	22-28	23-34
Asthenia	5-63	7-10			
Back pain	1-15	23-42	4	5-9	
Myalgia	16-75	51-58	16-45	37-40	54-56
<b>Respiratory</b>					
Asthma	<5				
Bronchitis	<5-10	1-6			
Cough	<1-31	11-22		4-10	8-23
Dyspnea	<1-34	7-12		4-13	4-26
Pharyngitis	1-31	17-34			10-12
Rhinitis	<5	7-13			2-8
Sinusitis	1-21	12-17			6-7
Respiratory tract infections		16-31			
<b>Other</b>					
Anaphylaxis	<5	3-7			
Chills	45-54		14-87		
Edema		3-9			
Fever	34-94	55-61	40-81	37-54	22-46
Flu-like syndrome	<1-79	8-15			
Pain	3-18	39-54		10-11	
Visual disturbances	<5	3-5	6	4-5	2-5

#### **Black Box Warning for Interferon Alfa-2B and Interferon Alfacon-1**

Alpha interferons, including alfa-2b and interferon alfacon-1, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy from patients with persistently severe or worsening signs or symptoms of these conditions. In many but not all cases these disorders resolve after stopping interferon alfa-2b or interferon alfacon-1 therapy.

### Black Box Warning for Peginterferon Alfa-2a and Peginterferon Alfa-2b

Alpha interferons, including peginterferon alfa-2a and peginterferon alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all, cases these disorders resolve after stopping peginterferon alfa-2a or peginterferon alfa-2b therapy.

Combination therapy with ribavirin: Ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in women taking peginterferon alfa-2a or peginterferon alfa-2b and in female partners of men taking peginterferon alfa-2a or peginterferon alfa-2b. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Because ribavirin is genotoxic and mutagenic, consider it a potential carcinogen.

## VII. Dosage and Administration

### Usual Dosing Regimens for Interferons

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Interferon alfa-2b	<p><u>AIDS-related Kaposi's sarcoma:</u> 30 MIU/m<sup>2</sup> SC or IM three times a week (TIW) until disease progression or maximal response after 16 weeks.</p> <p><u>Chronic hepatitis B:</u> 30 to 35 MIU per week, administered SC or IM, either as 5 MIU daily or as 10 MIU TIW for 16 weeks.</p> <p><u>Chronic hepatitis C:</u> 3 MIU TIW administered SC or IM up to 18-24 months. Patients who do not normalize their ALT after 16 weeks should be considered for treatment discontinuation.</p> <p><u>Condylomata acuminata:</u> 1 MIU per lesion in a maximum of 5 lesions in a single course. The lesions should be injected TIW on alternate days for 3 weeks. An additional course may be administered at 12 to 16 weeks.</p> <p><u>Follicular lymphoma:</u> 5 MIU SC TIW for up to</p>	<p>Children ≥1 year of age: <u>Chronic hepatitis B:</u> 3 MIU/m<sup>2</sup> SC TIW for 1 week, then 6MIU/m<sup>2</sup> TIW for a total duration of 16 to 24 weeks.</p>	<p>Pen Injection Kit: 3 MIU/0.2mL 5 MIU/0.2mL 10 MIU/0.2mL</p> <p>Vial: 10 MIU/mL 6 MIU/mL 10 MIU 18 MIU 50 MIU</p>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<p>18 months in conjunction with an anthracycline-containing chemotherapy regimen and following completion of the chemotherapy regimen.</p> <p><u>Hairy cell leukemia:</u> 2 MIU/m<sup>2</sup> administered IM or SC TIW for up to 6 months. Patients with platelet counts of less than 50,000/mm<sup>3</sup> should not be administered interferon alfa-2b IM, but instead by SC administration.</p> <p><u>Malignant melanoma:</u> Induction-20 MIU/m<sup>2</sup> as an IV infusion, over 20 minutes, 5 consecutive days per week, for 4 weeks. Maintenance-10 MIU/m<sup>2</sup> as a SC injection TIW for 48 weeks.</p>		
Interferon alfacon-1	<p><u>Chronic hepatitis C:</u> 9 mcg TIW administered SC as a single injection for 24 weeks. At least 48 hours should elapse between doses of interferon alfacon-1.</p> <p>No response or relapse upon discontinuation: 15 mcg TIW for up to 48 weeks.</p>	Safety and effectiveness of interferon alfacon-1 have not been established in patients younger than 18 years.	Vial: 9 mcg/0.3mL 15 mcg/0.5mL
Interferon alfa-n3	<u>Condylomata acuminata:</u> 0.05mL (250,000 IU) per wart administered twice weekly for up to 8 weeks.	Safety and effectiveness of interferon alfa-n3 have not been established in patients younger than 18 years.	Vial: 5 MIU/mL
Peginterferon alfa-2a	<p><u>Chronic hepatitis B:</u> 180 mcg once weekly for 48 weeks by SC administration in the abdomen or thigh.</p> <p><u>Chronic hepatitis C:</u> 180 mcg once weekly for 48 weeks by SC administration in the abdomen or thigh.</p>	Safety and effectiveness have not been established in patients younger than 18 years.	Kit: 180 mcg/0.5mL  Vial: 180 mcg/mL

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
	<u>Combination therapy with ribavirin:</u> 180 mcg SC once weekly. The recommended dose of ribavirin and duration for peginterferon therapy is based on viral genotype. The daily dose of ribavirin is 800 to 1,200 mg administered orally in 2 divided doses.		
Peginterferon alfa-2b	<u>Chronic hepatitis C:</u> 1mcg/kg/wk SC for 1 year.  <u>Combination with ribavirin:</u> 1.5 mcg/kg/wk SC with ribavirin 800 to 1,400 mg capsules.	Children 3-17 years of age: <u>Chronic hepatitis C:</u> 60 mcg/m <sup>2</sup> /wk SC in combination with ribavirin 15 mg/kg/day orally in 2 divided doses.	Kit: 50 mcg/0.5mL 80 mcg/0.5mL 120 mcg/0.5mL 150 mcg/0.5mL  Pen Injection Kit: 50 mcg/0.5mL 80 mcg/0.5mL 120 mcg/0.5mL 150 mcg/0.5mL

### VIII. Utilization

SD Medicaid			
Interferon Utilization			
05/01/10 - 04/30/11			
Label Name	Rx Num	Total Reimb Amt	Avg Cost per Script
INFERGEN 15 MCG/0.5 ML VIAL	1	\$4,216.07	\$4,216.07
PEGINTRON REDIPEN 150 MCG	5	\$10,013.46	\$2,002.69
PEGASYS 180 MCG/ML VIAL	10	\$22,530.12	\$2,253.01
PEGASYS 180 MCG/0.5 ML CONV.PK	17	\$38,781.01	\$2,281.24
9 recipients/6 prescribers*	33	\$75,540.66	
*2 gastroenterologists, 2 internal medicine, 1 family practice, 1 NP, 1 PA			
Incivek and Victrelis approximate cost per course of treatment \$26,500 - \$49,000			

## References

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2. Lok A. American Association for the Study of Liver Diseases. Chronic Hepatitis B: Update 2009. Accessed July 2010. Available at <http://www.aasld.org>.
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**South Dakota Department of Social Services  
P&T Meeting  
Incivek and Victrelis Overview**

Two new agents have recently been approved for the treatment of Hepatitis C. Incivek (telaprevir) and Victrelis (boceprevir) are protease inhibitors for use with peginterferon alfa and ribavirin. Currently, the gold standard of treatment is peginterferon alfa plus ribavirin. Genotype 1 is the most common genotype in the U.S. and also the hardest to treat. These patients require longer treatment duration than genotype 2 or 3 patients (48 weeks vs. 24 weeks).

The chance of achieving a sustained virologic response (i.e., clearance of hepatitis C RNA from the serum at the end of treatment and six months afterward) is only 50% in patients with genotype 1. Patients who do not achieve a sustained viral response are said to be nonresponders. Null responders are those who have less than a two-log<sub>10</sub> decrease in viral load at treatment week 12. Furthermore, patients may also relapse after attaining a sustained viral response. Guidelines from 2004 from the American Association for the Study of Liver Disease recommended that these patients may be retreated if they have significant fibrosis or compensated cirrhosis, or if they were treated with nonpegylated interferon. Otherwise, retreatment was not recommended.

Incivek and Victrelis are protease inhibitors indicated for the treatment of genotype 1 hepatitis C in adults with compensated liver disease. They will be used in combination with peginterferon alfa and ribavirin in treatment-naive patients as well as in patients who have failed interferon plus ribavirin. Boceprevir has not been studied in patients known to be null responders by history. Neither drug has been tested in patients co-infected with hepatitis B or HIV.

The safety and effectiveness of boceprevir was evaluated in two phase 3 clinical trials with 1500 adult patients. In both trials, about two-thirds of patients receiving boceprevir in combination with peginterferon alfa and ribavirin experienced a sustained virologic response, more than with peginterferon alfa and ribavirin alone (38% for treatment-naive patients, 23% for previously treated patients).

The safety and effectiveness of telaprevir was evaluated in three phase 3 clinical trials with about 2250 adult patients. In all studies patients also received the drug with peginterferon alfa and ribavirin. In previously untreated patients, 79% of those receiving telaprevir experienced a sustained virologic response compared to 46% with standard treatment alone. In patients who had previously failed interferon plus ribavirin, 66% of those receiving telaprevir experienced a sustained virologic response compared to 16% with standard therapy. The studies also indicate that treatment with telaprevir can be shortened from 48 weeks to 24 weeks in some treatment-naive or prior relapse patients. Sixty percent of previously untreated patients achieved an early response and received only 24 weeks of treatment. The sustained virologic response for these patients was 90%.

The following table compares boceprevir and telaprevir dosing, treatment duration, common adverse effects, contraindications, and drug interactions.

<b><i>Victrelis (Boceprevir)</i></b>	<b><i>Incivek (Telaprevir)</i></b>
<p><u>Dose/duration:</u> 800 mg three times daily (every 7 to 9 hours) with food starting on week five of peginterferon plus ribavirin. For patients with compensated cirrhosis, treatment is continued for 44 more weeks (48 weeks total treatment duration). For patients without cirrhosis, total treatment duration is 28 to 48 weeks, depending on viral response and response history. (Not studied in known prior null responders.)</p> <p><u>Common Adverse Effects (over 35% of patients):</u> fatigue, anemia (over 40% of patients need erythropoiesis-stimulating agent), nausea, headache, dysgeusia.</p> <p><u>Contraindications:</u> Pregnancy-patients must have a negative pregnancy test prior to therapy; use two or more forms of contraception, and have monthly pregnancy tests. (Female partners of male patients should also avoid pregnancy.)</p> <p>Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.</p> <p>Potent CYP3A4/5 inducers where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy.</p> <p><u>Warnings:</u> The addition of boceprevir to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations compared with peginterferon and ribavirin alone.</p> <p>The addition of boceprevir to peginterferon alfa and ribavirin may result in worsening of neutropenia associated with peginterferon alfa and ribavirin therapy alone.</p>	<p><u>Dose/duration:</u> 750 mg three times daily (7 to 9 hours apart) with food (not low fat), plus peginterferon alfa plus ribavirin for 12 weeks. This is followed by an additional 12 to 36 weeks of peginterferon alfa plus ribavirin, based on viral response and response history (24 to 48 weeks total treatment duration).</p> <p><u>Common Adverse Effects (at least 5% higher with Incivek than in controls):</u> rash (discontinue all treatment components if progressive or severe), pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting and anal pruritus.</p> <p><u>Contraindications:</u> Pregnancy-patients must have a negative pregnancy test prior to therapy; use two or more forms of contraception, and have monthly pregnancy tests. (Female partners of male patients should also avoid pregnancy.)</p> <p>Coadministration with drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events.</p> <p>Potent CYP3A4/5 inducers where significantly reduced boceprevir plasma concentrations may be associated with reduced efficacy.</p> <p><u>Warnings:</u> Serious skin reactions including drug rash with eosinophilia and systemic symptoms and Stevens-Johnson syndrome have been reported. For serious skin reactions, all components of telaprevir combination treatment should be discontinued immediately.</p> <p>Patients with mild to moderate rash should be monitored for progression. If rash progresses and becomes severe, telaprevir should be discontinued.</p> <p>Monitor hemoglobin prior to and at regular intervals during telaprevir combination treatment. Follow dose modifications for ribavirin; discontinue telaprevir if required.</p>

<i>Victrelis (Boceprevir)</i>	<i>Incivek (Telaprevir)</i>
<b>Drug Interactions</b>	
Boceprevir is CYP3A substrate and strong inhibitor. It is also a p-glycoprotein inhibitor <i>in vitro</i> .	Telaprevir is a CYP3A substrate and strong inhibitor. It is also a p-glycoprotein substrate and inhibitor.
<b>Drugs that are contraindicated:</b> CYP3A substrates with serious side effects associated with elevated plasma levels, and potent CYP3A4/5 inducers.	
Alfuzosin Carbamazepine Cisapride Drospirenone Ergots Lovastatin Midazolam Pimozide Phenobarbital Phenytoin Rifampin Sildenafil Simvastatin St. John's wort Tadalafil Triazolam	Alfuzosin Atorvastatin Cisapride Ergots Lovastatin Midazolam Pimozide Rifampin Sildenafil Simvastatin St. John's wort Tadalafil Triazolam
<b>Drugs that should be used with caution (e.g., monitoring, dose reduction, risk/benefit consideration). Based on studies or prediction.</b>	
<u>Anticonvulsants</u> : See contraindicated drugs, above	<u>Anticonvulsants</u> (telaprevir levels decreased): carbamazepine (levels increased), phenobarbital (levels increased or decreased), phenytoin (levels increased or decreased)
<u>Antiarrhythmics</u> (levels increased): amiodarone, bepridil, digoxin, flecainide, propafenone, quinidine	<u>Antiarrhythmics</u> (levels increased): amiodarone, bepridil, digoxin, flecainide, lidocaine (systemic), propafenone, quinidine
<u>Antidepressants</u> (levels increased): trazodone, desipramine	<u>Antidepressants</u> : escitalopram (levels decreased), trazodone (levels increased), desipramine (levels increased)
<u>Azole antifungals</u> (levels of azole and boceprevir increased): ketoconazole (max ketoconazole dose 200 mg daily), itraconazole (max itraconazole dose 200 mg daily), posaconazole, voriconazole	<u>Azole antifungals</u> (telaprevir levels increased): ketoconazole (levels increased; max ketoconazole dose 200 mg daily), itraconazole (levels increased; max itraconazole dose 200 mg daily), posaconazole (levels increased), voriconazole (levels increased or decreased)

<b><i>Victrelis (Boceprevir)</i></b>	<b><i>Incivek (Telaprevir)</i></b>
<u>Benzodiazepines</u> (levels increased): alprazolam, midazolam (IV; oral contraindicated)	<u>Benzodiazepines</u> (levels increased): alprazolam, midazolam (IV; oral contraindicated)  Zolpidem levels decreased
<u>Bosentan</u> : levels increased	<u>Bosentan</u> : levels increased
<u>Colchicine</u> (levels increased):  Gout prevention: patients taking 0.6 mg twice a day should be adjusted to 0.3 mg once a day. Patients taking 0.6 mg daily should be adjusted to 0.3 mg once every other day  Gout flare: max 0.6 mg, followed by 0.3 mg one hour later, not to be repeated before 3 days  Mediterranean fever: max 0.3 mg twice daily  Avoid colchicine plus boceprevir in renal or hepatic impairment	<u>Colchicine</u> (levels increased):  Gout prevention: patients taking 0.6 mg twice a day should be adjusted to 0.3 mg once a day. Patients taking 0.6 mg daily should be adjusted to 0.3 mg once every other day  Gout flare: max 0.6 mg x 1 dose, followed by 0.3 mg one hour later, not to be repeated before 3 days  Mediterranean fever: max 0.3 mg twice daily  Avoid colchicine plus telaprevir in renal or hepatic impairment
<u>Calcium channel blockers</u> (levels increased): felodipine, nifedipine, nicardipine	<u>Calcium channel blockers</u> (levels increased): amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil
<u>Corticosteroids</u> : dexamethasone (boceprevir levels decreased; avoid), budesonide, fluticasone (levels increased; avoid)	<u>Corticosteroids</u> : dexamethasone (telaprevir levels decreased avoid), budesonide, fluticasone, methylprednisolone, prednisone (levels increased; avoid)
<u>Ethinyl estradiol</u> levels decreased; potential contraceptive failure	<u>Ethinyl estradiol</u> : levels decreased; potential contraceptive failure
<u>HIV protease inhibitors</u> ritonavir decreases boceprevir levels; effect of others on boceprevir and vice versa unknown	<u>HIV protease inhibitors</u> ritonavir decreases telaprevir levels; telaprevir has varying effects on other protease inhibitors; all ritonavir combinations except atazanavir/ritonavir “not recommended”
<u>HIV reverse transcriptase inhibitors</u> : efavirenz (boceprevir levels decreased; avoid)	<u>HIV reverse transcriptase inhibitors</u> : efavirenz (telaprevir and efavirenz levels decreased), tenofovir (levels increased)
<u>Immunosuppressants</u> (levels increased): cyclosporine, sirolimus, tacrolimus	<u>Immunosuppressants</u> (levels increased): cyclosporine, sirolimus, tacrolimus
<u>Macrolides</u> (levels increased): clarithromycin (consider clarithromycin dose reduction in renal impairment)	<u>Macrolides</u> (levels increased): clarithromycin, erythromycin, telithromycin
<u>Opioids</u> (levels increased or decreased): methadone, buprenorphine	<u>Opioids</u> (levels decreased): methadone
<u>Phosphodiesterase-5 inhibitors for erectile dysfunction</u> (levels increased): sildenafil max 25 mg every 48 hours; tadalafil max 10 mg every 72 hours, vardenafil (max 2.5 mg every 24 hours)	<u>Phosphodiesterase-5 inhibitors for erectile dysfunction</u> (levels increased): sildenafil max 25 mg every 48 hours; tadalafil max 10 mg every 72 hours, vardenafil (max 2.5 mg every 72 hours)
<u>Rifabutin</u> : boceprevir levels decreased, rifabutin levels increased; avoid	<u>Rifabutin</u> : telaprevir levels decreased, rifabutin levels increased; avoid

<b><i>Victrelis (Boceprevir)</i></b>	<b><i>Incivek (Telaprevir)</i></b>
<u>Salmeterol</u> : levels increased; avoid	<u>Salmeterol</u> : levels increased; avoid
<u>Statins (levels increased)</u> : atorvastatin (max atorvastatin dose 20 mg daily); also see contraindicated drugs, above	<u>Statins (levels increased)</u> : see contraindicated drugs, above
<u>Warfarin</u> : INR may increase or decrease	<u>Warfarin</u> : INR may increase or decrease

## References

1. Incivek<sup>®</sup> [prescribing information]. Cambridge, MA: Vertex Pharmaceuticals; May 2011.
2. Victrelis<sup>®</sup> [prescribing information]. Whitehouse Station, NY: Schering Corporation, a subsidiary of Merck & Co., Inc; May 2011.
3. PL Detail Document, Victrelis (boceprevir) and Incivek (telaprevir) for Hepatitis C. Pharmacist's Letter/Prescriber's Letter. August 2011.

**South Dakota Medicaid  
P&T Meeting  
Acne Agents, Topical**

**I. Overview**

Acne vulgaris is a common skin disease that affects 60-70% of Americans at some time during their lives. Twenty percent will have severe acne, which results in permanent scarring. Acne vulgaris is characterized by noninflammatory, open or closed comedones and by inflammatory papules, pustules, and nodules. Acne vulgaris may be present in newborns, adolescents (with onset of puberty) and to a lesser degree in adults.

There are different types of lesions associated with acne. Whiteheads or closed comedones are clogged follicles that stay beneath the skin and appear as round white bumps. Blackheads are open comedones that reach the surface of the skin and have a blackish appearance. Papules are small solid lesions that are slightly inflamed and elevated above the surface of the skin. Pustules are inflamed pus-filled lesions. Nodules and cysts are large, inflamed, pus-filled lesions and are likely to cause scarring.

Medications included in this Review

Generic Name	Brand Name	Manufacturer	Availability
Adapalene	Differin	Galderma	0.1% cream, gel (generic)
		Various generic manufacturers	0.1% lotion (brand only) 0.3% gel (brand only)
Azelaic acid	Azelex	Allergan	20% cream
Benzoyl peroxide/adapalene	Epiduo	Galderma	0.1% (adapalene)-2.5% (benzoyl peroxide) gel
Benzoyl peroxide	Benzac AC	Galderma	10% gel, cleanser 5% gel, cleanser
	Benzac W Wash	Galderma	10% cleanser
			5% cleanser
	Benzefoam	Onset Therapeutics	5.3% foam
	Brevoxyl	Stiefel	4% gel
			8% gel
	Clinac BPO	Ferndale	7% gel
			10% cleanser
	Desquam X	Ranbaxy	5% cleanser
			4%-5% (vit E) combo 8%-5% (vit E) combo
Inova	JSJ	4% cleanser 8% cleanser	
Lavoclen	Prasco	5.5% cream 3% cleanser, med. pad 6% cleanser, med. pad 9% cleanser, med. pad	
Neobenz Micro Oscion	Intendis Prasco	4.25% med. pad 7% med. pad	
Pacnex	Medimetriks	3% towelette 6% towelette 7% cleanser 9% towelette	
SE BPO	Seton	3% cleanser, med. pad,	

Generic Name	Brand Name	Manufacturer	Availability
	Triaz	Medicis	towelette 6% cleanser, med. pad, towelette 9% cleanser, med. pad, towelette 4% lotion
	Zaclir	Hawthorn	8% lotion
	Zoderm	Doak	4.5%-10% (urea) cream, gel, cleanser, med. pad 5.75%-10% (urea) cleanser 6.5%-10% (urea) cream, gel, cleanser, med. pad 8.5%-10% (urea) cream, gel, cleanser, med. pad
		Various generic manufacturers	
Benzoyl peroxide/clindamycin	Acanya BenzaClin	Valeant Dermik Mylan (generic)	1.2%-2.5% gel 1%-5% gel
Benzoyl peroxide/erythromycin	Benzamycin	Sanofi-Aventis Various generic manufacturers	3%-5% gel
Benzoyl peroxide/hyaluronate sodium	Zacare	Hawthorne	4%-0.2% combo 8%-0.2% combo
Benzoyl peroxide/salicylic acid/tocopherol	Inova 4/1, 8/2	JSJ	1%-4%-5% combo 2%-8%-5% combo
Benzoyl peroxide/sulfur	NuOx	Gentex Breckenridge (generic)	6%-3% gel
Clindamycin	Cleocin T	Pharmacia	1% solution, med. swab, lotion, gel
	Clindagel	Galderma	1% gel
	Evoclin	Stiefel Various generic manufacturers	1% foam
Dapsone	Aczone	Allergan	5% gel
Erythromycin	Akne-Mycin	Valeant Various generic manufacturers	2% ointment
Sodium sulfacetamide	Klaron	Dermik	10% suspension
Sodium sulfacetamide/sulfur	Avar LS	Tiber	10%-2% cleanser
	Avar-E LS	Tiber	10%-2% cream
	Cerisa	Stratus	10%-1% cleanser
	Clarifoam EF	Onset Therapeutics	10%-5% foam
	Rosac	Stiefel	10%-1% cleanser 10%-5% cream
	Plexion	Medicis	10%-5% med. pad, cream
	Prascion	Prasco Various generic manufacturers	10%-5% med. pad, cream
Tazarotene	Tazorac	Allergan	0.05% gel, cream 0.1% gel, cream
Tretinoin	Atralin	Valeant	0.05% gel

Generic Name	Brand Name	Manufacturer	Availability
	Avita Retin-A Micro  Retin-A	Mylan Ortho  Ortho  Various generic manufacturers	0.025% gel, cream 0.04% gel 0.1% gel 0.01% gel 0.025% cream, gel 0.05% cream 0.01% cream
Clindamycin/tretinoin	Veltin Ziana	Stiefel Medicis	1.2-0.025% gel 1.2-0.025% gel

## II. Indications

All products included in this review are indicated for the topical treatment of acne vulgaris. Some of the products have additional indications of plaque psoriasis, acne rosacea and seborrheic dermatitis.

## III. Guidelines

The American Academy of Dermatology updated guidelines for the management of acne vulgaris in 2007.

- Topical therapy is a standard of care in acne treatment.
- Topical retinoids are important in acne treatment.
- Benzoyl peroxide and combinations with erythromycin and clindamycin are effective acne treatments.
- Topical antibiotics are effective acne treatments. However, the use of these agents along can be associated with the development of bacterial resistance.
- Salicylic acid is moderately effective in the treatment of acne.
- Azelaic acid has been shown to be effective in clinical trials, but its clinical use, compared to other agents, has limited efficacy according to experts.
- Data from peer-reviewed literature regarding the efficacy of sulfur, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc are limited.
- Employing multiple topical agents that affect different aspects of acne pathogenesis can be useful. However, it is the opinion of the work group that such agents not be applied simultaneously unless they are known to be compatible.

## IV. Pharmacology

- Adapalene: Adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene may normalize the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

- Azelaic acid: The exact mechanism of action of azelaic acid is not known. Azelaic acid has been shown to possess antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. The antimicrobial action may be attributable to inhibition of microbial cellular protein synthesis. A normalization of keratinization leading to an anticomedonal effect of azelaic acid may also contribute to its clinical activity. Electron microscopic and immunohistochemical evaluation of skin biopsies from human subjects treated with azelaic acid demonstrated a reduction in the thickness of the stratum corneum, a reduction in number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin (a protein component of keratohyalin) in epidermal layers. This is suggestive of the ability to decrease microcomedone formation.
- Benzoyl peroxide: Benzoyl peroxide is an antibacterial agent and has been shown to be effective against *Propionibacterium acnes*, an anaerobe found in sebaceous follicles and comedones. The antibacterial action of benzoylperoxide is believed to be due to the release of active oxygen, it also has a keratolytic and desquamative effect, which may also contribute to its efficacy. When benzoyl peroxide is applied to the skin, it is absorbed and converted to benzoic acid. It is available in combination with other agents such as antibiotics and sulfur, which contributes a mild keratolytic action. Salicylic acid causes desquamation of hyperkeratotic epithelium.
- Dapsone: The exact mechanism of action of dapsone in the treatment of acne vulgaris is unknown, but in vitro studies suggest that it may suppress neutrophil recruitment oxidation, which may help prevent the production of toxic respiratory and secretory products. It may also have antimicrobial activity.
- Erythromycin/Clindamycin: Erythromycin and clindamycin are antibiotics that reduce lesions of acne vulgaris in part due to the antibacterial activity; however, the exact mechanism is not fully known. Erythromycin and clindamycin act by inhibition of protein synthesis in susceptible organisms by reversibly binding to 50 S ribosomal subunits, thereby inhibiting translocation of aminoacyl transfer-RNA and inhibiting polypeptide synthesis. Antagonism has been demonstrated in vitro between erythromycin, lincomycin, chloramphenicol, and clindamycin.
- Sodium sulfacetamide: Sulfonamides act as a competitive inhibitor of para-aminobenzoic acid (PABA) utilization, an essential component for bacterial growth.
- Tazarotene: A retinoid prodrug that, when activated, has antihyperproliferative, differentiation normalizing, and anti-inflammatory effects. The exact mechanism of action is unknown. Tretinoin, another retinoid, works by decreasing cohesiveness of follicular epithelial cells and decreasing microcomedone

formation. It may also stimulate mitotic activity and increase turnover of follicular epithelial cells, causing extrusion of the comedones.

- Tretinoin: Decreases cohesiveness and stimulates mitotic activity and turnover of follicular epithelial cells, resulting in decreased formation and increased extrusion of comedones.

## V. Pharmacokinetics

Clindamycin is only one percent available systemically when administered topically. The low levels seen in the plasma are excreted unchanged in the urine.

Topically administered erythromycin is not detectable in the plasma.

Less than two percent of benzoyl peroxide is absorbed in the systemic circulation. Due to the lipophilic nature, benzoyl peroxide concentrates in the lipid-rich sebaceous follicles. The small amount that is systemically absorbed is converted to benzoic acid, which is further metabolized to benzoate. Benzoate is then excreted in the urine.

The systemic exposure to dapsone 5% gel versus oral dapsone 100 mg was studied for 14 days. The results indicated that twice daily topical application of the agent leads to less systemic exposure to the drug than the 100 mg once daily oral administration of the drug. Patients applying the drug topically had approximately 100-times less exposure to the active drug, as measured by the area-under-the curve (AUC), than patients taking the drug orally.

Tazarotene is converted by ester hydrolysis to its active metabolite, tazarotenic acid. There is little parent compound absorbed in the plasma, and the small amount is highly plasma protein-bound. Tazarotenic acid is eliminated by the urinary and fecal routes. Its half-life is about 18 hours.

Tretinoin has only been found in trace amounts in plasma when applied topically. It is a metabolite of Vitamin A.

Sulfacetamide is approximately four percent bioavailable and is excreted in the urine unchanged. The half-life of sulfacetamide varies between seven and 13 hours. Absorption through intact skin has not been determined for sodium sulfacetamide. Approximately one percent of topical sulfur is systemically absorbed.

Pharmacokinetic studies with adapalene and the combination product with benzoyl peroxide have only found trace amounts of adapalene in plasma when administered topically. Excretion is primarily by the biliary route. Azelaic acid is approximately four percent bioavailable, and any absorbed drug is excreted unchanged in the urine. Its half-life is about 12 hours.

## **VI. Contraindications/Warnings**

Products containing clindamycin or erythromycin are contraindicated in patients with a history of regional enteritis, ulcerative colitis, or antibiotic-associated colitis.

Sulfacetamide is contraindicated in patients with hypersensitivity to sulfonamides.

Sodium sulfacetamide/sulfur is not to be used by patients with kidney disease.

Tazarotene is contraindicated in pregnant women or women who may become pregnant. Do not use retinoids on eczematous skin, as they may cause severe irritation.

Some glucose-6-phosphate dehydrogenase (G6PD) deficient patients using dapsone gel developed laboratory changes suggestive of mild hemolysis. Medication should be discontinued if suggestive signs and symptoms of hemolytic anemia occur. Topical administration of dapsone gel did not demonstrate peripheral neuropathy or skin reactions as reported with oral administration.

For patients using adapalene, tretinoin, or benzoyl peroxide-containing products, excessive or prolonged exposure to sunlight should be limited. Patients taking other photosensitizing medications should use additional caution. Weather extremes such as wind or cold may also be irritating. Patients should use caution to avoid contamination of hair, fabrics, and carpet with benzoyl peroxide products as bleaching and/or discoloration may result.

Erythema, scaling, dryness, and stinging/burning may be experienced with the use of adapalene/benzoyl peroxide gel. These reactions are most likely to occur during the first four weeks of treatment. Reactions are generally mild to moderate in intensity and typically lessen with continued use. Depending upon severity, patients should be advised to use a moisturizer and/or reduce the frequency of application. Adapalene/benzoyl peroxide gel should not be applied to cuts, abrasions, eczematous or sunburned skin. As with other retinoids, the use of 'waxing' as a depilatory method should be avoided on skin surfaces treated with adapalene/benzoyl peroxide gel.

Pseudomembranous colitis has been reported with bacterial agents such as clindamycin and erythromycin, ranging in severity from mild to life-threatening, when administered orally or parenterally. Absorption of these antibiotics through the skin is minimal, however.

Concomitant topical acne treatment, as well as cosmetic products with drying effects, should be used with caution, as possible cumulative irritancy may occur.

During the early weeks of therapy, apparent exacerbations of acne may occur. This is caused by the product's action on previously unseen lesions and should not be viewed as a reason to discontinue therapy.

Fatalities have rarely occurred due to severe reactions to sulfonamides such as sulfacetamide. Sulfacetamide also contains sodium metabisulfite, which may cause allergic-type reactions in patients.

Azelaic acid can cause hypopigmentation.

Contact with eyes, eyelids, lips, and mucous membranes should be avoided. Breaks in the skin should also not come into contact with these products.

Avoid fire, flame, and smoking following use of any gel; they are flammable.

Tretinoin gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish.

## **VII. Adverse Effects**

### **Adapalene**

*Gel:* Some adverse effects such as erythema, scaling, dryness, pruritus, and burning will occur in 10% to 40% of patients with adapalene gel. Pruritus or burning immediately after application also occurs in approximately 20% of patients with adapalene gel. The following additional adverse experiences were reported in 1% or less of patients: Skin irritation, burning/stinging, erythema, sunburn, and acne flares. These are most commonly seen during the first month of therapy and decrease in frequency and severity thereafter. All adverse effects with use of adapalene during clinical trials were reversible upon discontinuation of therapy.

*Cream:* Patients noted mild to moderate effects in the following: erythema (10-38%), scaling (6-35%), dryness (9-42%), persistent pruritis (4-21%), and burning/stinging (4-24%). Other reported local cutaneous adverse events in patients who used adapalene cream once daily included: sunburn (2%), skin discomfort-burning and stinging (1%), and skin irritation (1%).

### **Azelaic acid**

*Cream:* The most common adverse reactions occurring in approximately 1% to 5% of patients were pruritus, burning, stinging and tingling. Other adverse reactions such as erythema, dryness, rash, peeling, irritation, dermatitis, and contact dermatitis were reported in less than 1% of subjects. In patients using azelaic acid formulations, the following additional adverse reactions have been reported rarely: Worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

*Gel:* Patients using the gel formulation noted mild to moderate effects in the following: burning/stinging/tingling (9-20%), pruritis (4-7%), scaling/dry skin/xerosis (2-6%), and erythema/irritation (2%).

### **Benzoyl peroxide**

Adverse effects may include excessive drying manifested by marked peeling, erythema, possible edema, and allergic contact sensitization/dermatitis.

### **Clindamycin**

Cases of diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported as adverse reactions in patients treated with oral and parenteral formulations of clindamycin and, rarely, with topical clindamycin. Abdominal pain and GI disturbances, as well as gram-negative folliculitis, have been reported in association with the use of topical formulations of clindamycin.

### **Erythromycin**

Peeling, dryness, burning, itching, desquamation, erythema, and oiliness have been reported occasionally. Irritation of the eyes and tenderness of the skin have also been reported with the topical use of erythromycin. A generalized urticarial reaction, possibly related to the use of erythromycin, which required systemic steroid therapy has been reported.

*Gel:* In controlled clinical trials, the incidence of burning associated with erythromycin topical gel was approximately 25 percent.

*Ointment:* In clinical trials, there was one report of a possible contact sensitization, which could not be confirmed. There were isolated reports of skin irritation, such as erythema and peeling.

### **Sodium Sulfacetamide**

It has been reported that sodium sulfacetamide may cause local irritation or sensitization with long term therapy – if such irritation occurs, therapy should be discontinued. Sulfacetamide sodium occasionally may cause reddening and scaling of the skin.

### **Sulfur**

Contact sensitization reactions are associated with the use of topical benzoyl peroxide and sulfur products and may be expected to occur in 10 to 25 of 1000 patients. The most frequent adverse reactions associated with benzoyl peroxide and sulfur use are excessive erythema and peeling which may be expected to occur in five of 100 patients. Excessive erythema and peeling most frequently appear during the initial phase of drug use and may normally be controlled by reducing frequency of use.

### **Tazarotene**

*Gel:* Desquamation, burning/stinging, dry skin, erythema, pruritus (10% to 30%); irritation, skin pain, fissuring, localized edema, skin discoloration (1% to 10%).

*Cream:* Desquamation, dry skin, erythema, burning sensation (10% to 30%); pruritus, irritation, face pain, stinging (1% to 5%).

**Tretinoin**

Almost all patients reported 1 or more local reactions such as peeling, dry skin, burning, stinging, erythema, and pruritus during therapy with tretinoin. Sensitive skin may become excessively red, edematous, blistered, or crusted. If these effects occur, discontinue medication until skin integrity is restored or adjust to a tolerable level. True contact allergy is rare. Temporary hyperpigmentation or hypopigmentation has been reported with repeated application. Some individuals have a heightened susceptibility to sunlight while under treatment. All adverse effects have been reversible upon discontinuation.

## References

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South Dakota Medicaid			
Acne Agents, Topical			
05/01/10 - 04/30/11			
Label Name	Rx Num	Total Reimb Amt	Avg Cost Per Script
ACANYA GEL	50	\$8,712.24	\$174.24
ACANYA GEL PUMP	8	\$1,700.76	\$212.60
ACNECLEAR GEL	47	\$414.86	\$8.83
ACZONE 5% GEL	53	\$8,969.28	\$169.23
ADAPALENE 0.1% CREAM	101	\$18,582.78	\$183.99
ADAPALENE 0.1% GEL	204	\$32,425.24	\$158.95
ATRALIN 0.05% GEL	44	\$7,557.01	\$171.75
AVITA 0.025% CREAM	1	\$22.95	\$22.95
AZELEX 20% CREAM	94	\$15,034.38	\$159.94
BENPROX 5.25% WASH	23	\$1,427.00	\$62.04
BENZAC AC WASH 10% LIQUID	5	\$142.40	\$28.48
BENZAC AC WASH 5% LIQUID	11	\$1,283.79	\$116.71
BENZACLIN CAREKIT	11	\$1,864.77	\$169.52
BENZACLIN GEL	133	\$15,163.87	\$114.01
BENZACLIN GEL 35G PUMP	3	\$442.86	\$147.62
BENZACLIN GEL 50G PUMP	434	\$69,639.61	\$160.46
BENZAMYCINPAK GEL	34	\$4,185.88	\$123.11
BENZOYL PEROX 4% CREAMY WASH	35	\$1,243.78	\$35.54
BENZOYL PEROX 8% CREAMY WASH	18	\$391.53	\$21.75
BENZOYL PEROXIDE 10% GEL	85	\$2,151.41	\$25.31
BENZOYL PEROXIDE 10% WASH	154	\$4,084.07	\$26.52
BENZOYL PEROXIDE 2.5% GEL	22	\$441.77	\$20.08
BENZOYL PEROXIDE 2.5% WASH	8	\$228.15	\$28.52
BENZOYL PEROXIDE 4% LOTION	4	\$206.38	\$51.60
BENZOYL PEROXIDE 4% WASH KIT	19	\$973.99	\$51.26
BENZOYL PEROXIDE 4.5% CLEANSER	1	\$58.19	\$58.19
BENZOYL PEROXIDE 5% GEL	213	\$3,628.72	\$17.04
BENZOYL PEROXIDE 5% WASH	285	\$7,476.05	\$26.23
BENZOYL PEROXIDE 6.5% CLEANSER	1	\$58.18	\$58.18
BENZOYL PEROXIDE 8% WASH KIT	18	\$723.28	\$40.18
BP 7% WASH KIT	1	\$119.43	\$119.43
BPO 4% CREAMY WASH PACK	29	\$1,982.87	\$68.37
BPO 4% GEL	17	\$1,254.54	\$73.80
BPO 8% CREAMY WASH PACK	2	\$158.08	\$79.04
BPO 8% GEL	1	\$71.99	\$71.99
BREVOXYL-4 COMPLETE PACK	27	\$1,959.89	\$72.59
BREVOXYL-4 GEL	5	\$422.15	\$84.43
BREVOXYL-8 COMPLETE PACK	3	\$260.37	\$86.79
CLENIA EMOLLIENT CREAM	4	\$209.88	\$52.47
CLENIA FOAMING WASH	14	\$481.30	\$34.38
CLINDAGEL 1% GEL	7	\$100.00	\$14.29
CLINDAMYCIN PH 1% GEL	363	\$7,628.55	\$21.02
CLINDAMYCIN PH 1% SOLUTION	329	\$4,494.64	\$13.66

<b>South Dakota Medicaid</b>			
<b>Acne Agents, Topical</b>			
<b>05/01/10 - 04/30/11</b>			
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>	<b>Avg Cost Per Script</b>
CLINDAMYCIN PHOS 1% PLEDGET	191	\$6,821.50	\$35.71
CLINDAMYCIN PHOSP 1% LOTION	190	\$5,108.94	\$26.89
CLINDAMYCIN PHOSPHATE 1% FOAM	6	\$1,201.50	\$200.25
CLINDAMYCIN-BENZOYL PEROX GEL	525	\$72,644.18	\$138.37
DIFFERIN 0.1% CREAM	74	\$14,492.10	\$195.84
DIFFERIN 0.1% GEL	86	\$18,144.59	\$210.98
DIFFERIN 0.1% LOTION	17	\$3,403.02	\$200.18
DIFFERIN 0.3% GEL	190	\$35,542.18	\$187.06
DUAC CS CONVENIENCE KIT	221	\$34,122.34	\$154.40
EPIDUO GEL	223	\$44,457.96	\$199.36
ERY 2% PADS	35	\$2,206.27	\$63.04
ERYTHROMYCIN 2% GEL	89	\$1,655.11	\$18.60
ERYTHROMYCIN 2% PLEDGETS	1	\$64.75	\$64.75
ERYTHROMYCIN 2% SOLUTION	94	\$1,422.89	\$15.14
ERYTHROMYCIN-BENZOYL GEL	348	\$18,039.42	\$51.84
EVOCLIN 1% FOAM	6	\$1,251.26	\$208.54
LAVOCLEN-4 ACNE WASH KIT	23	\$1,283.24	\$55.79
LAVOCLEN-4 CREAMY WASH	43	\$1,305.56	\$30.36
LAVOCLEN-8 ACNE WASH KIT	12	\$597.00	\$49.75
LAVOCLEN-8 CREAMY WASH	16	\$348.16	\$21.76
NEOBENZ MICRO SD 5.5% CREAM	1	\$178.69	\$178.69
NEOBENZ MICRO WASH PLUS PACK	2	\$296.21	\$148.11
PR BENZOYL PEROXIDE 7% WASH	1	\$90.29	\$90.29
PRASCION CLEANSER	11	\$379.20	\$34.47
PRASCION RA CREAM	18	\$1,300.50	\$72.25
RE BENZOYL PEROXIDE 7% WASH	3	\$353.31	\$117.77
RETIN-A 0.025% GEL	1	\$8.44	\$8.44
RETIN-A MICRO 0.04% GEL	37	\$5,004.53	\$247.07
RETIN-A MICRO 0.1% GEL	62	\$9,814.19	\$158.29
RETIN-A MICRO PUMP 0.04% GEL	26	\$5,364.20	\$206.32
RETIN-A MICRO PUMP 0.1% GEL	24	\$3,736.97	\$155.71
ROSAC CREAM	3	\$207.75	\$69.25
ROSADERM CLEANSER	16	\$499.24	\$31.20
SOD SULFACETAMIDE-SULFUR LOTN	21	\$1,302.35	\$62.02
SODIUM SULF-SULFUR CLEANSER	12	\$422.75	\$35.23
SODIUM SULF-SULFUR WASH	4	\$161.36	\$40.34
TAZORAC 0.05% CREAM	37	\$5,163.17	\$139.55
TAZORAC 0.05% GEL	22	\$4,753.07	\$216.05
TAZORAC 0.1% CREAM	38	\$9,337.48	\$245.72
TAZORAC 0.1% GEL	29	\$5,701.06	\$196.59
TRETINOIN 0.01% GEL	81	\$4,670.00	\$57.65
TRETINOIN 0.025% CREAM	315	\$11,808.06	\$37.49
TRETINOIN 0.025% GEL	70	\$4,461.19	\$63.73

<b>South Dakota Medicaid</b>			
<b>Acne Agents, Topical</b>			
<b>05/01/10 - 04/30/11</b>			
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>	<b>Avg Cost Per Script</b>
TRETINOIN 0.05% CREAM	237	\$12,964.74	\$54.70
TRETINOIN 0.1% CREAM	45	\$1,800.16	\$40.00
VELTIN GEL	1	\$159.26	\$159.26
ZIANA GEL	4	\$1,474.48	\$368.62
2,681 recipients (1,618 have acne diagnosis)	6432	\$583,903.49	

<b>Top 25 Prescribers of Topical Acne Agents</b>		
<b>Specialty</b>	<b>Script Count</b>	<b>Claim Amounts</b>
FAMILY MEDICINE	544	\$62,182.42
DERMATOLOGY	813	\$83,114.09
INTERNAL MEDICINE	131	\$13,754.48
PSYCHIATRIST	206	\$18,871.11
PEDIATRICS	342	\$30,781.13

**South Dakota Medicaid  
Acne Agents, Topical  
Summary by Recipient Age**

Summary by Age			
Age	Recip Count	Rx Count	Total Dollars
0	10	13	\$517.12
1	36	38	\$2,880.56
2	39	41	\$4,100.15
3	49	56	\$7,029.94
4	36	42	\$4,218.07
5	38	40	\$4,214.17
6	19	21	\$2,613.32
7	13	15	\$1,740.54
8	25	29	\$3,662.82
9	27	36	\$4,932.01
10	23	31	\$4,043.54
11	31	62	\$7,063.34
12	67	124	\$13,147.40
13	146	304	\$25,324.50
14	226	574	\$54,797.15
15	289	731	\$62,991.14
16	337	1019	\$94,852.71
17	323	900	\$83,677.33
18	281	848	\$84,066.55
19	137	323	\$31,154.39
20	45	99	\$11,014.72
21	21	86	\$5,318.02
22	27	94	\$6,451.90
23	28	57	\$3,766.82
24	32	56	\$5,288.05
25	35	92	\$10,538.35
26	27	73	\$7,210.59
27	31	98	\$7,433.76
28	26	79	\$6,650.24
29	24	70	\$5,668.23
30	19	62	\$3,669.62
31	23	45	\$4,138.42

Summary by Age			
Age	Recip Count	Rx Count	Total Dollars
32	24	57	\$6,034.87
33	20	81	\$5,077.71
34	13	34	\$3,581.23
35	15	30	\$3,060.79
36	8	42	\$3,231.05
37	10	37	\$1,922.38
38	8	30	\$2,459.00
39	6	17	\$1,261.13
40	9	60	\$5,869.55
41	7	18	\$1,212.46
42	5	28	\$1,655.13
43	3	6	\$673.80
44	6	17	\$1,419.25
45	4	7	\$424.73
46	7	15	\$2,383.28
47	5	11	\$1,079.62
48	5	12	\$694.97
49	3	11	\$1,227.37
50	3	11	\$937.54
51	4	52	\$4,141.27
52	6	20	\$2,631.53
53	1	2	\$372.97
54	1	2	\$36.50
55	2	3	\$330.45
56	5	10	\$267.40
57	2	5	\$769.11
58	1	11	\$794.75
59	1	1	\$228.58
60	2	8	\$598.69
61	3	7	\$439.35
62	1	1	\$10.75
64	1	3	\$63.15

**South Dakota Medicaid  
P&T Meeting  
Gralise® Review**

**I. Overview**

Gralise is a once-daily gabapentin approved for the management of postherpetic neuralgia (PHN).

**II. Dosage and Administration**

Gralise should be titrated to an 1800 mg dose taken orally, once-daily, with the evening meal.

Gralise recommended Titration Schedule

	<b>Day 1</b>	<b>Day 2</b>	<b>Days 3-6</b>	<b>Days 7-10</b>	<b>Days 11-14</b>	<b>Day 15</b>
Daily Dose	300 mg	600 mg	900 mg	1200 mg	1500 mg	1800 mg

**III. Warnings/Precautions**

- Gralise has differing pharmacokinetic profiles from gabapentin that affects the frequency of administration.
- The safety and effectiveness of Gralise in patients with epilepsy has not been studied.
- Antiepileptic drugs, including gabapentin, the active ingredient in Gralise, increase the risk of suicidal thoughts or behavior.
- Increased seizure frequency may occur in patients with seizure disorders if Gralise is rapidly discontinued. Withdraw Gralise gradually over a minimum of 1 week.

**IV. Adverse Reactions**

The most common adverse reaction (greater than or equal to 5% and twice placebo) is dizziness.

**V. Drug Interactions**

- An increase in gabapentin AUC values have been reported when administered with hydrocodone.
- An increase in gabapentin AUC values have been reported when administered with morphine.
- An antacid containing aluminum hydroxide and magnesium hydroxide reduced the bioavailability of gabapentin immediate release by about approximately 20%, but by only 5% when gabapentin was taken 2 hours after antacids. It is recommended that Gralise be taken at least 2 hours following antacid administration.

## VI. Pharmacology/Pharmacokinetics

The mechanism of action by which gabapentin exerts its analgesic action is unknown but in animal models of analgesia, gabapentin prevents allodynia (pain-related behavior in response to a normally innocuous stimulus) and hyperalgesia (exaggerated response to painful stimuli). Gabapentin prevents pain-related responses in several models of neuropathic pain in rats and mice (e.g., spinal nerve ligation models, spinal cord injury model, acute herpes zoster infection model). Gabapentin also decreases pain-related responses after peripheral inflammation (carrageenan footpad test, late phase of formulin test), but does not alter immediate pain-related behaviors (rat tail flick test, formalin footpad acute phase). The relevance of these models to human pain is not known.

Gabapentin is absorbed from the proximal small bowel by a saturable L-amino transport system. Gabapentin bioavailability is not dose proportional; as the dose is increased, bioavailability decreases. Time to reach maximum plasma concentration for Gralise is 8 hours, which is about 4-6 hours longer compared to gabapentin immediate release.

**Table 5: Mean (SD) Steady-State Pharmacokinetics for GRALISE and Gabapentin Immediate Release in Plasma of Healthy Subjects (Day 5, n = 21)**

<b>Pharmacokinetic Parameters (Mean ± SD)</b>	<b>GRALISE 1800 mg QD</b>	<b>Gabapentin Immediate Release 600 mg TID</b>
<b>AUC<sub>0-24</sub> (ng • hr/mL)</b>	132,808 ± 34,701	141,301 ± 29,759
<b>C<sub>max</sub> (ng/mL)</b>	9,585 ± 2,326	8,536 ± 1,715
<b>C<sub>min</sub> (ng/mL)</b>	1,842 ± 654	2,588 ± 783
<b>T<sub>max</sub> (hr) median (range)</b>	8 (3-12)	2 (1-5)*

\*relative to most recent dose

Gabapentin is eliminated by renal excretion as unchanged drug. Dosage adjustment in patients with compromised renal function is necessary.

## VII. Gabapentin Utilization

<b>SD Medicaid Gabapentin Utilization</b>		
<b>05/01/10 - 04/30/11</b>		
<b>Label Name</b>	<b>Rx Num</b>	<b>Total Reimb Amt</b>
GABAPENTIN 100 MG CAPSULE	736	\$8,544.09
GABAPENTIN 300 MG CAPSULE	2023	\$31,765.10
GABAPENTIN 400 MG CAPSULE	246	\$4,596.75
GABAPENTIN 600 MG TABLET	945	\$24,393.86
GABAPENTIN 800 MG TABLET	200	\$5,988.83
<b>867 recipients</b>	<b>4150</b>	<b>\$75,288.63</b>

## References

1. Gralise<sup>®</sup> [prescribing information]. Menlo Park, CA. Depomed, Inc.; April 2011.

**South Dakota Medicaid  
P&T Meeting  
Dificid<sup>®</sup> Review**

**I. Overview**

Dificid is a new macrolide antibacterial drug indicated in adults for treatment of *Clostridium difficile*-associated diarrhea.

**II. Dosage and Administration**

The recommended dose is one 200mg tablet orally twice daily for 10 days with or without food. A ten-day regimen costs approximately \$3,000.

**III. Warnings/Precautions**

- **Not for Systemic Infections**: Since there is minimal systemic absorption of fidaxomicin, Dificid is not effective for treatment of systemic infections.
- **Development of Drug Resistant Bacteria**: Only use Dificid for infection proven or strongly suspected to be caused by *C. difficile*.

**IV. Adverse Reactions**

The most common adverse reactions are nausea (11%), vomiting (7%), abdominal pain (6%), gastrointestinal hemorrhage (4%), anemia (2%), and neutropenia (2%).

**V. Drug Interactions**

Fidaxomicin and its main metabolite, OP-1118, are substrates of the efflux transporter, P-glycoprotein (P-gp), which is expressed in the gastrointestinal tract. Cyclosporine is an inhibitor of P-gp, however, concomitant P-gp inhibitor use had no attributable effect on safety or treatment outcome of fidaxomicin-treated patients in controlled clinical trials.

**VI. Pharmacology/Pharmacokinetics**

Fidaxomicin is bactericidal against *C. difficile* in vitro, inhibiting RNA synthesis by RNA polymerases. Fidaxomicin acts locally in the gastrointestinal tract on *C. difficile*. It has minimal systemic absorption following oral administration.

Fidaxomicin is primarily transformed by hydrolysis at the isobutyryl ester to form its main and microbiologically active metabolite, OP-1118. Metabolism of fidaxomicin and formation of OP-1118 are not dependent on cytochrome P450 enzymes. At the therapeutic dose, OP-1118 was the predominant circulating compound in healthy adults, followed by fidaxomicin.

**VII. Treatment Regimens for *Clostridium difficile* Infections**

<b>Infection Characteristics</b>	<b>Clinical Status</b>	<b>Treatment Regimen</b>
Initial episode Mild to moderate severity	WBC 15,000 cells/mcL or lower <b>AND</b> SCr less than 1.5 times baseline	Metronidazole 500mg PO tid for 10 to 14 days
Initial episode Severe	WBC 15,000 cells/mcL or greater <b>OR</b> SCr 1.5 times or greater versus baseline	Vancomycin 125mg PO qid for 10 to 14 days
Initial episode Severe, complicated	WBC 15,000 cells/mcL or greater <b>OR</b> SCr 1.5 times or greater versus baseline with hypotension/shock, ileus, megacolon	Vancomycin 500 mg PO/NG qid x 10 to 14 days PLUS metronidazole 500 mg IV q8h If ileus, consider adding rectal vancomycin
First recurrence	-	Same regimen as first episode
Second recurrence	-	Oral vancomycin in tapered regimen

## References

1. Difucid<sup>®</sup> [prescribing information]. San Diego, CA. Optimer Pharmaceuticals, Inc.; May 2011.
2. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infections Diseases Society of America (IDSA). Accessed online July 2011 at [www.idsociety.org](http://www.idsociety.org).