

South Dakota Department of Social Services

Medicaid P&T Committee Meeting

December 9, 2011

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

STATE OF SOUTH DAKOTA
OFFICE OF THE GOVERNOR
EXECUTIVE ORDER 2011-23

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 Medicaid Program under the provisions of SDCL 28-6; and,

WHEREAS, The number of eligibles for the Medicaid 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 ensure beneficiaries have access to medically necessary medication 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 Medicaid 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.

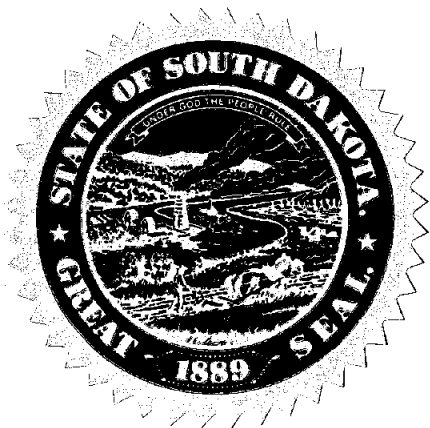
Section 9. The South Dakota Medicaid P & T Committee shall be administered by the South Dakota Department of Social Services.


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.

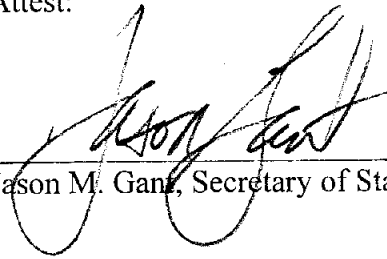
Section 12. Executive Order 2005-09 is hereby rescinded.

Dated in Pierre, South Dakota, this Twenty-fourth day of October, 2011.




Dennis Dugaard, Governor

Attest:


Jason M. Ganz, Secretary of State



DEPARTMENT OF SOCIAL SERVICES

MEDICAL SERVICES

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Pierre, South Dakota 57501-2291

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

Friday, December 9, 2011

1:00 – 3:00 PM

DDN Locations:

Sioux Falls

University Center

Room FADM253

4801 North 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

Medications used to treat Hepatitis C

New Business

Medications used to treat ADHD

Juvisync

Narrow Therapeutic Index Drugs

New Oral Anticoagulants (Pradaxa, Xarelto, etc.)

ODT Preparations

Oral Presentations and Comments by Manufacturers' Representatives

Next Meeting Date/Adjournment

**Minutes of the September 9, 2011
Pharmacy & Therapeutics (P&T) Committee Meeting
SD Department of Social Services, Medical Services Division**

Members present

Rick Holm, MD, Debra Farver, PharmD; Dana Darger, RPh

Members absent

Timothy Soundy, MD; Bill Ladwig, RPh; James Engelbrecht, MD

DSS staff present

Mike Jockheck, RPh

HID staff present

Candace Rieth, PharmD

Administrative Business

The P&T meeting was called to order by R. Holm at approximately 1:08pm. The minutes of the June 10, 2011 meeting were presented. D. Farver made a motion to approve. R. Holm 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 June 2011. There were a total of 1,838 PAs processed in the month of June, with 96.95% of those requests responded to in less than 8 hours. There were 1,395 (85%) requests received electronically and 242 (15%) 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 04/01/2011 – 06/30/2011. The top five classes were antipsychotics, cerebral stimulants, amphetamines, adrenals, and antidepressants. The top 15 therapeutic classes make up 40.51% 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 13.31% of total claims. D. Farver made a suggestion that the P&T committee review medications used to treat ADHD at the next meeting. This item will be added to the agenda for December.

Ophthalmic Antihistamine Review

The committee placed ophthalmic antihistamines on prior authorization at the March meeting. C. Rieth presented the prior authorization form. E. Byrnes, representing Alcon, spoke regarding Patanol and Pataday. A motion was made by D. Farver to add Patanol to the list of ophthalmic antihistamines that require a prior authorization. R. Holm seconded the motion. The motion was approved unanimously.

Less Sedating Antihistamines

The committee asked that less sedating antihistamines be reviewed with recent changes in the class; Allegra gaining OTC status. There was no public comment. A motion was made by D. Farver to place all OTC antihistamines on prior authorization for recipients 18 years of age and older and to place chewable antihistamines on prior authorization for recipients under the age of 18. R. Holm seconded the motion. The motion was approved unanimously.

Colcrys Review

A recommendation was made at the June meeting to review Colcrys and include colchicine data. This topic was tabled.

Medications used to treat RLS Review

C. Rieth presented clinical information for medications used to treat RLS. B. Felt, representing GSK, spoke regarding Horizant. A motion was made by D. Farver to place Horizant on prior authorization with criteria including 1) diagnosis 2) quantity limit of 600mg per day and 3) failure on other agents. A bullet point should be added to the form that gabapentin and benzodiazepines do not require a prior authorization. R. Holm seconded the motion. The motion passed unanimously.

Nexiclon Review

C. Rieth presented clinical information for Nexiclon. There was no public comment. D. Farver made a motion to place Nexiclon on prior authorization with failure of clonidine as the criteria for coverage. R. Holm seconded the motion. The motion passed unanimously.

Medications used to treat Hepatitis C Review

C. Rieth presented clinical information for medications used to treat Hepatitis C. C. Gillespie, representing Merck, spoke regarding Victrelis. L. Borland, representing Vertex, spoke regarding Incivek. A motion was made by D. Farver to place Incivek and Victrelis on prior authorization with criteria including 1) verification of triple therapy and 2) genotype 1. R. Holm seconded the motion. The motion passed unanimously. A prior authorization form will be brought to the December meeting for board approval.

Topical Acne Agents Review

C. Rieth presented clinical information for topical acne agents. There was no public comment. A motion was made by D. Farver to place topical acne agents on prior authorization with criteria including failure of generic acne agents. R. Holm seconded the motion. The motion passed unanimously.

Gralise Review

C. Rieth presented clinical information for Gralise. There was no public comment. A motion was made by R. Holm to place Gralise on prior authorization with criteria including 1) failure of gabapentin and 2) trial to last 3 months. The motion was seconded by D. Farver. The motion passed unanimously.

Dificid Review

C. Rieth presented clinical information for Dificid. There was no public comment. A motion was made by D. Farver to place Dificid on prior authorization with criteria including failure of Vancomycin. R. Holm seconded the motion. The motion passed unanimously.

The next meeting date is scheduled for December 9, 2011. The location will be updated on the website as soon as possible. A motion was made by R. Holm at 2:50pm to adjourn the SD Medicaid P&T meeting. D. Farver seconded the motion. Motion passed unanimously and the meeting was adjourned.



**South Dakota Medicaid
Monthly Prior Authorization Report
October 1, 2011 – October 31, 2011**

Time Ratio

Total PAs	Response Under 8 Hours	Response Over 8 Hours	% Under 8 Hours	% Over 8 Hours
1,783	1,756	27	98.49%	1.51%

By Form Type

Form Type	Description	Approve	Deny
ADP	Antidepressant	74	124
AFX	Amrix and Fexmid	0	3
ALT	Altabax	0	1
AMB	Ambien CR	7	22
ANF	Anti-Infectives(anti-biotic)	0	1
ANT	Antihistamines	20	76
APS	Antipsychotic	11	29
ARB	ARBS	14	17
DAW	Dispense As Written	17	49
GIA	Gastrointestinal Agents	1	1
GRH	Growth Hormone	10	10
HLM	Head Lice Medication	41	99
MAX	Max Units Override	65	815
NAR	Name Brand Narcotics	3	9
NUC	Opioids	3	29
PPI	Proton Pump Inhibitors	50	97
QUA	Quaaluaquin	0	1
STI	Stimulants	7	19
SUB	Suboxone/Subutex	4	6
TIM	Targeted Immune Modulators	1	4
TRP	Triptans	4	2
ULT	Ultram ER	4	30
XOI	Xanthine Oxidase Inhibitor	1	1
XOL	Xolair	1	0
Totals		338	1445



**South Dakota Medicaid
Monthly Prior Authorization Report
October 1, 2011 – October 31, 2011**

By Request Type

10/01/11 - 10/31/11	# of Requests	Electronic Requests		Faxed Requests	
		#	%	#	%
Prior Authorizations:					
Antidepressant	198	166	84%	32	16%
Amrix and Fexmid	3	2	67%	1	33%
Altabax	1	1	100%	0	0%
Ambien CR	29	22	76%	7	24%
Anti-Infectives(anti-biotic)	1	1	100%	0	0%
Antihistamines	96	79	82%	17	18%
Antipsychotic	40	29	73%	11	28%
ARBS	31	24	77%	7	23%
Dispense As Written	66	48	73%	18	27%
Gastrointestinal Agents	2	1	50%	1	50%
Growth Hormone	20	6	30%	14	70%
Head Lice Medication	140	87	62%	53	38%
Max Units Override	880	822	93%	58	7%
Name Brand Narcotics	12	9	75%	3	25%
Opioids	32	24	75%	8	25%
Proton Pump Inhibitors	147	110	75%	37	25%
Qalakin	1	1	100%	0	0%
Stimulants	26	17	65%	9	35%
Suboxone/Subutex	10	4	40%	6	60%
Targeted Immune Modulators	5	5	100%	0	0%
Triptans	6	5	83%	1	17%
Ultram ER	34	31	91%	3	9%
Xanthine Oxidase Inhibitor	2	1	50%	1	50%
Xolair	1	0	0%	1	100%
Prior Authorization Totals	1,783	1,495	84%	288	16%



**South Dakota Medicaid
Monthly Prior Authorization Report
October 1, 2011 – October 31, 2011**

Electronic PAs (unique)

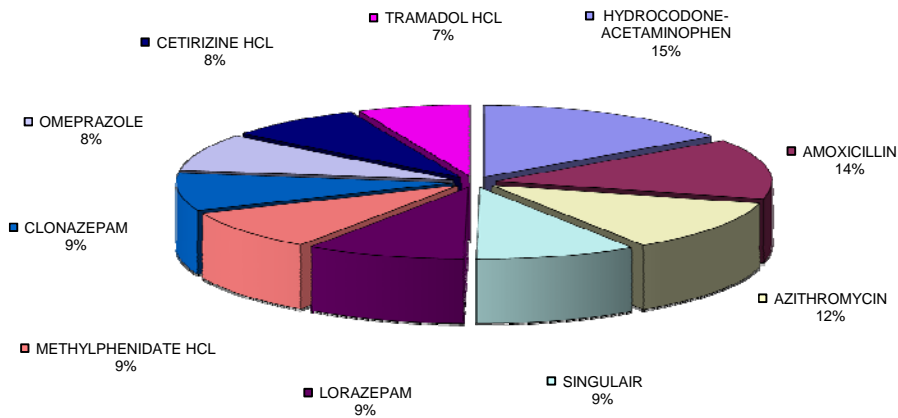
10/01/11 - 10/31/11	# Unique Approved	# Unique Denied	# Unique Incomplete	Unique Total	Approval %	Total Transactions
Prior Authorizations:						
Antidepressant	49	109	0	158	0.31	166
Amrix and Fexmid	0	2	0	2	0	2
Altabax	0	1	0	1	0	1
Ambien CR	1	21	0	22	0.045	22
Anti-Infectives(antibiotic)	0	1	0	1	0.00%	1
Antihistamines	10	67	0	77	13.00%	79
Antipsychotic	2	27	0	29	6.90%	29
ARBS	8	16	0	24	33.30%	24
Dispense As Written	0	48	0	48	0.00%	48
Gastrointestinal Agents	0	1	0	1	0.00%	1
Growth Hormone	0	5	0	5	0.00%	6
Head Lice Medication	0	82	0	82	0.00%	87
Max Units Override	22	766	0	788	2.80%	822
Name Brand Narcotics	0	9	0	9	0.00%	9
Opioids	1	23	0	24	4.20%	24
Proton Pump Inhibitors	21	82	0	103	20.40%	110
Qualaquin	0	1	0	1	0.00%	1
Stimulants	1	16	0	17	5.90%	17
Suboxone/Subutex	0	4	0	4	0.00%	4
Targeted Immune Modulators	1	4	0	5	20.00%	5
Triptans	3	2	0	5	60.00%	5
Ultram ER	1	29	0	30	3.30%	31
Xanthine Oxidase Inhibitor	0	1	0	1	0.00%	1
Prior Authorization Totals:	120	1317	0	1437	8.40%	1495

TOP 25 DRUGS BASED ON NUMBER OF CLAIMS FROM 07/01/2011 - 09/30/2011

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
HYDROCODONE-ACETAMINOPHEN	OPIATE AGONISTS	6,323	\$ 72,306.74	\$ 11.44	3.07%
AMOXICILLIN	PENICILLINS	5,612	\$ 52,433.24	\$ 9.34	2.72%
AZITHROMYCIN	MACROLIDES	4,823	\$ 82,051.46	\$ 17.01	2.34%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,885	\$ 525,891.61	\$ 135.36	1.89%
LORAZEPAM	BENZODIAZEPINES (ANXIOLYTIC, SEDATIV/HYP)	3,828	\$ 32,248.13	\$ 8.42	1.86%
METHYLPHENIDATE HCL	ANOREX., RESPIR., CEREBRAL STIMULANTS, MISC	3,758	\$ 587,401.51	\$ 156.31	1.82%
CLONAZEPAM	BENZODIAZEPINES (ANTICONVULSANTS)	3,479	\$ 28,950.77	\$ 8.32	1.69%
OMEPRAZOLE	PROTON-PUMP INHIBITORS	3,444	\$ 57,527.37	\$ 16.70	1.67%
CETIRIZINE HCL	SECOND GENERATION ANTIHISTAMINES	3,262	\$ 60,846.98	\$ 18.65	1.58%
TRAMADOL HCL	OPIATE AGONISTS	2,684	\$ 29,432.15	\$ 10.97	1.30%
CEPHALEXIN	CEPHALOSPORINS	2,582	\$ 31,545.97	\$ 12.22	1.25%
SULFAMETHOXAZOLE-TRIMETHOPRIM	SULFONAMIDES (SYSTEMIC)	2,504	\$ 22,030.87	\$ 8.80	1.22%
FLUOXETINE HCL	ANTIDEPRESSANTS	2,424	\$ 20,861.99	\$ 8.61	1.18%
LEVOTHYROXINE SODIUM	THYROID AGENTS	2,399	\$ 21,173.66	\$ 8.83	1.16%
SERTRALINE HCL	ANTIDEPRESSANTS	2,268	\$ 19,674.31	\$ 8.67	1.10%
LORATADINE	SECOND GENERATION ANTIHISTAMINES	2,195	\$ 15,442.30	\$ 7.04	1.07%
TRAZODONE HCL	ANTIDEPRESSANTS	2,122	\$ 14,649.97	\$ 6.90	1.03%
VYVANSE	AMPHETAMINES	2,122	\$ 296,322.05	\$ 139.64	1.03%
VENTOLIN HFA	BETA-ADRENERGIC AGONISTS	2,112	\$ 80,691.66	\$ 38.21	1.02%
CITALOPRAM HBR	ANTIDEPRESSANTS	1,953	\$ 12,255.91	\$ 6.28	0.95%
LISINAPRIL	ANGIOTENSIN-CONVERTING ENZYME INHIBITORS	1,908	\$ 12,243.44	\$ 6.42	0.93%
ALBUTEROL SULFATE	BETA-ADRENERGIC AGONISTS	1,797	\$ 28,184.14	\$ 15.68	0.87%
AMOX TR-POTASSIUM CLAVULANATE	PENICILLINS	1,749	\$ 48,816.14	\$ 27.91	0.85%
RISPERIDONE	ANTIPSYCHOTIC AGENTS	1,718	\$ 27,962.14	\$ 16.28	0.83%
IBUPROFEN	NONSTEROIDAL ANTI-INFLAMMATORY AGENTS	1,689	\$ 9,915.45	\$ 5.87	0.82%
TOTAL TOP 25		72,640	\$ 2,190,859.96	\$ 30.16	35.25%

Total Rx Claims From 07/01/2011 - 09/30/2011	206,063
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Top 10 Drugs
Based on Number of Claims

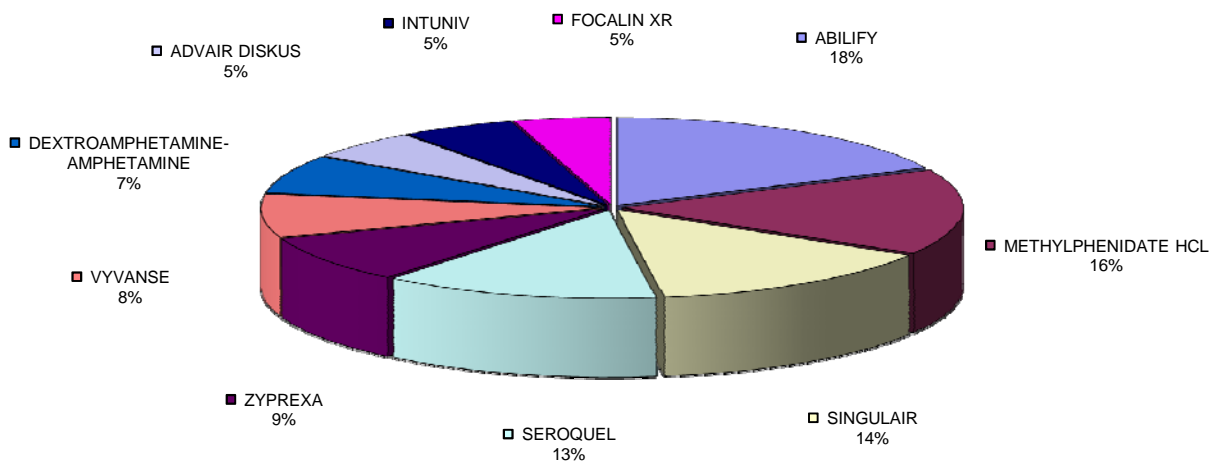


TOP 25 DRUGS BASED ON TOTAL CLAIMS COST FROM 07/01/2011 - 09/30/2011

Drug	AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ABILIFY	ANTIPSYCHOTIC AGENTS	1,449	\$ 668,339.75	\$ 461.24	0.70%
METHYLPHENIDATE HCL	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	3,758	\$ 587,401.51	\$ 156.31	1.82%
SINGULAIR	LEUKOTRIENE MODIFIERS	3,885	\$ 525,891.61	\$ 135.36	1.89%
SEROQUEL	ANTIPSYCHOTIC AGENTS	1,496	\$ 487,445.61	\$ 325.83	0.73%
ZYPREXA	ANTIPSYCHOTIC AGENTS	441	\$ 323,356.50	\$ 733.23	0.21%
VYVANSE	AMPHETAMINES	2,122	\$ 296,322.05	\$ 139.64	1.03%
DEXTROAMPHETAMINE-AMPHETAMINE	AMPHETAMINES	1,536	\$ 263,427.49	\$ 171.50	0.75%
ADVAIR DISKUS	ADRENALS	975	\$ 202,956.11	\$ 208.16	0.47%
INTUNIV	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	1,316	\$ 200,576.69	\$ 152.41	0.64%
FOCALIN XR	ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	1,035	\$ 171,279.98	\$ 165.49	0.50%
STRATTERA	CENTRAL NERVOUS SYSTEM AGENTS, MISC.	963	\$ 163,374.36	\$ 169.65	0.47%
LANSOPRAZOLE	PROTON-PUMP INHIBITORS	1,420	\$ 145,117.26	\$ 102.20	0.69%
CYMBALTA	ANTIDEPRESSANTS	813	\$ 144,724.50	\$ 178.01	0.39%
OXYCONTIN	OPIATE AGONISTS	463	\$ 140,642.61	\$ 303.76	0.22%
INVEGA SUSTENNA	ANTIPSYCHOTIC AGENTS	112	\$ 138,050.55	\$ 1,232.59	0.05%
NOVOLOG	INSULINS	607	\$ 130,234.23	\$ 214.55	0.29%
PULMOZYME	ENZYMES	51	\$ 126,602.08	\$ 2,482.39	0.02%
GEODON	ANTIPSYCHOTIC AGENTS	310	\$ 125,904.18	\$ 406.14	0.15%
GENOTROPIN	PITUITARY	73	\$ 123,397.98	\$ 1,690.38	0.04%
ADDERALL XR	AMPHETAMINES	541	\$ 117,483.44	\$ 217.16	0.26%
FLOVENT HFA	ADRENALS	907	\$ 115,300.99	\$ 127.12	0.44%
LEXAPRO	ANTIDEPRESSANTS	1,005	\$ 106,860.72	\$ 106.33	0.49%
SEROQUEL XR	ANTIPSYCHOTIC AGENTS	281	\$ 105,845.81	\$ 376.68	0.14%
ONE TOUCH ULTRA TEST STRIP	DIABETES MELLITUS	726	\$ 103,659.95	\$ 142.78	0.35%
HELIXATE FS	HEMOSTATICS	3	\$ 101,582.82	\$ 33,860.94	0.00%
TOTAL TOP 25		26,288	\$ 5,615,778.78	\$ 213.63	12.76%

Total Rx Claims From 07/01/2011 - 09/30/2011	206,063
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Top 10 Drugs
Based on Total Claims Cost



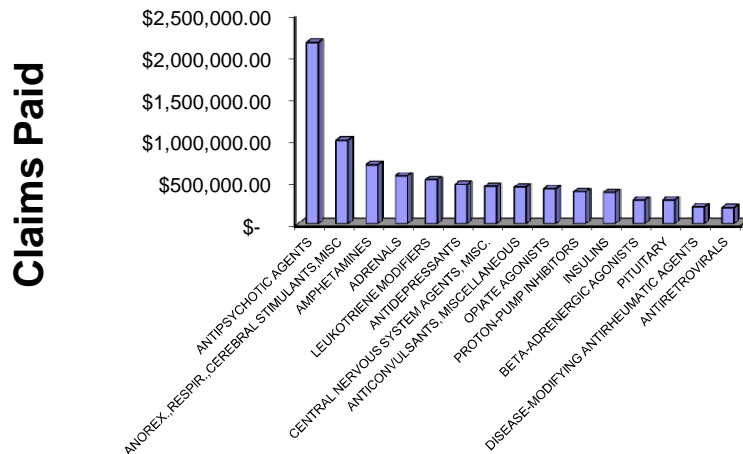
**SOUTH DAKOTA MEDICAID
Cost Management Analysis**

TOP 15 THERAPEUTIC CLASSES BY TOTAL COST OF CLAIMS FROM 07/01/2011 - 09/30/2011

AHFS Therapeutic Class	Rx	Paid	Paid/Rx	% Total Claims
ANTIPSYCHOTIC AGENTS	6,958	\$ 2,169,055.62	\$ 311.74	3.38%
ANOREX.,RESPIR.,CEREBRAL STIMULANTS,MISC	6,348	\$ 1,000,103.31	\$ 157.55	3.08%
AMPHETAMINES	4,892	\$ 706,029.35	\$ 144.32	2.37%
ADRENALS	5,996	\$ 573,599.23	\$ 95.66	2.91%
LEUKOTRIENE MODIFIERS	3,895	\$ 526,517.80	\$ 135.18	1.89%
ANTIDEPRESSANTS	15,511	\$ 470,758.14	\$ 30.35	7.53%
CENTRAL NERVOUS SYSTEM AGENTS, MISC.	2,339	\$ 448,486.92	\$ 191.74	1.14%
ANTICONSULSANTS, MISCELLANEOUS	7,447	\$ 441,091.45	\$ 59.23	3.61%
OPIATE AGONISTS	14,511	\$ 421,877.59	\$ 29.07	7.04%
PROTON-PUMP INHIBITORS	6,004	\$ 385,121.90	\$ 64.14	2.91%
INSULINS	2,043	\$ 375,343.03	\$ 183.72	0.99%
BETA-ADRENERGIC AGONISTS	6,327	\$ 283,972.04	\$ 44.88	3.07%
PITUITARY	553	\$ 283,577.89	\$ 512.80	0.27%
DISEASE-MODIFYING ANTIRHEUMATIC AGENTS	122	\$ 204,170.25	\$ 1,673.53	0.06%
ANTIRETROVIRALS	238	\$ 194,267.92	\$ 816.25	0.12%
TOTAL TOP 15	83,184	\$ 8,483,972.44	\$ 101.99	40.37%

Total Rx Claims From 07/01/2011 - 09/30/2011	206,063
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**Top 15 Therapeutic Classes
Based on Total Cost of Claims**



**South Dakota Department of Social Services
Pharmacotherapy Review
Medications for
Attention Deficit Hyperactivity Disorder (ADHD)
December 9, 2011**

I. Overview

ADHD is a severe, debilitating condition diagnosed in approximately 8.4% (5.2 million) of youth aged 3-17 years. Children with ADHD are usually diagnosed between the ages of 6 to 12. Suboptimal academic performance is often the reason for initial screening. A diagnosis of ADHD is subjective in nature, with the provider looking for symptoms of inattention, hyperactivity, and impulsivity: symptoms that are frequent and severe enough to interfere with the child's, and often the family's, ability to lead a normal life. These children, left undiagnosed or untreated, are at higher risk of self-injury, depression, low self-esteem, delinquent behavior, antisocial personality traits, substance abuse and other comorbidities.

Most medications for Attention Deficit Hyperactivity Disorder (ADHD) are CNS stimulants, which are thought to work by blocking reuptake of norepinephrine and dopamine in the presynaptic neurons and increasing release of these neurotransmitters into the extraneural space. There are three non-stimulant medications also approved to treat ADHD, atomoxetine (Strattera[®]), guanfacine (Intuniv[®]), and clonidine (Kapvay[®]). Strattera is classified as a norepinephrine reuptake inhibitor and works by selectively inhibiting presynaptic norepinephrine transporters. Intuniv is classified as a selective alpha_{2A}-adrenergic receptor agonist that reduces sympathetic nerve impulses to the heart and blood vessels resulting in a decrease in peripheral vascular resistance and a reduction in heart rate. Kapvay is a centrally acting alpha₂-adrenergic agonist.

Pharmacotherapy, along with behavior therapy and counseling, can help those patients diagnosed with ADHD lead a normal and productive life. For many years, CNS stimulants have been considered first-line therapy for the treatment of ADHD. With the approval of atomoxetine in late 2002, patients now have another treatment option.

II. Current Treatment Guidelines

American Academy of Pediatrics Clinical Practice Guideline: ADHD Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents (2011)

1. The primary care clinician should initiate an evaluation for ADHD for any child 4 through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.
2. To make a diagnosis of ADHD, the primary care clinician should determine that Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria have been met. Information should be obtained from parents, guardians, teachers, and other school and mental health clinicians.
3. In the evaluation of a child for ADHD, the primary care clinician should include assessment for other conditions that might coexist with ADHD, including emotional or behavioral, developmental, and physical conditions.
4. The primary care clinician should recognize ADHD as a chronic condition and, therefore, consider children and adolescents with ADHD as children and youth with special health care needs. Management of children and youth with special health care needs should follow the principles of the chronic care model and the medical home.
5. Recommendations for treatment of children and youth with ADHD vary depending on the patient's age:

- a. For preschool-aged children (4-5 years of age), the primary care clinician should prescribe evidence-based parent and/or teacher-administered behavior therapy as the first line of treatment and may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. In areas where evidence-based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment.
 - b. For elementary school-aged children (6-11 years of age), the primary care clinician should prescribe FDA approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine (in that order).
 - c. For adolescents (12-18 years of age), the primary care clinician should prescribe FDA approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both.
6. The primary care clinician should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.

**American Academy of Child and Adolescent Psychiatry (AACAP)
Practice Parameter for the Use of Stimulant Medication in the Treatment of Children,
Adolescents, and Adults (2007)**

- 1) The first agent tried should have FDA approval for the treatment of ADHD; possible agents would be dextroamphetamine, methylphenidate (MPH), mixed salts of amphetamine, and atomoxetine.
- 2) Stimulants have been proven in many clinical trials to be highly effective in the treatment of ADHD.
- 3) The physician may choose either MPH or amphetamines, as data suggests equal efficacy between the two stimulant types.
- 4) Longer-acting formulations may be used as initial treatment and are associated with greater compliance. Physicians do not need to initiate treatment with the short-acting forms, or use them to titrate to the appropriate dosage of the long-acting forms. Short-acting forms may be used to initiate therapy in low-weight children where long-acting forms may not be available in the necessary smaller doses.
- 5) Once a medication is initiated, the dose should be titrated up every 1 to 3 weeks until the maximum dose for the stimulant is reached, the symptoms of ADHD remit, or side effects prevent further titration.
- 6) It is recommended that the patient be in contact with the physician during the titration period and visit the physician after 1 month of therapy to assess effectiveness and determine long-term therapy plans.
- 7) Patients may show an initial response rate of up to 85% when both stimulant forms are tried versus the response rate of only 65%-75% observed in clinical trials when patients were treated with only one stimulant. Therefore, if a patient fails one stimulant, it is recommended that another be tried.
- 8) For the treatment of preschoolers, the available evidence suggests that titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of methylphenidate (MPH) in preschoolers.
- 9) In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants.
- 10) Atomoxetine may be used as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants.

III. Drug Treatment for ADHD

Generic Name	Brand Name	Available Strengths	Initial Dosage	Maximum Dosage
Amphetamines				
Amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate	Adderall, Adderall XR, various generics	5, 7.5, 10, 12.5, 15, 20, 30 mg tablet; 5, 10, 15, 20, 25, 30 mg extended-release capsule	Adderall: (3-5 years) 2.5mg once daily; (≥ 6 years) 5mg once or twice daily. Adderall XR: (6-17 years) 5-10 mg once daily; (≥ 18 years) 20 mg once daily.	Adderall: 40 mg/day in two or three divided doses. Adderall XR: (≥ 6 years) 30 mg once daily.
Dextroamphetamine	Dexedrine, Procentra, various generics	5, 10 mg tablet; 5, 10, 15 mg extended-release capsule; 5mg/ml solution	Dextroamphetamine IR: (3-5 years) 2.5 mg once daily; (≥ 6 years) 5 mg once or twice daily. Dextroamphetamine ER: (≥ 5 years) Total daily IR dosage given once daily. Procentra: (3-5 years) 2.5 mg once daily; (≥ 6 years) 5mg once or twice daily.	Dextroamphetamine IR: (3-5 years) 40 mg/kg/day; (≥ 6 years) 40 mg/day in two or three divided doses. Dextroamphetamine ER: (≥ 5 years) 45-60 mg once daily. Procentra: (3-5 years) 40 mg per day; (≥ 6 years) 40 mg per day.
Lisdexamfetamine	Vyvanse	20, 30, 40, 50, 60, 70 mg capsule	(≥ 6 years) 30 mg daily in the morning.	70 mg daily in the morning.
Methamphetamine	Desoxyn, generic	5 mg tablet	(≥ 6 years) 5 mg once or twice daily.	20-25 mg/day in two divided doses.
Non-amphetamines				
Dexmethylphenidate	Focalin, Focalin XR	2.5, 5, 10 mg tablet; 5, 10, 15, 20, 25, 30, 35, 40 mg extended-release capsule	Focalin: (≥ 6 years) 2.5 mg twice daily. Focalin XR: (6-17 years) 5 mg once daily; (≥ 18 years) 10 mg once daily.	Focalin: 10 mg twice daily. Focalin XR: (6-17 years) 30 mg/day; (≥ 18 years) 40 mg/day.
Methylphenidate	Concerta, Daytrana, Metadate CD, Metadate ER, Methylin, Ritalin, Ritalin LA, Ritalin SR	18, 27, 36, 54 mg extended-release tablet (osmotic release); 10, 15, 20, 30 mg/9 hr transdermal patch;	Concerta: (6-17 years) 18 mg once daily; (18-65) 18 or 36 mg once daily. Daytrana: (≥ 6 years) 10 mg patch worn nine hours daily.	Concerta: (6-12 years) 54 mg once daily; (13-65) 72 mg once daily. Daytrana: (≥ 6 years) 30 mg patch worn nine hours daily.

Generic Name	Brand Name	Available Strengths	Initial Dosage	Maximum Dosage
		10, 20, 30, 40, 50, 60 mg extended-release capsule; 10, 20 mg extended-release tablet; 2.5, 5, 10 mg chewable tablet; 5, 10 mg/5 ml solution; 5, 10, 20 mg tablet	Metadate CD: (≥ 6 years) 20 mg once daily. Methylin ER, Metadate ER, Ritalin SR: (≥ 6 years) 20-60 mg/day in one or two divided doses. Methylin, Ritalin: (≥ 6 years) 5 mg twice daily. Ritalin LA: (≥ 6 years) 20 mg once daily.	Metadate CD: (≥ 6 years) 60 mg once daily. Methylin ER, Metadate ER, Ritalin SR: (≥ 6 years) 60 mg/day in one or two divided doses. Methylin, Ritalin: 60 mg/day in two or three divided doses. Ritalin LA: (≥ 6 years) 60 mg once daily.
Non-Stimulants				
Atomoxetine	Strattera	10, 18, 25, 40, 60, 80, 100 mg capsule	≥ 6 years and ≤ 70 kg: 0.5 mg/kg/day in one or two divided doses. ≥ 6 years and ≥ 70 kg and adults: 40 mg/day in one or two divided doses.	≥ 6 years and ≤ 70 kg: 1.4 mg/kg/day in one or two divided doses. ≥ 6 years and ≥ 70 kg: 100mg/day given in one or two divided doses.
Clonidine	Kapvay	0.1 mg extended-release tablet	0.1 mg at bedtime	0.2 mg twice daily.
Guanfacine	Intuniv	1, 2, 3, 4 mg extended-release tablet	1 mg once daily.	4 mg daily.

IV. Contraindications

Amphetamines

- Advanced arteriosclerosis
- Symptomatic cardiovascular disease
- Moderate to severe hypertension
- Hyperthyroidism
- Known hypersensitivity or idiosyncrasy to the sympathomimetic amines
- Glaucoma
- Agitated states
- History of drug abuse
- During or within 14 days following administration of a monoamine oxidase inhibitor (MAOI)

Methylphenidate and Dexmethylphenidate

- Marked anxiety, tension, and agitation
- Glaucoma
- Patients with motor tics or a family history of diagnosis of Tourette syndrome

- During treatment with a MAOI and within a minimum of 14 days following discontinuation of an MAOI
- **Metadate CD, Metadate ER, and Methylin ER are contraindicated in patients with severe hypertension, angina pectoris, cardiac arrhythmias, heart failure, recent myocardial infarction (MI), hyperthyroidism or thyrotoxicosis.**

Atomoxetine

- Hypersensitivity to atomoxetine or other constituents of the product
- Narrow-angle glaucoma
- Use with a MAOI or within 2 weeks of discontinuing a MAOI
- Pheochromocytoma or a history of pheochromocytoma

Guanfacine ER

- Hypersensitivity to guanfacine or any components of the product

Clonidine ER

- Known hypersensitivity to clonidine

V. **Black Box Warnings**

Black Box Warning for Amphetamines

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse events.

Black Box Warning for Methylphenidate and Dexmethylphenidate

Methylphenidate and dexmethylphenidate should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Black Box Warning for Atomoxetine

Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Atomoxetine is approved for ADHD in pediatric and adult patients. Atomoxetine is not approved for major depressive disorder.

Pooled analyses of short-term (6 to 18 weeks) placebo-controlled trials in children and adolescents (a total of 12 trials involving over 2200 patients, including 11 trials in ADHD and 1 trial in enuresis) have revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1357 patients), compared to none in placebo-treated patients (851 patients). No suicides occurred in these trials.

VI. Warnings and Precautions

Amphetamines

- Cardiovascular effects
- CNS effects
- Drug dependence
- Growth inhibition
- Hypertension
- Potentially hazardous tasks
- Tics
- Seizures
- Fatigue
- Visual disturbance
- Tartrazine sensitivity

Methylphenidate and Dexmethylphenidate

- Serious cardiovascular effects
- Contact sensitization (transdermal)
- External heat (transdermal)
- Depression
- Fatigue
- Hypertension
- Long-term suppression of growth
- Psychiatric effects
- Seizures
- Visual disturbances
- GI obstruction (Concerta only)
- Phenylketonurics
- Agitation
- Drug abuse and dependence
- Carcinogenesis

Atomoxetine

- Suicidal ideation
- Hepatic effects
- Cardiovascular effects
- Emergence of new psychotic or manic symptoms
- Comorbid bipolar disorder
- Aggressive behavior or hostility
- Urinary effects
- Priapism
- Effects on growth
- Narrow-angle glaucoma
- Pheochromocytoma
- Hypersensitivity reactions
- Drug abuse and dependence
- Hazardous tasks

Guanfacine ER

- Cardiovascular effects
- Sedation
- Rebound
- Renal function impairment

- Hepatic function impairment
- Special risk patients (severe coronary insufficiency, recent MI, cerebrovascular disease, or chronic renal or hepatic failure)
- Hazardous tasks

Clonidine ER

- Withdrawal
- Cardiovascular effects
- Perioperative use
- CNS effects
- Hypersensitivity reactions
- Renal function impairment
- Special risk patients (severe coronary insufficiency, conduction disturbances, recent MI, cerebrovascular disease, or chronic renal failure)
- Hazardous tasks

VII. ADHD Medication Drug Interactions

Clinically important drug interactions exist for the ADHD medications with certain, important differences among the classes. Each of the medications in this class should be used cautiously with antihypertensives, tricyclic antidepressants, and MAO inhibitors (can result in hypertensive crisis).

Amphetamines

- Furazolidone: Increased sensitivity to amphetamines may occur-reduce amphetamine dose accordingly.
- GI acidifying agents (ascorbic acid, guanethidine, fruit juice) decrease absorption of amphetamines and urinary acidifiers (aluminum chloride) increase excretion of amphetamines.
- GI alkalinizers (sodium bicarb): Increase absorption of amphetamines and urinary alkalinizers (acetazolamide) decrease excretion of amphetamines.
- Chlorpromazine/haloperidol: Block dopamine/norepinephrine receptors decreasing effects of amphetamines.
- Lithium carbonate: Inhibits stimulatory effects of amphetamines.
- MAOIs: Coadministration contraindicated during or within 14 days following the administration of MAOI.
- Methenamine: Urinary excretion of amphetamines is increased, and efficacy is reduced by acidifying agents used in methenamine therapy.
- Phenothiazines: Pharmacologic effects of amphetamines and congeners may be diminished. Amphetamines may exacerbate psychotic symptoms. (chlorpromazine can be used to treat amphetamine poisoning)
- SSRIs: Increased sensitivity to effect of sympathomimetics and increased risk of serotonin syndrome may occur.
- Adrenergic blockers: Inhibited by amphetamines.
- Antihistamines: Amphetamines may counteract the sedative effects of antihistamines.
- Antihypertensive agents: Amphetamines may antagonize the hypotensive effects of antihypertensives.
- Ethosuximide: Amphetamines may delay intestinal absorption of ethosuximide.
- Meperidine: Activity is potentiated by amphetamines.
- Phenobarbital and phenytoin: May delay intestinal absorption of phenobarbital and phenytoin producing a synergistic anticonvulsant action.
- Tricyclic antidepressants: Amphetamines may enhance the activity of tricyclic antidepressants. Cardiovascular effects may be potentiated.

Methylphenidate and Dexmethylphenidate

- Antacids/Acid suppressants: Because the modified release characteristics of Ritalin LA are pH dependent, the coadministration of antacids or acid suppressants could alter the release of methylphenidate.
- MAOIs: Contraindicated during treatment and within 14 days following discontinuation of an MAOI.
- Anticonvulsants: Levels may be increased resulting in increased pharmacologic and toxic effects of anticonvulsants.
- Antidepressants: Coadministration may cause an increased serum concentration of the tricyclic antidepressants and SSRIs.
- Antihypertensives: Coadministration may cause decreased efficacy of antihypertensives.
- Clonidine: Serious adverse events have been noted with concomitant use.
- Coumarin anticoagulants: Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants.
- Vasopressor agents: Because of possible adverse effects upon blood pressure, use cautiously with pressor agents.
- Halogenated anesthetics/dexmethylphenidate: Coadministration may cause a sudden increase in blood pressure during surgery.

Atomoxetine

- CYP2D6 inhibitors: Concomitant use may increase atomoxetine steady state plasma concentrations.
- The effects of albuterol on heart rate and blood pressure may be potentiated by atomoxetine.
- MAOIs: Coadministration is contraindicated.
- Antihypertensive drugs and pressor agents: Possible effects on blood pressure.

Guanfacine ER

- CYP3A4/5 inhibitors (e.g., ketoconazole): Coadministration may increase rate and extent of guanfacine exposure.
- CYP3A4 inducers (e.g., rifampin): Coadministration may decrease rate and extent of guanfacine exposure.
- Valproic acid: Coadministration may increase serum valproic acid concentrations.
- Antihypertensive drugs
- CNS depressants

Clonidine ER

- Sedating drugs: Clonidine may potentiate the CNS-depressive effects of alcohol, barbiturates, or other sedating drugs.
- Tricyclic antidepressants: May reduce the hypotensive effect of clonidine.
- Drugs known to affect sinus node function or AV nodal conduction: Caution is warranted due to a potential for additive effects such as bradycardia and AV block.
- Other products containing clonidine
- Antihypertensive drugs

VIII. Adverse Reactions

Adverse effects of stimulant medications are usually mild and of short duration. Most side effects, such as decreased appetite, headaches, stomachaches, insomnia, nervousness, and social withdrawal, can usually be managed by adjusting the dosage and/or timing of administration

Amphetamines

- Cardiovascular: Elevation of blood pressure, MI, palpitations, reflex decrease in heart rate, stroke, sudden death, tachycardia, arrhythmias (at larger doses). There have been isolated reports of cardiomyopathy associated with long-term amphetamine use.

- CNS: Affect lability, agitation, anxiety, changes in libido, depression, dizziness, dysphoria, dyskinesia, euphoria, feeling jittery, headache, insomnia, irritability, overstimulation, restlessness, seizure, somnolence, tremor, psychotic episodes at recommended doses (rare). CNS stimulants have exacerbated Tourette disorder and motor and phonic tics.
- GI: Abdominal pain, constipation, dry mouth, diarrhea, nausea, unpleasant taste, vomiting, other GI disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used other than for their anorectic effect.
- Hypersensitivity: Hypersensitivity reactions, including anaphylaxis and angioedema; urticaria. Serious skin rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Miscellaneous: Dyspnea, erectile dysfunction, hyperhidrosis, impotence, pyrexia, rash, suppression of growth in children with long term stimulant use.

Methylphenidate and Dexmethylphenidate

- Skin irritation (transdermal)
- Cardiovascular: Angina, arrhythmia, blood pressure increased or decreased, cerebral arteritis and/or occlusion, palpitations, pulse increased or decreased tachycardia.
- CNS: Dizziness, drowsiness, dyskinesia, headache, rare reports of Tourette syndrome, toxic psychosis.
- GI: Abdominal pain, nausea.
- Hypersensitivity: Hypersensitivity reactions including arthralgia, erythema multiforme with histopathological findings of necrotizing vasculitis, exfoliative dermatitis, fever, skin rash, thrombocytopenic purpura, and urticaria.
- Metabolic/Nutritional: Anorexia, weight loss during prolonged therapy.

Atomoxetine

- Children and adolescents: The most commonly observed adverse reactions in patients treated with atomoxetine (incidence of 5% or more and at least twice the incidence in placebo-treated patients, for twice-daily or once-daily dosing) were abdominal pain, decreased appetite, fatigue, nausea, somnolence, and vomiting.
- Adults: The most commonly observed adverse reactions in patients treated with atomoxetine (incidence of 5% or more and at least twice the incidence in placebo-treated patients) were constipation, decreased appetite, dry mouth, dysmenorrhea, erectile dysfunction, fatigue, hot flush, insomnia, nausea, and urinary hesitation and/or urinary retention and/or dysuria.

Guanfacine ER

- The most commonly reported adverse reactions (occurring in 2% or more of patients) that were considered drug-related and reported in a greater percentage of patients taking guanfacine ER compared with patients taking placebo include dizziness, fatigue, headache, irritability, lethargy, somnolence, abdominal pain, constipation, dry mouth, nausea, decreased appetite and hypotension.

Clonidine ER

- Common adverse reactions ($\geq 5\%$) reported during the treatment period were constipation, dry mouth, ear pain, emotional disorder, fatigue, increased body temperature, insomnia, irritability, nasal congestion, nightmares, somnolence, throat pain, and upper respiratory tract infection.

IX. Conclusion

Medication treatment for ADHD has increased dramatically over the past 10 years with stimulants becoming the most prescribed psychotropic drug for children. Scientific evidence shows that stimulants are an effective treatment for ADHD, with medication resulting in better symptomatic relief than treatment with behavioral therapy, alone. However, the evidence for comparative efficacy and adverse events of drugs for treating ADHD is severely lacking in measuring functional or long-term outcomes. More rigorous studies are needed to establish the comparative effectiveness of medications used to treat ADHD.

References

1. Wolters Kluwer Health, Inc, ed. Drug Facts & Comparisons. St. Louis, MO. 2011.
2. Centers for Disease Control and Prevention (CDC): FastStats for Attention Deficit Hyperactivity Disorder (ADHD). 2010. www.cdc.gov.
3. American Academy of Pediatrics (AAP): Subcommittee on ADHD, Steering Committee on Quality Improvement and Management. Clinical Practice Guideline: ADHD-Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of ADHD in Children and Adolescents. 2011. www.pediatrics.org/cgi/doi/10.1542/peds.2011-2654.
4. American Academy of Child and Adolescent Psychiatry: Practice Parameter for the Assessment and Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. 2007. www.aacap.org/galleries/PracticeParameters/JAACAP_ADHD_2007.pdf.
5. Adderall XR[®] [prescribing information]. Wayne, PA: Shire US Inc; August 2011.
6. Concerta[®] [prescribing information]. Titusville, NJ: McNeil Pediatrics; November 2010.
7. Focalin XR[®] [prescribing information]. East Hanover, NJ: Novartis; April 2011.
8. Metadate CD[®] [prescribing information]. Smyrna, GA: UCB, Inc.; June 2009.
9. ProCentra[®] [prescribing information]. Charlotte, NC: FSC Laboratories, Inc.; June 2010.
10. Ritalin LA[®] [prescribing information]. East Hanover, NJ: Novartis; December 2010.
11. Ritalin[®] and Ritalin SR[®] [prescribing information]. East Hanover, NY: Novartis; December 2010.
12. Strattera[®] [prescribing information]. Indianapolis, IN: Eli Lilly and Company; August 2011.
13. Vyvanse[®] [prescribing information]. Wayne, PA: Shire US Inc.; August 2011.
14. Daytrana[®] [prescribing information]. Miami, FL: Noven Pharmaceuticals, Inc.; November 2010.
15. Intuniv[®] [prescribing information]. Wayne, PA: Shire US Inc.; June 2011.
16. Kapvay[®] [prescribing information]. Atlanta, GA: Shionogi Pharma, Inc.; September 2010.

Consecutive Duplication**Number of Therapies ≥ 3**

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

METADATE CD , METHYLIN ER , METHYLPHENIDATE HCL

DEXMETHYLPHENIDATE HCL , FOCALIN XR , STRATTERA

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

DEXMETHYLPHENIDATE HCL , FOCALIN XR , INTUNIV

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

DEXMETHYLPHENIDATE HCL , FOCALIN XR , INTUNIV

ADDERALL XR , DEXTROAMPHETAMINE-AMPHETAMINE , INTUNIV

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

ADDERALL XR , DEXTROAMPHETAMINE-AMPHETAMINE , INTUNIV

CONCERTA , INTUNIV , METHYLPHENIDATE HCL , STRATTERA

AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE , INTUNIV

DEXMETHYLPHENIDATE HCL , FOCALIN XR , INTUNIV

METHYLPHENIDATE HCL , RITALIN , STRATTERA

CONCERTA , METHYLIN , METHYLPHENIDATE HCL

FOCALIN XR , METHYLIN , METHYLPHENIDATE HCL , VYVANSE

CONCERTA , METHYLIN , METHYLPHENIDATE HCL , RITALIN

DEXMETHYLPHENIDATE HCL , DEXTROAMPHETAMINE-AMPHETAMINE , FOCALIN XR

FOCALIN XR , INTUNIV , METHYLIN ER , STRATTERA

CONCERTA , INTUNIV , METHYLPHENIDATE HCL , STRATTERA

DEXMETHYLPHENIDATE HCL , FOCALIN , FOCALIN XR

DEXTROAMPHETAMINE-AMPHETAMINE , METADATE CD , METHYLIN , STRATTERA

CONCERTA , INTUNIV , METHYLIN , METHYLPHENIDATE HCL

DEXMETHYLPHENIDATE HCL , DEXTROAMPHETAMINE-AMPHETAMINE , FOCALIN XR

FOCALIN XR , METHYLIN , METHYLPHENIDATE HCL

DEXMETHYLPHENIDATE HCL , FOCALIN XR , INTUNIV

CONCERTA , METHYLPHENIDATE HCL , STRATTERA

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

AMPHETAMINE SALT COMBO , INTUNIV , VYVANSE

ADDERALL XR , DEXTROAMPHETAMINE-AMPHETAMINE , INTUNIV

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

ADDERALL XR , CONCERTA , DEXTROAMPHETAMINE-AMPHETAMINE , INTUNIV

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

ADDERALL XR , AMPHETAMINE SALT COMBO , DEXTROAMPHETAMINE-AMPHETAMINE

36 recipients, 68 prescribers

SD Medicaid ADHD Utilization			
11/01/10 - 10/31/11			
Label Name	Rx	Total Reimb	Average Cost per Script
ADDERALL 10 MG TABLET	4	\$145.26	\$36.32
ADDERALL 15 MG TABLET	1	\$32.24	\$32.24
ADDERALL 20 MG TABLET	23	\$4,145.01	\$180.22
ADDERALL XR 10 MG CAPSULE	369	\$72,233.58	\$195.75
ADDERALL XR 15 MG CAPSULE	244	\$50,212.85	\$205.79
ADDERALL XR 20 MG CAPSULE	877	\$213,408.19	\$243.34
ADDERALL XR 25 MG CAPSULE	202	\$41,369.89	\$204.80
ADDERALL XR 30 MG CAPSULE	661	\$144,714.26	\$218.93
ADDERALL XR 5 MG CAPSULE	38	\$7,294.53	\$191.96
AMPHETAMINE SALTS 10 MG TAB	689	\$12,635.54	\$18.34
AMPHETAMINE SALTS 12.5 MG TB	5	\$589.41	\$117.88
AMPHETAMINE SALTS 15 MG TAB	139	\$4,878.29	\$35.10
AMPHETAMINE SALTS 20 MG TABLET	598	\$13,056.50	\$21.83
AMPHETAMINE SALTS 30 MG TAB	250	\$4,920.91	\$19.68
AMPHETAMINE SALTS 5 MG TAB	507	\$8,412.43	\$16.59
AMPHETAMINE SALTS 7.5 MG TAB	1	\$40.73	\$40.73
CONCERTA ER 18 MG TABLET	1809	\$281,982.41	\$155.88
CONCERTA ER 27 MG TABLET	1666	\$266,761.03	\$160.12
CONCERTA ER 36 MG TABLET	3770	\$786,685.65	\$208.67
CONCERTA ER 54 MG TABLET	2770	\$502,399.46	\$181.37
D-AMPHETAMINE ER 10 MG CAPSULE	230	\$29,651.55	\$128.92
D-AMPHETAMINE ER 15 MG CAPSULE	169	\$20,251.17	\$119.83
D-AMPHETAMINE ER 5 MG CAPSULE	52	\$3,686.66	\$70.90
DAYTRANA 10 MG/9 HR PATCH	134	\$18,366.62	\$137.06
DAYTRANA 15 MG/9 HR PATCH	156	\$25,599.79	\$164.10
DAYTRANA 20 MG/9 HOUR PATCH	118	\$18,163.09	\$153.92
DAYTRANA 30 MG/9 HOUR PATCH	138	\$20,801.05	\$150.73
DEXEDRINE SPANSULE 10 MG	7	\$1,843.94	\$263.42
DEXEDRINE SPANSULE 15 MG	7	\$704.83	\$100.69
DEXMETHYLPHENIDATE 10 MG TAB	206	\$9,366.48	\$45.47
DEXMETHYLPHENIDATE 2.5 MG TAB	40	\$947.17	\$23.68
DEXMETHYLPHENIDATE 5 MG TAB	388	\$15,044.23	\$38.77
DEXTROAMP-AMPHET ER 10 MG CAP	1089	\$167,183.11	\$153.52
DEXTROAMP-AMPHET ER 15 MG CAP	936	\$151,618.70	\$161.99
DEXTROAMP-AMPHET ER 20 MG CAP	2300	\$438,059.20	\$190.46
DEXTROAMP-AMPHET ER 25 MG CAP	594	\$88,104.89	\$148.32
DEXTROAMP-AMPHET ER 30 MG CAP	1643	\$282,248.00	\$171.79
DEXTROAMP-AMPHET ER 5 MG CAP	369	\$56,189.25	\$152.27
DEXTROAMPHETAMINE 10 MG TAB	202	\$4,920.48	\$24.36
DEXTROAMPHETAMINE 5 MG TAB	59	\$1,828.87	\$31.00
FOCALIN 10 MG TABLET	2	\$90.74	\$45.37
FOCALIN 2.5 MG TABLET	8	\$196.56	\$24.57
FOCALIN 5 MG TABLET	47	\$1,702.38	\$36.22
FOCALIN XR 10 MG CAPSULE	1104	\$172,883.65	\$156.60

SD Medicaid ADHD Utilization			
11/01/10 - 10/31/11			
Label Name	Rx	Total Reimb	Average Cost per Script
FOCALIN XR 15 MG CAPSULE	938	\$152,348.08	\$162.42
FOCALIN XR 20 MG CAPSULE	1213	\$194,637.01	\$160.46
FOCALIN XR 30 MG CAPSULE	444	\$73,691.34	\$165.97
FOCALIN XR 40 MG CAPSULE	75	\$10,957.42	\$146.10
FOCALIN XR 5 MG CAPSULE	587	\$102,799.55	\$175.13
INTUNIV ER 1 MG TABLET	810	\$122,201.04	\$150.87
INTUNIV ER 2 MG TABLET	2068	\$306,866.33	\$148.39
INTUNIV ER 3 MG TABLET	1421	\$213,250.96	\$150.07
INTUNIV ER 4 MG TABLET	635	\$90,730.56	\$142.88
KAPVAY ER 0.1 MG TABLET	2	\$27.36	\$13.68
METADATE CD 10 MG CAPSULE	148	\$18,729.77	\$126.55
METADATE CD 20 MG CAPSULE	324	\$40,069.08	\$123.67
METADATE CD 30 MG CAPSULE	156	\$18,648.74	\$119.54
METADATE CD 40 MG CAPSULE	141	\$20,633.71	\$146.34
METADATE CD 50 MG CAPSULE	26	\$5,171.03	\$198.89
METADATE CD 60 MG CAPSULE	2	\$446.76	\$223.38
METADATE ER 20 MG TABLET	29	\$1,425.80	\$49.17
METHAMPHETAMINE 5 MG TABLET	5	\$7,230.85	\$1,446.17
METHYLIN 10 MG CHEWABLE TABLET	41	\$8,813.64	\$214.97
METHYLIN 10 MG TABLET	475	\$5,909.31	\$12.44
METHYLIN 10 MG/5 ML SOLUTION	33	\$8,387.92	\$254.18
METHYLIN 2.5 MG CHEWABLE TAB	30	\$5,332.41	\$177.75
METHYLIN 20 MG TABLET	214	\$3,779.98	\$17.66
METHYLIN 5 MG CHEWABLE TABLET	72	\$13,280.55	\$184.45
METHYLIN 5 MG TABLET	417	\$4,180.59	\$10.03
METHYLIN 5 MG/5 ML SOLUTION	4	\$1,220.85	\$305.21
METHYLIN ER 10 MG TABLET	104	\$2,635.51	\$25.34
METHYLIN ER 20 MG TABLET	87	\$1,777.15	\$20.43
METHYLPHENIDATE 10 MG TABLET	600	\$7,513.57	\$12.52
METHYLPHENIDATE 10 MG/5 ML SOL	13	\$2,702.64	\$207.90
METHYLPHENIDATE 20 MG TABLET	260	\$4,641.15	\$17.85
METHYLPHENIDATE 5 MG TABLET	460	\$5,060.87	\$11.00
METHYLPHENIDATE ER 10 MG TAB	2	\$51.24	\$25.62
METHYLPHENIDATE ER 18 MG TAB	967	\$135,921.88	\$140.56
METHYLPHENIDATE ER 20 MG TAB	21	\$824.67	\$39.27
METHYLPHENIDATE ER 27 MG TAB	915	\$134,675.31	\$147.19
METHYLPHENIDATE ER 36 MG TAB	2501	\$483,015.80	\$193.13
METHYLPHENIDATE ER 54 MG TAB	1656	\$278,164.73	\$167.97
METHYLPHENIDATE SR 20 MG TAB	175	\$4,562.03	\$26.07
RITALIN 10 MG TABLET	7	\$77.20	\$11.03
RITALIN 20 MG TABLET	4	\$7.47	\$1.87
RITALIN 5 MG TABLET	10	\$173.02	\$17.30
RITALIN LA 10 MG CAPSULE	143	\$19,120.68	\$133.71
RITALIN LA 20 MG CAPSULE	342	\$47,088.57	\$137.69

SD Medicaid ADHD Utilization			
11/01/10 - 10/31/11			
Label Name	Rx	Total Reimb	Average Cost per Script
RITALIN LA 30 MG CAPSULE	269	\$39,896.11	\$148.31
RITALIN LA 40 MG CAPSULE	166	\$23,523.31	\$141.71
STRATTERA 10 MG CAPSULE	281	\$48,635.14	\$173.08
STRATTERA 100 MG CAPSULE	164	\$29,859.51	\$182.07
STRATTERA 18 MG CAPSULE	313	\$47,989.22	\$153.32
STRATTERA 25 MG CAPSULE	1116	\$180,432.01	\$161.68
STRATTERA 40 MG CAPSULE	1161	\$194,904.66	\$167.88
STRATTERA 60 MG CAPSULE	804	\$127,973.87	\$159.17
STRATTERA 80 MG CAPSULE	390	\$65,198.37	\$167.18
VYVANSE 20 MG CAPSULE	1104	\$149,838.71	\$135.72
VYVANSE 30 MG CAPSULE	2111	\$296,057.47	\$140.25
VYVANSE 40 MG CAPSULE	1	\$181.35	\$181.35
VYVANSE 40 MG CAPSULE	1552	\$216,187.85	\$139.30
VYVANSE 50 MG CAPSULE	1566	\$216,759.77	\$138.42
VYVANSE 60 MG CAPSULE	867	\$123,268.46	\$142.18
VYVANSE 70 MG CAPSULE	1460	\$199,353.16	\$136.54
6,424 recipients	56,538	\$8,473,294.64	

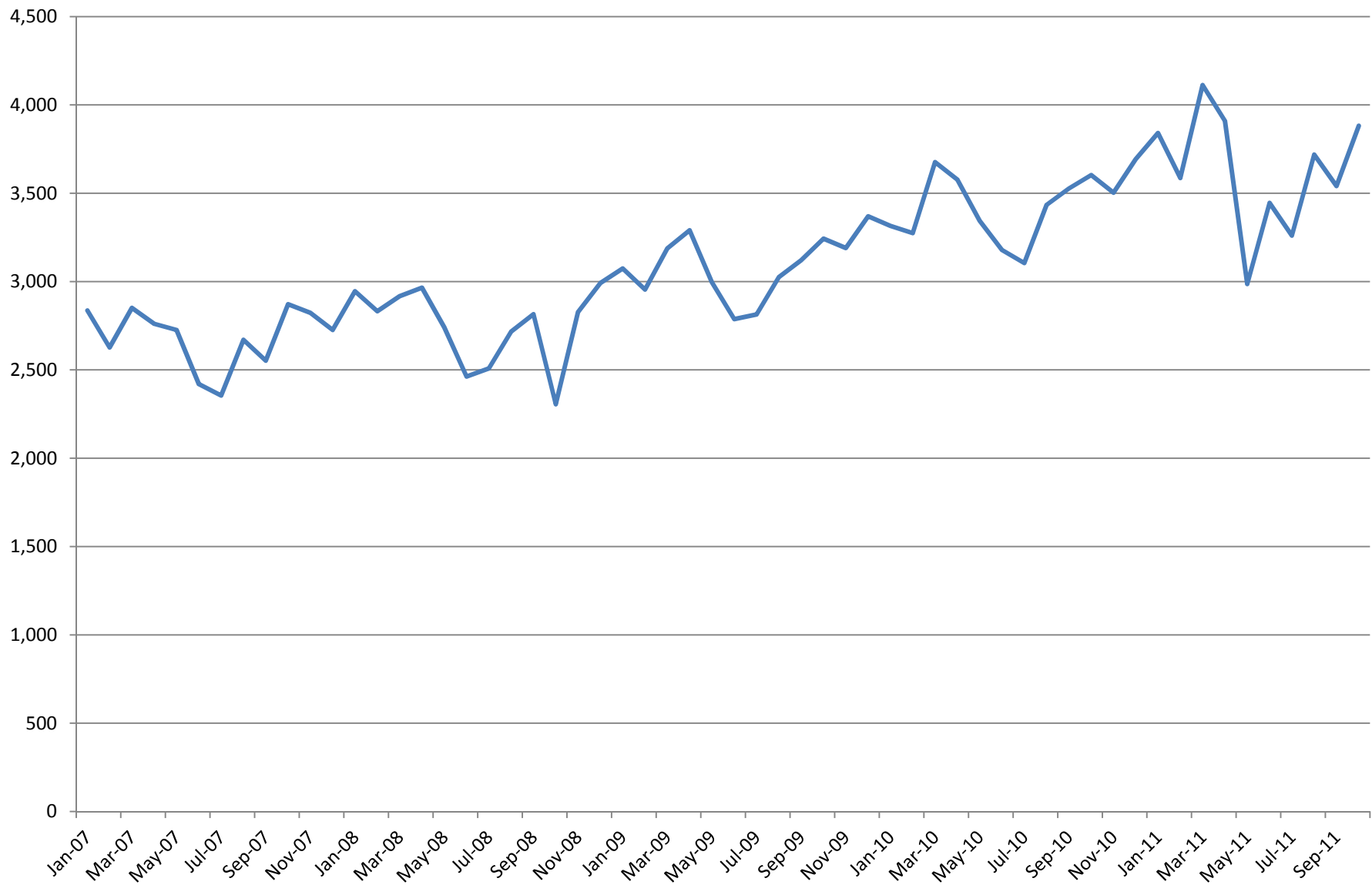
<p>Providers (top 20)</p> <p>12 Psychiatrists</p> <p>5 Pediatricians</p> <p>1 NP</p> <p>1 PA</p> <p>1 Hospital ID</p> <p>Top 20 prescribers make up ~40% of claims</p>
--

Summary by Age			
Age	Recip Count	Rx	Total Dollars
0	9	10	\$5,322.88
1	1	1	\$1,174.75
2	3	7	\$1,023.42
3	9	42	\$4,687.22
4	50	263	\$37,617.74
5	149	1113	\$151,285.84
6	280	2072	\$287,996.66
7	388	3347	\$473,894.04
8	487	4493	\$631,201.64
9	549	5496	\$777,574.26
10	524	5025	\$746,146.09
11	496	4722	\$708,489.13
12	512	5046	\$777,467.49
13	441	4204	\$645,528.63
14	404	3902	\$619,755.72
15	372	3308	\$541,762.65
16	360	3167	\$549,828.33
17	308	2439	\$392,192.90
18	230	1649	\$261,407.97
19	145	956	\$163,451.52
20	61	524	\$74,427.28
21	46	283	\$40,833.69
22	48	395	\$60,174.28
23	46	342	\$55,193.77
24	24	135	\$17,065.34
25	22	126	\$12,995.56
26	35	240	\$26,844.37
27	34	210	\$31,158.56
28	22	133	\$19,027.32
29	29	185	\$21,222.12
30	27	225	\$23,270.38
31	29	204	\$31,241.76
32	24	138	\$17,566.52
33	29	212	\$22,865.02
34	18	143	\$22,588.95
35	19	140	\$16,300.78
36	22	169	\$19,440.10
37	11	79	\$10,391.50
38	17	135	\$16,476.46
39	10	112	\$17,615.26
40	15	132	\$17,581.30
41	12	80	\$13,725.19
42	13	101	\$9,813.44
43	7	34	\$5,112.59
44	11	83	\$7,562.16
45	7	60	\$7,845.44
46	8	69	\$13,310.72
47	4	29	\$4,779.35
48	8	88	\$7,818.40
49	4	27	\$566.79

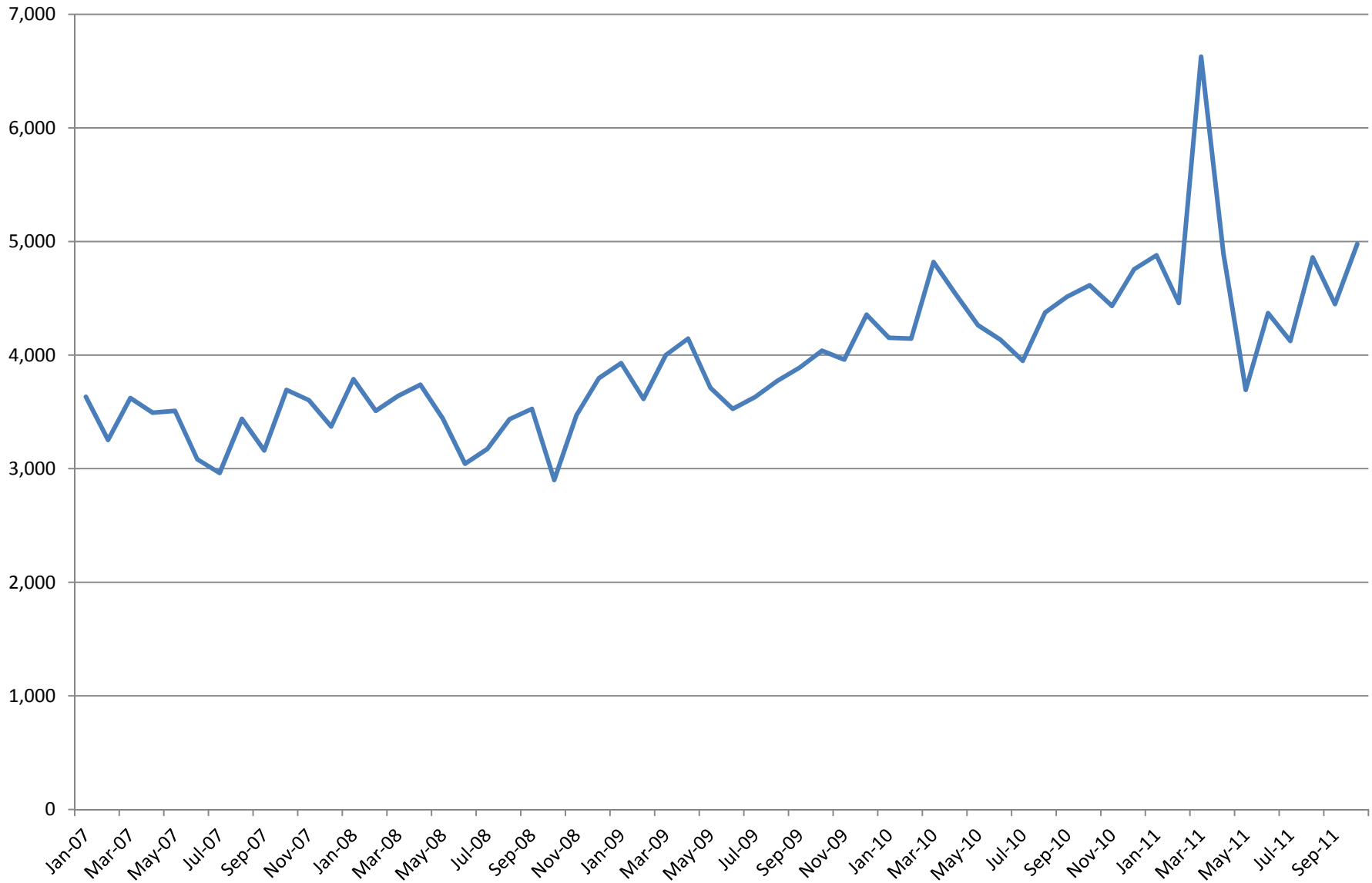
Summary by Age			
Age	Recip Count	Rx	Total Dollars
50	5	41	\$4,202.29
51	5	41	\$2,739.27
52	7	63	\$10,808.73
53	5	46	\$6,503.51
54	2	21	\$691.05
55	2	9	\$153.93
56	5	40	\$3,244.59
57	1	27	\$5,379.12
58	3	49	\$2,860.55
59	3	24	\$6,340.07
60	3	31	\$6,821.77
61	1	12	\$207.12
62	1	6	\$161.97
63	1	22	\$296.70
64	1	11	\$260.69

0-5	2.54% of claims
6-10	36.14% of claims
11-15	37.47% of claims
16-20	15.45% of claims
0-18	88.98% of claims

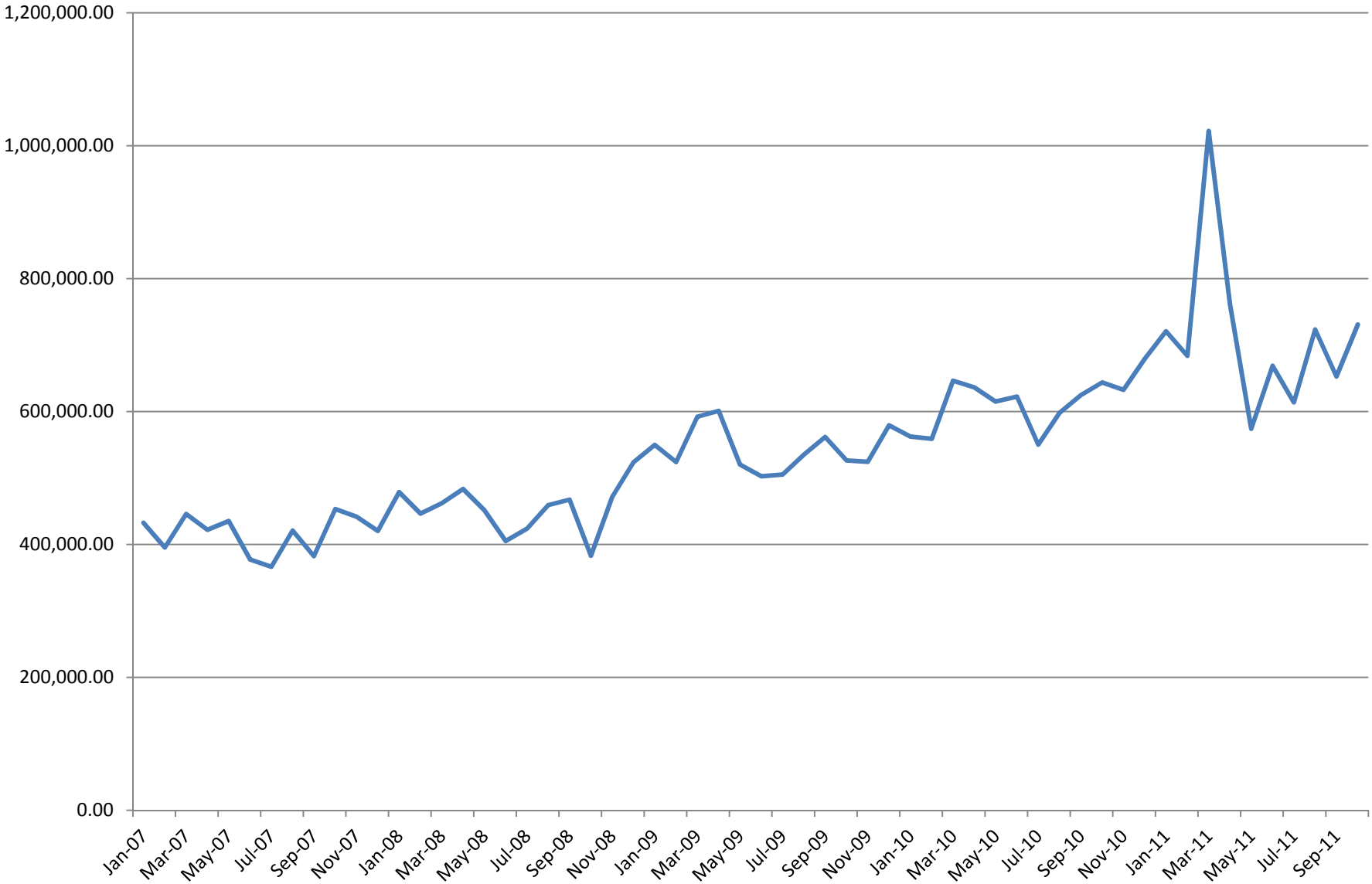
SD MEDICAID TOTAL PATIENTS RECEIVING ADHD MEDS



SD MEDICAID TOTAL ADHD RXS



SD MEDICAID TOTAL ADHD CLAIMS COST



South Dakota Department of Social Services
P&T Meeting
Juvisync[®] Review

I. Overview

The U.S. Food and Drug Administration recently approved Juvisync, the first combination pill to treat Type 2 diabetes and high cholesterol. Juvisync contains sitagliptin, a dipeptidyl peptidase 4 (DPP-4) inhibitor. Sitagliptin enhances the body's own ability to lower elevated blood sugar and is approved for use in combination with diet and exercise to improve glycemic control in adults with type 2 diabetes. Simvastatin is an HMG-CoA reductase inhibitor approved for use with diet and exercise to reduce cholesterol.

II. Dosage and Administration

Doses are 100mg/10mg, 100mg/20mg, and 100mg/40mg per day. Recommended usual starting dose is 100mg/40mg once a day in the evening. Patients already taking simvastatin (10, 20, or 40mg) can initiate Juvisync at a dose of 100mg sitagliptin and the dose of simvastatin already being taken.

III. Contraindications

- History of a serious hypersensitivity reaction, such as anaphylaxis or angioedema, to any component of this medication.
- Concomitant administration of strong CYP3A4 inhibitors.
- Concomitant administration of gemfibrozil, cyclosporine, danazol.
- Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels.
- Women who are pregnant or may become pregnant.
- Nursing mothers.

IV. Warnings/Precautions

- Postmarketing reports of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- Skeletal muscle effects (e.g., myopathy and rhabdomyolysis): Risks increase with higher doses and concomitant use of certain medicines. Predisposing factors include advanced age (≥ 65), female gender, uncontrolled hypothyroidism, and renal impairment. Patients should be advised to report any symptoms of myopathy.
- Persistent elevations in hepatic transaminase can occur. Check liver enzyme tests before initiating therapy and as clinically indicated thereafter.

- Increased risk of hypoglycemia when added to an insulin secretagogue (e.g., sulfonylurea) or insulin therapy. Consider lowering the dose of the sulfonylurea or insulin to reduce the risk of hypoglycemia.
- Postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with sitagliptin such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. In such cases, promptly stop medication, assess for other potential causes, institute appropriate monitoring and treatment, and initiate alternative treatment.

V. Adverse Reactions

Most common adverse reactions (incidence $\geq 5\%$) with simvastatin are: upper respiratory infection, headache, abdominal pain, constipation, and nausea. Adverse reactions reported in $\geq 5\%$ of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache. In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo.

VI. Drug Interactions

Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, danazol	Contraindicated with Juvisync
Verapamil, diltiazem	Do not exceed 100mg/10mg Juvisync daily
Amiodarone, amlodipine, ranolazine	Do not exceed 100mg/20mg Juvisync daily
Grapefruit juice	Avoid large quantities of grapefruit juice (>1 quart daily)

Coumarin anticoagulants: Concomitant use with simvastatin prolongs INR. Achieve stable INR prior to starting Juvisync. Monitor INR frequently until stable upon initiation or alteration of Juvisync therapy.

Other Lipid-lowering Medications: Use with other fibrate products or lipid-modifying doses (≥ 1 g/day) of niacin increases the risk of adverse skeletal muscle effects. Caution should be used when prescribing with Juvisync.

References

1. Juvisync[®] [prescribing information]. Whitehouse Station, NJ. Merck & Co., Inc.; October 2011.

SOUTH DAKOTA NARROW THERAPEUTIC INDEX LIST

Therapeutic Class	Example Brand Name(s)
Carbamazepine	Tegretol
Cyclosporine	Neoral, Sandimmune
Digoxin	Lanoxin; Digitek
Lithium	Lithobid; Eskalith
Pancreatic Drug Products	Creon; Pancrease
Phenytoin	Dilantin; Phenytek
Procainamide	Pronestyl, Procanbid
Quinidine	Quinidex, Quinaglute, Quinamm
Thyroid preparations	Synthroid; Levothroid; Armour Thyroid
Theophylline	Elixophyllin, Aminophylline, Theo-24, Theo-Dur, Theo-chron, Uniphyl
Valproic Acid	Depakene
Warfarin	Coumadin; Jantoven

SD Medicaid NTI Utilization		
05/01/10 - 04/30/11		
Label Name	Rx Num	Total Reimb Amt
ARMOUR THYROID 30 MG TABLET	18	\$111.57
ARMOUR THYROID 60 MG TABLET	76	\$592.78
ARMOUR THYROID 90 MG TABLET	1	\$11.37
CARBATROL ER 100 MG CAPSULE	71	\$10,318.70
CARBATROL ER 200 MG CAPSULE	302	\$32,968.93
CARBATROL ER 300 MG CAPSULE	323	\$38,557.72
COUMADIN 2 MG TABLET	17	\$695.62
COUMADIN 5 MG TABLET	16	\$743.01
CREON DR 12,000 UNITS CAPSULE	18	\$8,408.67
CREON DR 12,000 UNITS CAPSULE	33	\$12,002.78
CREON DR 24,000 UNITS CAPSULE	41	\$24,495.02
CREON DR 24,000 UNITS CAPSULE	45	\$55,454.89
CREON DR 6,000 UNITS CAPSULE	46	\$18,451.30
DILANTIN 100 MG CAPSULE	48	\$1,727.51
DILANTIN 100 MG CAPSULE	173	\$6,649.28
DILANTIN 30 MG KAPSEAL	11	\$530.40
DILANTIN 50 MG INFATAB	224	\$4,927.92
EPITOL 200 MG TABLET	81	\$443.00
EQUETRO 200 MG CAPSULE	1	\$113.98
GENGRAF 100 MG CAPSULE	20	\$449.62
GENGRAF 25 MG CAPSULE	19	\$56.73
JANTOVEN 1 MG TABLET	3	\$24.55
JANTOVEN 10 MG TABLET	3	\$38.08
JANTOVEN 2 MG TABLET	2	\$6.59
JANTOVEN 2 MG TABLET	3	\$21.15
JANTOVEN 2.5 MG TABLET	2	\$6.76
JANTOVEN 3 MG TABLET	1	\$7.97
JANTOVEN 4 MG TABLET	3	\$26.67
JANTOVEN 4 MG TABLET	6	\$51.24
JANTOVEN 5 MG TABLET	2	\$7.03
JANTOVEN 5 MG TABLET	3	\$31.01
JANTOVEN 5 MG TABLET	13	\$130.34
JANTOVEN 6 MG TABLET	1	\$3.76
JANTOVEN 6 MG TABLET	2	\$10.88
JANTOVEN 7.5 MG TABLET	2	\$18.70
LANOXIN 125 MCG TABLET	2	\$17.24
LANOXIN 125 MCG TABLET	22	\$155.18
LANOXIN 125 MCG TABLET	27	\$234.95
LANOXIN 250 MCG TABLET	8	\$29.76
LANOXIN 250 MCG TABLET	13	\$84.09
LEVOTHROID 100 MCG TABLET	32	\$265.76
LEVOTHROID 112 MCG TABLET	9	\$68.99
LEVOTHROID 125 MCG TABLET	26	\$222.86

SD Medicaid NTI Utilization		
05/01/10 - 04/30/11		
Label Name	Rx Num	Total Reimb Amt
LEVOTHROID 137 MCG TABLET	1	\$6.85
LEVOTHROID 150 MCG TABLET	8	\$78.80
LEVOTHROID 175 MCG TABLET	10	\$91.80
LEVOTHROID 200 MCG TABLET	14	\$130.76
LEVOTHROID 25 MCG TABLET	14	\$106.44
LEVOTHROID 50 MCG TABLET	30	\$169.33
LEVOTHROID 75 MCG TABLET	17	\$99.76
LEVOXYL 100 MCG TABLET	37	\$311.14
LEVOXYL 112 MCG TABLET	8	\$134.68
LEVOXYL 125 MCG TABLET	32	\$353.82
LEVOXYL 137 MCG TABLET	4	\$33.36
LEVOXYL 200 MCG TABLET	6	\$61.41
LEVOXYL 25 MCG TABLET	29	\$319.22
LEVOXYL 50 MCG TABLET	56	\$769.84
LEVOXYL 75 MCG TABLET	47	\$500.37
LEVOXYL 88 MCG TABLET	48	\$680.56
NEORAL 100 MG GELATN CAPSULE	12	\$2,191.17
NEORAL 100 MG/ML SOLUTION	8	\$2,376.92
NEORAL 25 MG GELATIN CAPSULE	12	\$2,956.95
PANCREASE MT-10 EC CAPSULE	6	\$759.97
PANCREASE MT-16 EC CAPSULE	10	\$2,380.41
PANCREASE MT-4 EC CAPSULE	4	\$573.99
SANDIMMUNE 100 MG/ML SOLN	8	\$3,493.90
SANDIMMUNE 25 MG CAPSULE	9	\$1,737.80
SYNTHROID 100 MCG TABLET	37	\$597.66
SYNTHROID 100 MCG TABLET	119	\$2,290.39
SYNTHROID 112 MCG TABLET	20	\$444.34
SYNTHROID 112 MCG TABLET	105	\$2,365.17
SYNTHROID 125 MCG TABLET	17	\$351.03
SYNTHROID 125 MCG TABLET	215	\$4,906.25
SYNTHROID 137 MCG TABLET	122	\$2,657.60
SYNTHROID 150 MCG TABLET	8	\$9.92
SYNTHROID 150 MCG TABLET	22	\$456.44
SYNTHROID 150 MCG TABLET	97	\$1,959.81
SYNTHROID 175 MCG TABLET	72	\$1,738.40
SYNTHROID 200 MCG TABLET	11	\$256.67
SYNTHROID 200 MCG TABLET	74	\$1,701.55
SYNTHROID 25 MCG TABLET	30	\$494.81
SYNTHROID 300 MCG TABLET	37	\$1,439.43
SYNTHROID 50 MCG TABLET	85	\$1,230.63
SYNTHROID 50 MCG TABLET	173	\$2,724.79
SYNTHROID 75 MCG TABLET	56	\$938.00
SYNTHROID 75 MCG TABLET	317	\$4,904.82

SD Medicaid NTI Utilization		
05/01/10 - 04/30/11		
Label Name	Rx Num	Total Reimb Amt
SYNTHROID 88 MCG TABLET	8	\$143.74
SYNTHROID 88 MCG TABLET	130	\$2,276.49
TEGRETOL 100 MG TABLET CHEW	20	\$1,769.14
TEGRETOL 100 MG/5 ML SUSP	57	\$5,101.86
TEGRETOL 200 MG TABLET	15	\$2,521.51
TEGRETOL XR 100 MG TABLET	223	\$9,702.81
TEGRETOL XR 200 MG TABLET	6	\$455.40
TEGRETOL XR 200 MG TABLET	23	\$1,284.85
TEGRETOL XR 400 MG TABLET	25	\$1,966.53
THEO-24 ER 200 MG CAPSULE	3	\$234.51
ULTRASE MT-12 EC CAPSULE	1	\$61.96
ULTRASE MT-20 EC CAPSULE	1	\$65.78
ULTRASE MT-20 EC CAPSULE	4	\$1,831.06
UNIPHYL CR 400 MG TABLET	6	\$250.32
VIOKASE 8 TABLET	6	\$1,574.42
570 recipients	4344	\$300,201.70

**South Dakota Department of Social Services
P&T Meeting
Pradaxa[®] Review**

I. Overview

Pradaxa is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

II. Dosage and Administration

Recommended Dose:

For patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of Pradaxa is 150 mg taken orally, twice daily, with or without food. For patients with severe renal impairment (CrCl 15-30 mL/min), the recommended dose is 75 mg twice daily. Dosing recommendations for patients with a CrCL <15 mL/min or on dialysis cannot be provided.

Instruct patients to swallow the capsules whole. Breaking, chewing, or emptying the contents of the capsule can result in increased exposure.

If the dose of Pradaxa is not taken at the scheduled time, the dose should be taken as soon as possible on the same day; the missed dose should be skipped if it cannot be taken at least 6 hours before the next scheduled dose. The dose of Pradaxa should not be doubled to make up for a missed dose.

Converting from or to Warfarin:

When converting patients from warfarin therapy to Pradaxa, discontinue warfarin and start Pradaxa when the international normalized ratio (INR) is below 2.0. When converting from Pradaxa to warfarin, adjust the starting time of warfarin based on creatinine clearance as follows:

- For CrCl >50 mL/min, start warfarin 3 days before discontinuing Pradaxa.
- For CrCl 30-50 mL/min, start warfarin 2 days before discontinuing Pradaxa.
- For CrCl 15-30 mL/min, start warfarin 1 day before discontinuing Pradaxa.
- For CrCl <15 mL/min, no recommendations can be made.

Because Pradaxa can contribute to an elevated INR, the INR will better reflect warfarin's effect after Pradaxa has been stopped for at least 2 days.

Converting from or to Parenteral Anticoagulants:

For patients currently receiving a parenteral anticoagulant, start Pradaxa 0 to 2 hours before the time that the next dose of the parenteral drug was to have been administered or at the time of discontinuation of a continuously administered parenteral drug (e.g., intravenous unfractionated heparin).

For patients currently taking Pradaxa, wait 12 hours ($\text{CrCl} \geq 30 \text{ mL/min}$) or 24 hours ($\text{CrCl} < 30 \text{ mL/min}$) after the last dose of Pradaxa before initiating treatment with a parenteral anticoagulant.

Surgery and Interventions:

If possible, discontinue Pradaxa 1 to 2 days ($\text{CrCl} \geq 50 \text{ mL/min}$) or 3 to 5 days ($\text{CrCl} < 50 \text{ mL/min}$) before invasive or surgical procedures because of the increased risk of bleeding. Consider longer times for patients undergoing major surgery, spinal puncture, or placement of a spinal or epidural catheter or port, in who complete hemostasis may be required.

If surgery cannot be delayed, there is an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention. Bleeding risk can be assessed by the ecarin clotting time (ECT). This test is a better marker of the anticoagulant activity of dabigatran than activated partial thromboplastin time (aPTT) or thrombin time (TT). If ECT is not available, the aPTT test provides an approximation of Pradaxa's anticoagulant activity. INR tests are unreliable in patients on Pradaxa.

III. Contraindications

Pradaxa is contraindicated in patients with:

- Active pathological bleeding.
- History of a serious hypersensitivity reaction to Pradaxa.

IV. Warnings/Precautions

Risk of Bleeding:

Pradaxa increases the risk of bleeding and can cause significant and, sometimes, fatal bleeding. Risk factors for bleeding include the use of drugs that increase the risk of bleeding in general (e.g., anti-platelet agents, heparin, fibrinolytic therapy, and chronic use of NSAIDs) and labor and delivery. Promptly evaluate any signs or symptoms of blood loss (e.g., a drop in hemoglobin and/or hematocrit or hypotension). Consider evaluation of renal function. Discontinue Pradaxa in patients with active pathological bleeding.

In the RE-LY (Randomized Evaluation of Long-term Anticoagulant Therapy) study, a life-threatening bleed (bleeding that met one or more of the following criteria: fatal, symptomatic intracranial, reduction in hemoglobin of at least 5 grams per deciliter, transfusion of at least 4 units of blood, associated with hypotension requiring the use of intravenous inotropic agents, or necessitating surgical intervention) occurred at an annualized rate of 1.5% and 1.8% for PRADAXA 150 mg and warfarin.

Temporary Discontinuation of Pradaxa:

Discontinuing anticoagulants, including Pradaxa, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of stroke. Lapses in therapy

should be avoided, and if anticoagulation with Pradaxa must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

Effect of P-gp Inducers and Inhibitors on Dabigatran Exposure:

The concomitant use of Pradaxa with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided.

P-gp inhibition and impaired renal function are the major independent factors that result in increased exposure to dabigatran. Concomitant use of P-gp inhibitors in patients with renal impairment is expected to produce increased exposure of dabigatran compared to that seen with either factor alone.

Consider reducing the dose of Pradaxa to 75mg twice daily when dronedarone or systemic ketoconazole is coadministered with Pradaxa in patients with moderate renal impairment (CrCl 30-50 mL/min). The use of Pradaxa and P-gp inhibitors in patients with severe renal impairment (CrCl 15-30 mL/min) should be avoided.

V. Adverse Reactions

The RE-LY study provided safety information on the use of two doses of Pradaxa and warfarin. The rates of adverse reactions leading to treatment discontinuation were 21% for Pradaxa 150mg and 16% for warfarin. The most frequent adverse reactions leading to discontinuation of Pradaxa were bleeding and gastrointestinal events (e.g., dyspepsia, nausea, upper abdominal pain, gastrointestinal hemorrhage, and diarrhea).

Bleeding:

The risk of major bleeds was similar with Pradaxa 150 mg and warfarin across major subgroups defined by baseline characteristics, with the exception of age, where there was a trend towards a higher incidence of major bleeding on Pradaxa (hazard ratio 1.2, 95% CI: 1.0 to 1.4) for patients ≥ 75 years of age.

There was a higher rate of major gastrointestinal bleeds in patients receiving Pradaxa 150 mg than in patients receiving warfarin (1.6% vs. 1.1%, respectively, with a hazard ratio vs. warfarin of 1.5, 95% CI, 1.2 to 1.9), and a higher rate of any gastrointestinal bleeds (6.1% vs. 4.0%, respectively).

Gastrointestinal Adverse Reactions:

Patients on Pradaxa 150 mg had an increased incidence of gastrointestinal adverse reactions (35% vs. 24% on warfarin). These were commonly dyspepsia (including abdominal pain upper, abdominal pain, abdominal discomfort, and epigastric discomfort) and gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis, and gastrointestinal ulcer).

Hypersensitivity Reactions:

In the RE-LY study, drug hypersensitivity (including urticaria, rash, and pruritus), allergic edema, anaphylactic reaction, and anaphylactic shock were reported in <0.1% of patients receiving Pradaxa.

VI. Drug Interactions

The concomitant use of Pradaxa with P-gp inducers (e.g., rifampin) reduces exposure to dabigatran and should generally be avoided. P-gp inhibitors ketoconazole, verapamil, amiodarone, quinidine, and clarithromycin do not require dose adjustments.

VII. Pharmacology/Pharmacokinetics

Dabigatran and its acyl glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.

Dabigatran etexilate mesylate is absorbed as the dabigatran etexilate ester. The ester is then hydrolyzed, forming dabigatran, the active moiety. Dabigatran is metabolized to four different acyl glucuronides and both the glucuronides and dabigatran have similar pharmacological activity.

Absorption:

The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate is approximately 3 to 7%. Dabigatran etexilate is a substrate of the efflux transporter P-gp. Pradaxa may be administered with or without food. Pradaxa capsules should not be broken, chewed, or opened before administration.

Distribution:

Dabigatran is approximately 35% bound to human plasma proteins. The volume of distribution of dabigatran is 50 to 70 L.

Elimination:

Dabigatran is eliminated primarily in the urine. After oral administration of radiolabeled dabigatran, 7% of radioactivity is recovered in urine and 86% in feces. The half-life of dabigatran in healthy subjects is 12 to 17 hours.

Metabolism:

After oral administration, dabigatran etexilate is converted to dabigatran. The cleavage of the dabigatran etexilate by esterase-catalyzed hydrolysis to the active principal dabigatran is the predominant metabolic reaction. Dabigatran is not a substrate, inhibitor, or inducer of CYP450 enzymes. Dabigatran is subject to conjugation forming pharmacologically active acyl glucuronides.

References

1. Pradaxa[®] [prescribing information]. Ridgefield, CT. Boehringer Ingelheim Pharmaceuticals, Inc.; November 2011.

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

I. Overview

Xarelto (rivaroxaban) is a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE) in patients undergoing knee or hip replacement surgery.

II. Dosage and Administration

Nonvalvular Atrial Fibrillation: For patients with creatinine clearance (CrCl) >50 mL/min, the recommended dose of Xarelto is 20 mg taken orally once daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal.

Switching from or to Warfarin: When switching patients from warfarin to Xarelto, discontinue warfarin and start Xarelto as soon as the International Normalized Ratio (INR) is below 3.0 to avoid periods of inadequate anticoagulation.

No clinical trial data are available to guide converting patients from Xarelto to warfarin. Xarelto affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining the appropriate dose of warfarin. One approach is to discontinue Xarelto and begin both a parenteral anticoagulant and warfarin at the time the next dose of Xarelto would have been taken.

Switching from or to Anticoagulants other than Warfarin: For patients currently receiving an anticoagulant other than warfarin, start Xarelto 0 to 2 hours prior to the next scheduled evening administration of the drug (e.g., low molecular weight heparin or non-warfarin oral anticoagulant) and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop the infusion and start Xarelto at the same time.

For patients currently taking Xarelto and transitioning to an anticoagulant with rapid onset, discontinue Xarelto and give the first dose of the other anticoagulant (oral or parenteral) at the time that the next XARELTO dose would have been taken.

Prophylaxis of Deep Vein Thrombosis: 10mg taken orally once daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established.

- For patients undergoing hip replacement surgery, treatment duration of 35 days is recommended.

- For patients undergoing knee replacement surgery, treatment duration of 12 days is recommended.

III. Contraindications

Xarelto is contraindicated in patients with:

- Active pathological bleeding
- Severe hypersensitivity reaction to Xarelto

IV. Warnings/Precautions

- **Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation:** Discontinuing Xarelto in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from Xarelto to warfarin, in clinical trials in atrial fibrillation patients. If Xarelto must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant.
- **Spinal/Epidural Anesthesia or Puncture:** When neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, patients treated with anticoagulant agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

An epidural catheter should not be removed earlier than 18 hours after the last administration of Xarelto. The next dose is not to be administered earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs, the administration of Xarelto is to be delayed for 24 hours.

- **Risk of Bleeding:** Xarelto increases the risk of bleeding and can cause serious or fatal bleeding. In deciding whether to prescribe XARELTO to patients at increased risk of bleeding, the risk of thrombotic events should be weighed against the risk of bleeding.

Promptly evaluate any signs or symptoms of blood loss. Discontinue Xarelto in patients with active pathological hemorrhage.

A specific antidote for rivaroxaban is not available. Because of high plasma protein binding, rivaroxaban is not expected to be dialyzable. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving rivaroxaban. Use of procoagulant reversal agents such as prothrombin complex concentrate (PCC),

activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (rFVIIa) may be considered, but has not been evaluated in clinical trials. Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs).

Concomitant use of drugs that are combined P-gp and CYP3A4 inhibitors (e.g. ketoconazole and ritonavir) increases rivaroxaban exposure and may increase bleeding risk.

- **Risk of Pregnancy Related Hemorrhage**: Xarelto should be used with caution in pregnant women and only if the potential benefit justifies the potential risk to the mother and fetus. Xarelto dosing in pregnancy has not been studied. The anticoagulant effect of Xarelto cannot be monitored with standard laboratory testing nor readily reversed. Promptly evaluate any signs or symptoms suggesting blood loss (e.g., a drop in hemoglobin and/or hematocrit, hypotension, or fetal distress).
- **Severe Hypersensitivity Reactions**: There were postmarketing cases of anaphylaxis in patients treated with Xarelto to reduce the risk of DVT. Patients who have a history of a severe hypersensitivity reaction should not receive Xarelto.

V. Adverse Reactions

The most common adverse reactions with Xarelto were bleeding complications. The rates of various types of bleeding events in the ROCKET AF study are shown below.

Parameter	Xarelto N=7111 n (%)	Event Rate (per 100 Pt-yrs)	Warfarin N=7125 n (%)	Event Rate (per 100 Pt- yrs)
Major bleeding	395 (5.6)	3.6	386 (5.4)	3.5
Bleeding into a critical organ	91 (1.3)	0.8	133 (1.9)	1.2
Fatal bleeding	27 (0.4)	0.2	55 (0.8)	0.5
Bleeding resulting in transfusion of ≥ 2 units of whole blood or packed red blood cells	183 (2.6)	1.7	149 (2.1)	1.3
Gastrointestinal bleeding	221 (3.1)	2.0	140 (2.0)	1.2

The rates of major bleeding events and any bleeding events observed in patients in the RECORD clinical trials are shown below.

	Xarelto 10mg
Total treated patients	N=4487
	n (%)
Major bleeding event	14 (0.3)
Fatal bleeding	1 (<0.1)
Bleeding into a critical organ	2 (<0.1)
Bleeding that required re-operation	7 (0.2)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	4 (0.1)
Any bleeding event	261 (5.8)
Hip Surgery Study	N=3281
	n (%)
Major bleeding event	7 (0.2)
Fatal bleeding	1 (<0.1)
Bleeding into a critical organ	1 (<0.1)
Bleeding that required re-operation	2 (0.1)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	3 (0.1)
Any bleeding event	201 (6.1)
Knee Surgery Study	N=1206
	n (%)
Major bleeding event	7 (0.6)
Fatal bleeding	0
Bleeding into a critical organ	1 (0.1)
Bleeding that required re-operation	5 (0.4)
Extra-surgical site bleeding requiring transfusion of >2 units of whole blood or packed cells	1 (0.1)
Any bleeding event	60 (5.0)

Other adverse reactions reported by $\geq 1\%$ of Xarelto-Treated Patients in RECORD 1-3 studies

System/Organ Class	Xarelto 10mg
Adverse Reaction	N=4487
	n (%)
Injury, poisoning and procedural complications	
Wound secretion	125 (2.8)
Musculoskeletal and connective tissue disorders	
Pain in extremity	74 (1.7)
Muscle spasm	52 (1.2)
Nervous system disorders	
Syncope	55 (1.2)
Skin and subcutaneous tissue disorders	
Pruritus	96 (2.1)
Blister	63 (1.4)

VI. Drug Interactions

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Inhibitors and inducers of these CYP450 enzymes or transporters may result in changes in rivaroxaban exposure.

Drugs that inhibit cytochrome P450 3A4 enzymes and drug transport systems:

In drug interaction studies evaluating the concomitant use with drugs that are combined P-gp and CYP3A4 inhibitors, increases in rivaroxaban exposure and pharmacodynamic effects (i.e., factor Xa inhibition and PT prolongation) were observed. Significant increases in rivaroxaban exposure may increase bleeding risk.

- Ketoconazole (combined P-gp and strong CYP3A4 inhibitor): Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in pharmacodynamic effects were also observed.
- Ritonavir (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in pharmacodynamic effects were also observed.
- Clarithromycin (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- Erythromycin (combined P-gp and moderate CYP3A4 inhibitor): Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.
- Fluconazole (moderate CYP3A4 inhibitor): Single-dose rivaroxaban AUC and C_{max} increased by 40% and 30%, respectively.

Avoid concomitant administration of Xarelto with combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan) which cause significant increases in rivaroxaban exposure that may increase bleeding risk. When clinical data suggest a change in exposure is unlikely to affect bleeding risk (e.g., clarithromycin, erythromycin), no precautions are necessary during coadministration with drugs that are combined P-gp and CYP3A4 inhibitors.

Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems:

Based on simulated pharmacokinetic data, patients with renal impairment receiving full dose Xarelto in combination with drugs classified as combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., erythromycin, azithromycin, diltiazem, verapamil, quinidine, ranolazine, dronedarone, amiodarone, and felodipine), may have significant increases in exposure compared with patients with normal renal function and no inhibitor use, since both pathways of rivaroxaban elimination are affected.

While increases in rivaroxaban exposure can be expected under such conditions, results from an analysis in the ROCKET AF trial, which allowed concomitant use with combined P-gp and weak or moderate CYP3A4 inhibitors (e.g., amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine, and erythromycin), did not show an increase in bleeding in patients with CrCl 30 to <50 mL/min [Hazard Ratio (95% CI): 1.05 (0.77, 1.42)]. Xarelto should be used in patients with CrCL 15 to 50 mL/min who are receiving concomitant combined P-gp and weak or moderate CYP3A4 inhibitors only if the potential benefit justifies the potential risk.

Drugs that Induce Cytochrome P450 3A4 Enzymes and Drug Transport Systems:

In a drug interaction study, co-administration of Xarelto (20 mg single dose with food) with a drug that is a combined P-gp and strong CYP3A4 inducer (rifampicin titrated up to 600 mg once daily) led to an approximate decrease of 50% and 22% in AUC and Cmax, respectively. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to rivaroxaban may decrease efficacy. Avoid concomitant use of Xarelto with drugs that are combined P-gp and strong CYP3A4 inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort). Consider increasing the Xarelto dose if these drugs must be coadministered.

Anticoagulants:

In a drug interaction study, single doses of enoxaparin (40 mg subcutaneous) and Xarelto (10 mg) given concomitantly resulted in an additive effect on anti-factor Xa activity. Enoxaparin did not affect the pharmacokinetics of rivaroxaban. In another study, single doses of warfarin (15 mg) and Xarelto (5 mg) resulted in an additive effect on factor Xa inhibition and PT. Warfarin did not affect the pharmacokinetics of rivaroxaban.

Prophylaxis of Deep Vein Thrombosis-Avoid concurrent use of Xarelto with other anticoagulants due to the increased bleeding risk other than during therapeutic transition periods where patients should be observed closely. Promptly evaluate any signs or symptoms of blood.

NSAIDs/Aspirin:

In ROCKET AF, concomitant aspirin use (almost exclusively at a dose of 100mg or less) during the double-blind phase was identified as an independent risk factor for major bleeding. NSAIDs are known to increase bleeding, and bleeding risk may be increased when NSAIDs are used concomitantly with Xarelto. In a single-dose drug interaction study there were no pharmacokinetic or pharmacodynamic interactions observed after concomitant administration of naproxen or aspirin (acetylsalicylic acid) with Xarelto.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with aspirin, other platelet aggregation inhibitors, or NSAIDs.

Clopidogrel:

In two drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and Xarelto (15 mg single dose) were co-administered in healthy subjects, an increase in bleeding time to 45 minutes was observed in approximately 45% and 30% of subjects in these studies, respectively. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. There was no change in the pharmacokinetics of either drug.

Promptly evaluate any signs or symptoms of blood loss if patients are treated concomitantly with clopidogrel.

VII. Pharmacology/Pharmacokinetics

Xarelto is an orally bioavailable factor Xa inhibitor that selectively blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity. Activation of factor X to factor Xa (FXa) via the intrinsic and extrinsic pathways plays a central role in the cascade of blood coagulation.

Absorption

The absolute bioavailability of rivaroxaban is high (estimated to be 80% to 100%) for the 10 mg dose. The maximum concentrations appear 2 to 4 hours after tablet intake. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban via a method that could deposit drug directly into the proximal small intestine (e.g., feeding tube) which can result in reduced absorption and related drug exposure.

Distribution

Plasma protein binding of rivaroxaban in human plasma is approximately 92% to 95%, with albumin being the main binding component. The steady-state volume of distribution in healthy subjects is approximately 50 L.

Metabolism

Approximately 51% of an orally administered [¹⁴C]-rivaroxaban dose was recovered as metabolites in urine (30%) and feces (21%). Oxidative degradation catalyzed by CYP3A4/5 and CYP2J2 and hydrolysis are the major sites of biotransformation. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites.

Excretion

Following oral administration of a [¹⁴C]-rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in feces (7% as unchanged drug). Unchanged drug is excreted into urine, mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio).

Rivaroxaban is a low-clearance drug, with a systemic clearance of approximately 10 L/hr in healthy volunteers following intravenous administration. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years.

References

1. Xarelto[®] [prescribing information]. Gurabo, PR. Janssen Ortho, LLC; November 2011.

SD Medicaid Oral Anticoagulants Utilization			
11/01/10 - 10/31/11			
Label Name	Rx Num	Total Remb Amt	Average Cost per Script
COUMADIN 2 MG TABLET	14	\$505.73	\$36.12
COUMADIN 5 MG TABLET	17	\$747.48	\$43.97
JANTOVEN 1 MG TABLET	7	\$81.74	\$11.68
JANTOVEN 10 MG TABLET	3	\$31.35	\$10.45
JANTOVEN 2 MG TABLET	11	\$73.15	\$6.65
JANTOVEN 2.5 MG TABLET	2	\$6.76	\$3.38
JANTOVEN 4 MG TABLET	8	\$62.39	\$7.80
JANTOVEN 5 MG TABLET	44	\$380.29	\$8.64
JANTOVEN 6 MG TABLET	2	\$9.20	\$4.60
JANTOVEN 7.5 MG TABLET	10	\$56.34	\$5.63
PRADAXA 150 MG CAPSULE	30	\$6,165.87	\$205.53
WARFARIN SODIUM 1 MG TABLET	267	\$2,975.68	\$11.14
WARFARIN SODIUM 10 MG TABLET	171	\$1,499.15	\$8.77
WARFARIN SODIUM 2 MG TABLET	234	\$2,975.39	\$12.72
TABLET	159	\$1,484.19	\$9.33
WARFARIN SODIUM 3 MG TABLET	172	\$1,636.26	\$9.51
WARFARIN SODIUM 4 MG TABLET	291	\$3,361.42	\$11.55
WARFARIN SODIUM 5 MG TABLET	835	\$9,140.78	\$10.95
WARFARIN SODIUM 6 MG TABLET	133	\$1,281.76	\$9.64
TABLET	145	\$1,273.98	\$8.79
336 recipients	2555	\$33,748.91	Xarelto average cost per tablet \$7.29

Orally Disintegrating Tablets Currently Available

Drug name	Form	Generic name
ABILIFY DISCMELT	TAB RAPDIS	ARIPIRAZOLE
ALLEGRA ODT	TAB RAPDIS	FEXOFENADINE HCL
ALPRAZOLAM	TAB RAPDIS	ALPRAZOLAM
ARICEPT ODT	TAB RAPDIS	DONEPEZIL HCL
CARBIDOPA-LEVODOPA	TAB RAPDIS	CARBIDOPA/LEVODOPA
CLARINEX	TAB RAPDIS	DESLOMATADINE
CLONAZEPAM	TAB RAPDIS	CLONAZEPAM
DISPAS	TAB RAPDIS	HYOSCYAMINE SULFATE
ED-SPAZ	TAB RAPDIS	HYOSCYAMINE SULFATE
EXJADE	TAB DISPER	DEFERASIROX
FAZACLO	TAB RAPDIS	CLOZAPINE
HYOMAX-FT	TAB RAPDIS	HYOSCYAMINE SULFATE
HYOSCYAMINE SULFATE	TAB RAPDIS	HYOSCYAMINE SULFATE
KLONOPIN	TAB RAPDIS	CLONAZEPAM
LAMICTAL	TAB DISPER	LAMOTRIGINE
LAMICTAL ODT	TAB RAPDIS	LAMOTRIGINE
LAMOTRIGINE	TAB DISPER	LAMOTRIGINE
MACUTEK	TAB RAPDIS	VIT A
MAXALT MLT	TAB RAPDIS	RIZATRIPTAN BENZOATE
METOZOLV ODT	TAB RAPDIS	METOCLOPRAMIDE HCL
MIRTAZAPINE	TAB RAPDIS	MIRTAZAPINE
NIRAVAM	TAB RAPDIS	ALPRAZOLAM
NULEV	TAB RAPDIS	HYOSCYAMINE SULFATE
ONDANSETRON ODT	TAB RAPDIS	ONDANSETRON
ORAPRED ODT	TAB RAPDIS	PREDNISOLONE SOD PHOSPHATE
PARCOPA	TAB RAPDIS	CARBIDOPA/LEVODOPA
PEPCID RPD	TAB RAPDIS	FAMOTIDINE
PREVACID	TAB RAP DR	LANSOPRAZOLE
PROBARIMIN QT	TAB RAPDIS	MV
PRO-HYO	TAB RAPDIS	HYOSCYAMINE SULFATE
REMERON	TAB RAPDIS	MIRTAZAPINE
RESCRIPTOR	TAB DISPER	DELAVIRDINE MESYLATE
RISPERDAL M-TAB	TAB RAPDIS	RISPERIDONE
RISPERIDONE ODT	TAB RAPDIS	RISPERIDONE
RYBIX ODT	TAB RAPDIS	TRAMADOL HCL
SYMAX	TAB RAPDIS	HYOSCYAMINE SULFATE
ZELAPAR	TAB RAPDIS	SELEGILINE HCL
ZOFRAN ODT	TAB RAPDIS	ONDANSETRON
ZOMIG ZMT	TAB RAPDIS	ZOLMITRIPTAN
ZYPREXA ZYDIS	TAB RAPDIS	OLANZAPINE