Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
May 14, 2014
4 p.m.

Oklahoma Health Care Authority
4345 N. Lincoln Blvd.
Oklahoma City, OK 73105

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – May 14, 2014

DATE: May 1, 2014

NOTE: The DUR Board will meet at 4:00 p.m. The meeting will be held at 4345 N Lincoln Blvd.

Enclosed are the following items related to the May meeting. Material is arranged in order of the Agenda.

Call to Order

Public Comment Forum

Action Item – Approval of DUR Board Meeting Minutes – See Appendix A

Action Item – Vote to Change Meeting Time and Location – See Appendix B

Update of Medication Coverage Authorization Unit/ SoonerPsych Program Update – See Appendix C

Action Item – Vote to Prior Authorize Ophthalmic Anti-Inflammatories – See Appendix D

Action Item – Vote to Prior Authorize Lorzone™ (Chlorzoxazone) – See Appendix E

Action Item – Vote to Prior Authorize Farxiga™ (Dapagliflozin) and Invokana™ (Canagliflozin) – See Appendix F

Action Item – Vote to Prior Authorize Luzu® (Luliconazole) – Appendix G

Action Item – Vote to Prior Authorize Zorvolex™ (Diclofenac) and Tivorbex™ (Indomethacin) – Appendix H

Annual Review of Anticonvulsant Medications and 30-Day Notice to Prior Authorize Trokendi XR™ (Topiramate ER), Aptiom® (Eliscarbazepine Acetate), and Qudexy™ XR (Topiramate ER) – See Appendix I

30-Day Notice to Prior Authorize Sovaldi™ (Sofosbuvir), Olysio™ (Simeprevir), Victrelis® (Boceprevir), and Incivek® (Telaprevir) – See Appendix J

FDA and DEA Updates – See Appendix K

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board

(DUR Board)

Meeting – May 14, 2014 @ 4:00 p.m.

Oklahoma Health Care Authority
4345 N. Lincoln Blvd.
Oklahoma City, Oklahoma 73105

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. **Call To Order**
   A. Roll Call – Dr. Cothran

Items to be presented by Dr. Muchmore, Chairman:

2. **Public Comment Forum**
   A. Acknowledgment of Speakers and Agenda Items

Items to be presented by Dr. Muchmore, Chairman:

3. **Action Item – Approval of DUR Board Meeting Minutes – See Appendix A**
   A. April 9, 2014 DUR Minutes – Vote
   B. April 9, 2014 DUR Recommendation Memorandum

Items to be presented by Dr. Muchmore, Chairman:

4. **Action Item – Vote to Change Meeting Time and Location – See Appendix B**

Items to be presented by Dr. Holderread, Dr. Muchmore, Chairman:

5. **Update of Medication Coverage Authorization Unit/ SoonerPsych Program Update – See Appendix C**
   A. Medication Coverage Activity for April 2014
   B. Pharmacy Help Desk Activity for April 2014
   C. SoonerPsych Program Update

Items to be presented by Dr. Holderread, Dr. Muchmore, Chairman:

6. **Action Item – Vote to Prior Authorize Ophthalmic Anti-Inflammatories – See Appendix D**
   A. Introduction
   B. COP Recommendations

Items to be presented by Dr. Holderread, Dr. Muchmore, Chairman:

7. **Action Item – Vote to Prior Authorize Lorzone™ (Chlorzoxazone) – See Appendix E**
   A. COP Recommendations

Items to be presented by Dr. Teel, Dr. Muchmore, Chairman:

8. **Action Item – Vote to Prior Authorize Farxiga™ (Dapagliflozin) and Invokana™ (Canagliflozin) – See Appendix F**
   A. COP Recommendations

Items to be presented by Dr. Nawaz, Dr. Muchmore, Chairman:

9. **Action Item – Vote to Prior Authorize Luzu® (Luliconazole) – See Appendix G**
   A. COP Recommendations

Items to be presented by Dr. Adams, Dr. Muchmore, Chairman:

10. Action Item – Vote to Prior Authorize Zorvolex™ (Diclofenac) and Tivorbex™ (Indomethacin) – See Appendix H

A. COP Recommendations

Items to be presented by Dr. Adams, Dr. Muchmore, Chairman:

11. Annual Review of Anticonvulsant Medications and 30-Day Notice to Prior Authorize Trokendi XR™ (Topiramate ER), Aptiom® (Eliscarbazepine Acetate), and Qudexy™ XR (Topiramate ER) – See Appendix I

A. Current Prior Authorization Criteria
B. Utilization of Anticonvulsants
C. Prior Authorization of Anticonvulsants
D. Market News and Updates
E. COP Recommendations
F. Utilization Details
G. Product Details

Items to be presented by Dr. Holderread, Dr. Muchmore, Chairman:

12. 30-Day Notice to Prior Authorize Sovaldi™ (Sofosbuvir), Olysio™ (Simeprevir), Victrelis® (Boceprevir), and Incivek® (Telaprevir) – See Appendix J

A. Introduction
B. Utilization Details Sovaldi™ and Olysio™
C. Market News and Updates
D. Medication Summaries
E. COP Recommendations
F. Utilization Details
G. Product Details

Items to be presented by Dr. Cothran, Dr. Muchmore, Chairman:

13. FDA and DEA Updates – See Appendix K

14. Future Business

A. Annual Reviews
B. New Product Reviews

15. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF APRIL 9, 2014

BOARD MEMBERS:	PRESENT	ABSENT
Mark Feightner, Pharm.D.		x
Anetta Harrell, Pharm.D.	x	
Evie Knisely, Pharm.D.		x
John Muchmore, M.D., Ph.D.; Chairman	x	
Paul Louis Preslar, D.O., MBA	x	
James Rhymer, D.Ph.	x	
Bruna Varalli-Claypool, MHS, PA-C	x	
Eric Winegardener, D.Ph.	x	

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Bethany Holderread, Pharm. D.; Clinical Coordinator	x	
Shellie Keast, Ph.D.; Assistant Professor	x	
Carol Moore, Pharm.D.; Clinical Pharmacist	x	
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Leslie Robinson, D.Ph.; PA Coordinator		x
Jennifer Sipols, Pharm.D.; Clinical Pharmacist		x
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Graduate Students: Tim Pham	x	
Visiting Pharmacy Student(s): Jessica Lou	x	

	PRESENT	ABSENT
Marlene Asmussen, R.N.; Population Care Management Director	x	
Nico Gomez, Chief Executive Officer		x
Sylvia Lopez, M.D., FAAP; Chief Medical Officer	x	
Ed Long, Chief Communications Officer	x	
Jennie Melendez, Marketing Coordinator		x
Nancy Nesser, Pharm.D., J.D.; Pharmacy Director	x	
Rebecca Pasternik-Ikard, Deputy State Medicaid Director		x
Lynn Rambo-Jones, J.D.; Deputy General Counsel III	x	
Jill Ratterman, D.Ph.; Pharmacy Specialist	x	
Garth Splinter, M.D., M.B.A.; Medicaid Director		x
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Clint Degner, Novartis	Jim Chapman, Abbvie	Tone Jones, Sunovion
Melvin Nwamadi, ADC	Ron Cain, Pfiizer	Sharon Jackson, GSK
Toby Thompson, Pfizer	Russ Wilson, Johnson & Johnson	
Mark DeClerk, Lilly	Richard Uhles, Forest	
Warren Tayes, Merck	Charlene Kaiser, Amgen	

PRESENT FOR PUBLIC COMMENT:	
NONE	

AGENDA ITEM NO. 1: **CALL TO ORDER**

1A: ROLL CALL

Dr. Muchmore called the meeting to order. Roll call by Dr. Cothran established the presence of a quorum.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: **PUBLIC COMMENT FORUM**

NONE

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: **APPROVAL OF DUR BOARD MINUTES**

3A: MARCH 12, 2014 DUR MINUTES-VOTE

3B: MARCH 12, 2014 DUR RECOMMENDATION MEMORANDUM

Dr. Harrell moved to approve; seconded by Ms. Varalli-Claypool

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON DUR / MEDICATION COVERAGE AUTHORIZATION UNIT**

4A: MEDICATION COVERAGE ACTIVITY FOR MARCH 2014

4B: PHARMACY HELP DESK ACTIVITY FOR MARCH 2014

4C: NARCOTIC RETRODUR

Materials included in agenda packet; presented by Dr. Holderread

Dr. Muchmore requested details on monthly hydrocodone claims.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **FISCAL YEAR 2013 ANNUAL REPORT**

5A: UTILIZATION DETAILS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 6: **30-DAY NOTICE TO PRIOR AUTHORIZE OPHTHALMIC ANTI-INFLAMMATORY MEDICATIONS**

6A: INTRODUCTION

6B: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 7: **ANNUAL REVIEW OF ANTI-DIABETIC MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE FARXIGA™ (DAPAGLIFLOZIN) AND INVOKANA™ (CANAGLIFLOZIN)**

7A: CURRENT PRIOR AUTHORIZATION CRITERIA
7B: UTILIZATION OF ANTI-DIABETIC MEDICATIONS
7C: PRIOR AUTHORIZATION
7D: MARKET NEWS AND UPDATES
7E: MEDICATION SUMMARIES
7F: RECOMMENDATIONS
7G: UTILIZATION DETAILS
7H: PRODUCT DETAILS

Materials included in agenda packet; presented by Dr. Teel
Dr. Muchmore requested we move Acarbose to Tier-1.
ACTION: NONE REQUIRED

AGENDA ITEM NO. 8: **ANNUAL REVIEW OF TOPICAL ANTIFUNGALS AND 30-DAY NOTICE TO PRIOR AUTHORIZE LUZU® (LULICONAZOLE)**

8A: CURRENT PRIOR AUTHORIZATION CRITERIA
8B: UTILIZATION OF TOPICAL ANTIFUNGAL MEDICATIONS
8C: PRIOR AUTHORIZATION
8D: MARKET NEWS AND UPDATES
8E: MEDICATION SUMMARY
8F: COP RECOMMENDATIONS
8G: UTILIZATION DETAILS
8H: PRODUCT DETAILS

Materials included in agenda packet; presented by Dr. Nawaz
ACTION: NONE REQUIRED

AGENDA ITEM NO. 9: **ANNUAL REVIEW OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ZORVOLEX™ (DICLOFENAC) AND TIVORBEX™ (INDOMETHACIN)**

9A: CURRENT PRIOR AUTHORIZATION CRITERIA
9B: UTILIZATION OF NSAIDS
9C: PRIOR AUTHORIZATION
9D: MARKET NEWS AND UPDATES
9E: MEDICATION SUMMARIES
9F: COP RECOMMENDATIONS
9G: UTILIZATION DETAILS
9H: PRODUCT DETAILS

Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: **ANNUAL REVIEW OF BENIGN PROSTATIC HYPERPLASIA MEDICATIONS**

10A: CURRENT PRIOR AUTHORIZATION CRITERIA
10B: UTILIZATION OF BPH MEDICATIONS
10C: PRIOR AUTHORIZATION
10D: MARKET NEWS AND UPDATES
10E: COP RECOMMENDATIONS
10F: UTILIZATION DETAILS

Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: **ANNUAL REVIEW OF MUSCLE RELAXANTS AND 30-DAY NOTICE TO PRIOR AUTHORIZE LORZONE™ (CHLORZOXAZONE)**

11A: CURRENT PRIOR AUTHORIZATION CRITERIA
11B: UTILIZATION OF MUSCLE RELAXANTS
11C: PRIOR AUTHORIZATION
11D: MARKET NEWS AND UPDATES
11E: MEDICATION SUMMARY
11F: COP RECOMMENDATIONS
11G: UTILIZATION DETAILS
11H: PRODUCT DETAILS

Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: **FDA AND DEA UPDATES**
Materials included in agenda packet; presented by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **FUTURE BUSINESS**
13A: ANNUAL REVIEWS
13B: NEW PRODUCT REVIEWS
Materials included in agenda packet; submitted by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: **ADJOURNMENT**
The meeting was adjourned at 4:48 pm.

The University of Oklahoma
Health Sciences Center
COLLEGE OF PHARMACY
PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: April 10, 2014

To: Nancy Nesser, Pharm.D., J.D.
Pharmacy Director
Oklahoma Health Care Authority

From: Bethany Holderread, Pharm.D.
Clinical Pharmacist
Pharmacy Management Consultants

Subject: DUR Board Recommendations from Meeting of April 09, 2014

Recommendation 1: 30-Day Notice to Prior Authorize Ophthalmic Anti-Inflammatory Medications

NO ACTION REQUIRED.

Recommendation 2: Annual Review of Anti-Diabetic Medications and 30-Day Notice to Prior Authorize Farxiga™ (Dapagliflozin) and Invokana™ (Canagliflozin)

NO ACTION REQUIRED.

Recommendation 3: Annual Review of Topical Antifungals and 30-Day Notice to Prior Authorize Luzu® (Luliconazole)

NO ACTION REQUIRED.

Recommendation 4: Annual Review of Non-Steroidal Anti-Inflammatory Drugs and 30-Day Notice to Prior Authorize Zorvolex™ (Diclofenac) and Tivorbex™ (Indomethacin)

NO ACTION REQUIRED.

Recommendation 5: Annual Review of Benign Prostatic Hyperplasia Medications

NO ACTION REQUIRED.

Recommendation 6: Annual Review of Muscle Relaxants and 30-Day Notice to Prior Authorize Lorzone™ (Chlorzoxazone)

NO ACTION REQUIRED.

Appendix B

VOTE TO CHANGE MEEITNG TIME AND LOCATION

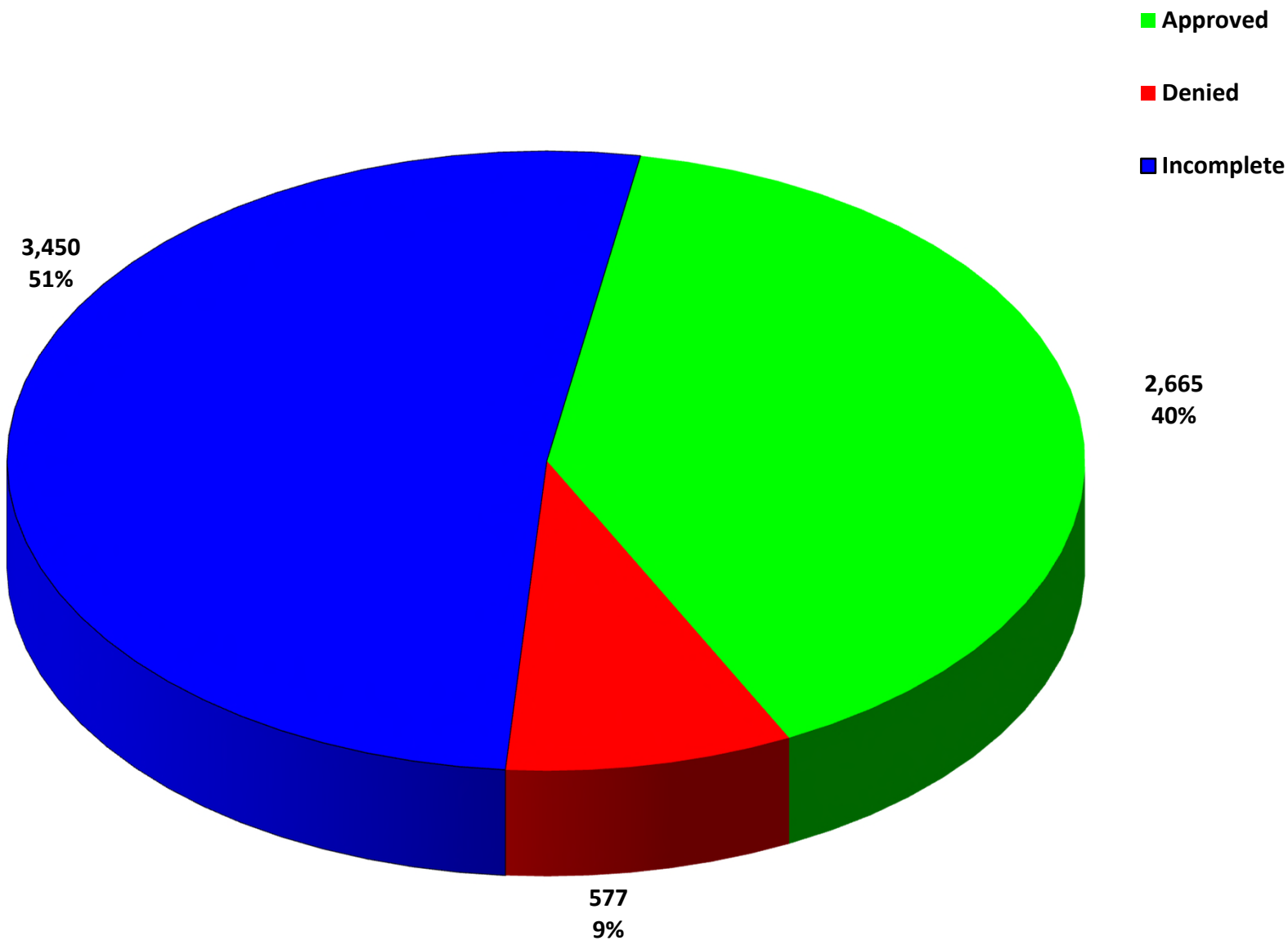
4345 N LINCOLN BLVD.

OKLAHOMA CITY, OK 73105

4:00PM

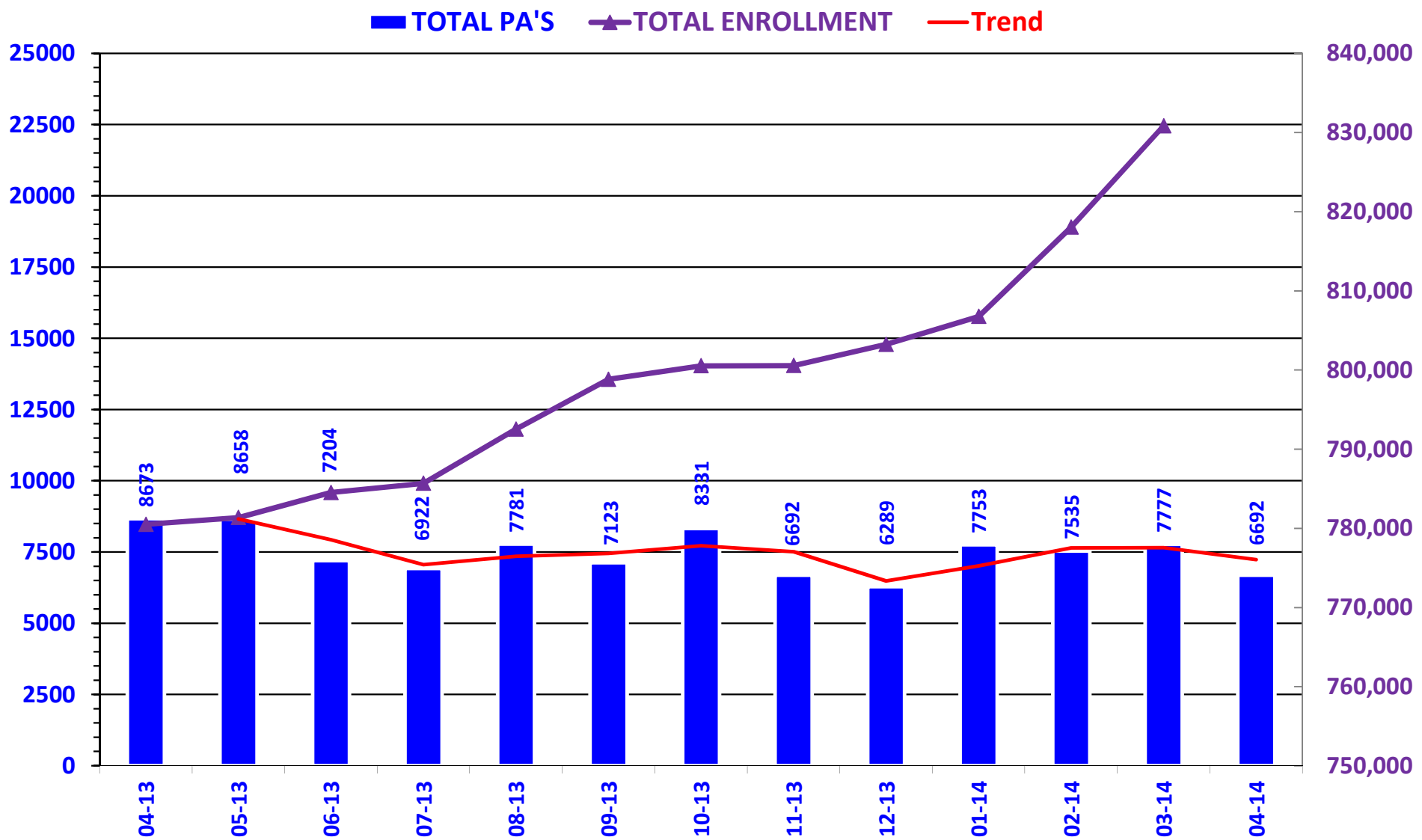
Appendix C

PRIOR AUTHORIZATION ACTIVITY REPORT: APRIL



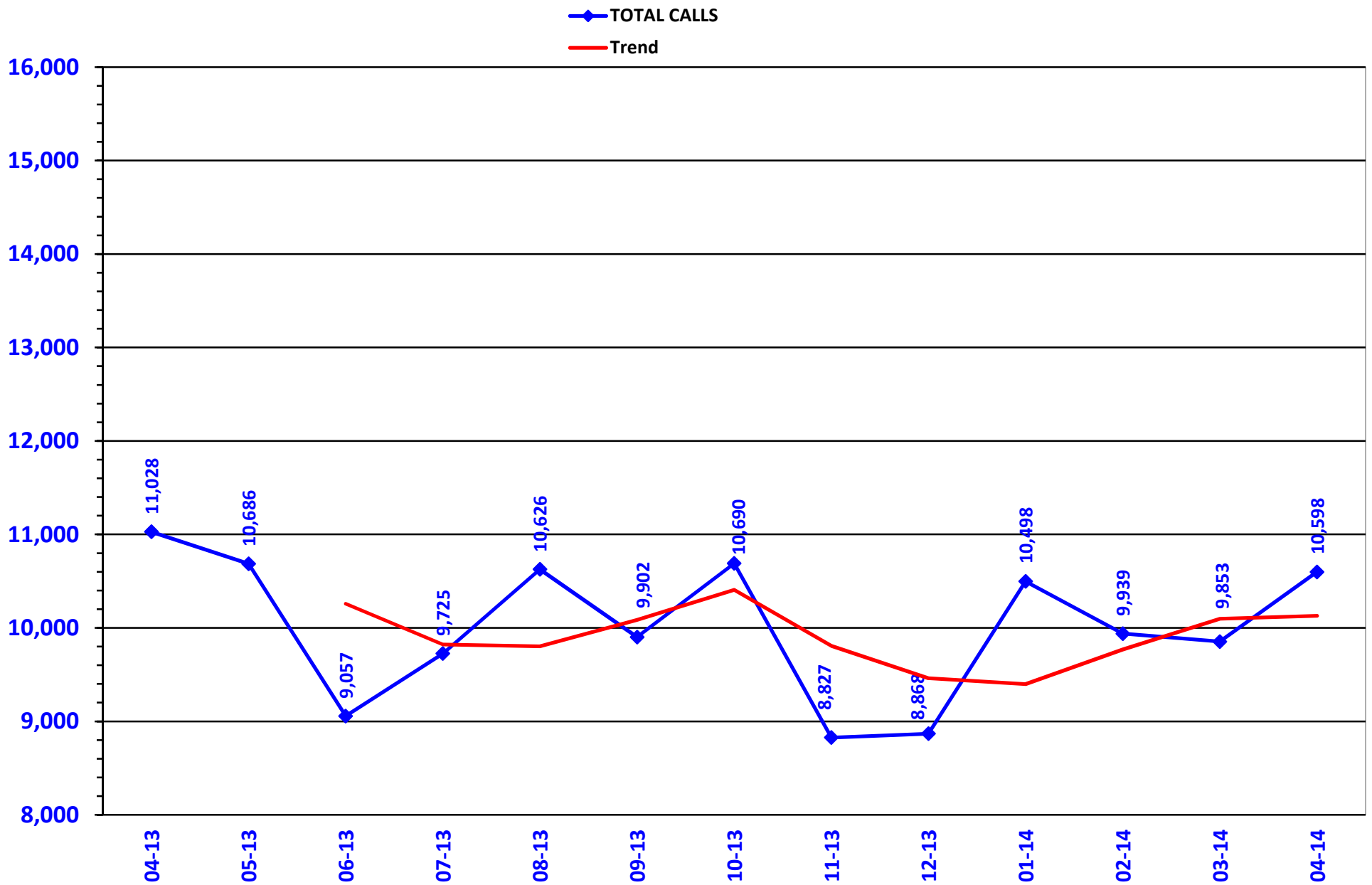
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: APRIL 2013– APRIL 2014



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
APRIL 2013- APRIL 2014



Prior Authorization Activity
4/1/2014 Through 4/30/2014

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	429	188	11	230	352
Analgesic - NonNarcotic	14	1	0	13	54
Analgesic, Narcotic	433	216	17	200	216
Angiotensin Receptor Antagonist	33	9	3	21	358
Antiasthma	330	184	12	134	307
Antibiotic	36	8	1	27	5
Anticoagulant	102	61	2	39	339
Anticonvulsant	64	28	7	29	344
Antidepressant	249	72	16	161	341
Antidiabetic	149	76	4	69	358
Antifungal	17	4	3	10	58
Antigout	11	2	0	9	359
Antihistamine	179	132	3	44	322
Antihyperlipidemic	20	5	1	14	359
Antimigraine	77	22	9	46	295
Antiplatelet	16	7	0	9	359
Antiulcers	246	56	72	118	172
Antiviral	12	4	3	5	160
Anxiolytic	74	50	5	19	256
Atypical Antipsychotics	416	237	4	175	354
Biologics	75	37	6	32	296
Bladder Control	49	5	15	29	290
Botox	18	9	4	5	318
Cardiovascular	46	24	1	21	287
Chronic Obstructive Pulmonary Disease	19	5	5	9	300
Dermatological	142	19	55	68	98
Endocrine & Metabolic Drugs	34	25	4	5	129
Erythropoietin Stimulating Agents	38	23	2	13	109
Fibromyalgia	173	48	21	104	318
Gastrointestinal Agents	153	31	17	105	122
Glaucoma	12	0	0	12	0
Growth Hormones	74	57	4	13	160
HFA Rescue Inhalers	64	19	2	43	333
Insomnia	64	8	13	43	255
Multiple Sclerosis	46	21	3	22	275
Muscle Relaxant	114	34	33	47	62
Nasal Allergy	155	7	51	97	185
Neurological Agents	61	51	2	8	352
Nsaids	192	28	21	143	256
Ocular Allergy	85	16	5	64	171
Ophthalmic Anti-infectives	19	4	3	12	23
Osteoporosis	35	10	3	22	359
Other*	138	21	30	87	231
Otic Antibiotic	25	10	1	14	8
Pediculicide	75	23	1	51	16
Prenatal Vitamins	12	0	0	12	0
Statins	74	29	0	45	359
Stimulant	1,165	474	40	651	334
Suboxone/Subutex	171	130	2	39	72
Testosterone	93	19	11	63	308
Topical Antibiotic	10	3	1	6	65
Topical Antifungal	60	4	4	52	97
Topical Corticosteroids	106	1	20	85	358
Vitamin	67	18	24	25	359
Pharmacotherapy	121	90	0	31	76
Emergency PAs	0	0	0	0	
Total	**6,692**	**2,665**	**577**	**3,450**	

* Includes any therapeutic category with less than 10 prior authorizations for the month.

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Overrides					
Brand	86	64	4	18	282
Cumulative Early Refill	5	5	0	0	180
Dosage Change	379	342	1	36	7
High Dose	2	1	0	1	359
Ingredient Duplication	57	44	4	9	5
Lost/Broken Rx	93	80	7	6	4
NDC vs Age	16	16	0	0	257
Nursing Home Issue	76	76	0	0	6
Other*	27	18	2	7	11
Quantity vs. Days Supply	648	427	35	186	253
STBS/STBSM	26	25	0	1	94
Stolen	11	11	0	0	4
Temporary Unlock	17	11	6	0	17
Third Brand Request	31	17	4	10	34
Overrides Total	**1,469**	**1,132**	**63**	**274**	
Total Regular PAs + Overrides	**8,161**	**3,797**	**640**	**3,724**	

Denial Reasons	
Unable to verify required trials.	3,172
Does not meet established criteria.	662
Lack required information to process request.	512

Other PA Activity	
Duplicate Requests	538
Letters	3,964
No Process	17
Changes to existing PAs	409
Helpdesk Initiated Prior Authorizations	948
PAs Missing Information	35

* Includes any therapeutic category with less than 10 prior authorizations for the month.

SoonerPsych Program Update

Oklahoma Health Care Authority
May 2014

Physician Response to January Mailing: Fazaclo™ and Clozapine ODT Prescribing

A recent review of pharmacy claims history for all prescribers indicated an increase in Fazaclo™ (clozapine orally disintegrating tablet (ODT)) and clozapine ODT prescriptions for SoonerCare members. A letter was sent to prescribers of these medications with the intent to provide information regarding other clozapine formulations which offer cost savings and similar therapeutic effectiveness. Approximately 61 prescribers for 167 members were listed on paid pharmacy claims for Fazaclo™ or clozapine ODT in the 12 month review period.

Packets were mailed to 61 prescribers. The packets included information related to the similar pharmacokinetic properties of the different clozapine formulations. The packets also contained a prescriber summary report showing how their prescribing compared to other prescribers of clozapine products with an optional response page for the prescriber to provide feedback.

Summary of Mailing

Letters/Prescribers	Count
Total Letters Mailed	61
Total Responses Received	19
Members	**Count**
Total Members Included	167

Prescriber Response Summary

Q#	Response	Total*
Q1	I was unaware of the similar pharmacokinetic profiles and will consider using the generic.	3
Q2	I am aware that my Fazaclo™ or clozapine ODT prescribing is above that of my peers and that it creates a significant cost impact to the state, but I do not plan to change my prescribing (please provide additional comments below; if applicable please include descriptions why Fazaclo™ or clozapine ODT is superior to clozapine).	0
Q3	I only prescribe Fazaclo™ or clozapine ODT when I am continuing it from an original psychiatric prescription.	10
Q4	I prescribe Fazaclo™ or clozapine ODT when my patients require a special formulation for administration (please provide additional comments below).	2
Q5	Possible billing error – I do not prescribe Fazaclo™ or clozapine ODT.	4
Q6	I would like to discuss the use of Fazaclo™ or clozapine ODT further. Please call me.	0
Q7	Other, comments.	14

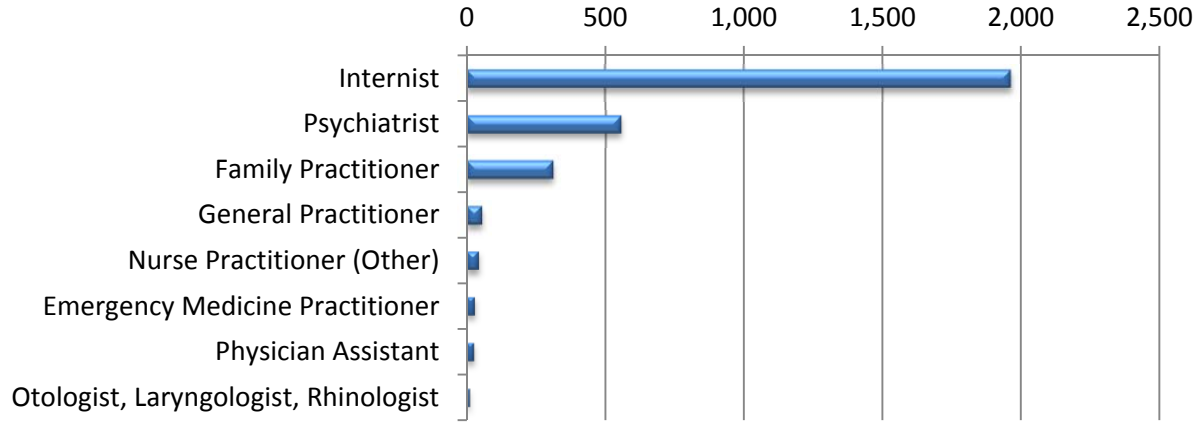
*Responses can be included in multiple categories.

Summary of Additional Comments Provided

Comment Category	Total*
Patient specific information provided.	5
Continuing medications from previous prescriber.	5
Patients are previously stabilized on these medications while inpatient.	4
Not my patient.	2
I plan to reevaluate current prescribing.	1
No longer my patient.	1

*Comments can be included in multiple categories, not all responses listed.

Top Prescriber Specialties of Fazaclo™ and Clozapine ODT by Number of Claims



Last Mailing –May 2014

In order to reach more prescribers and streamline mailings the SoonerPsych program will change its mailing style to a quarterly “report card” for prescribers. The mailing will include a gauge showing prescribers how their prescribing compares to other prescribers of atypical antipsychotics regarding potential differences from generally accepted evidence-based prescribing practices.

The most recent mailing was processed in May and addressed appropriate diagnosis for pediatric and adult members. For this project, inclusion based on diagnosis was determined by the absence of a diagnosis with a strong indication for prescribing an antipsychotic medication. The review period was for one year and was prevalent in nature (not based on a new start of an atypical antipsychotic). Prescribers were eligible for inclusion in the mailing if they had prescribed antipsychotics for members whose recent twelve month medical claims history lacked a diagnosis with a strong indication for prescribing an antipsychotic medication. A total of 200 prescribers were included in the mailing.

Appendix D

Vote to Prior Authorize Ophthalmic Anti-Inflammatory Medications

Oklahoma Health Care Authority
May 2014

Introduction

This category was introduced for possible inclusion in the Product Based Prior Authorization program in February 2014. See the February, March, and April 2014 DUR packet for a more complete discussion of the category. This notice is presented to meet the statutory requirements of 63 O.S. Sec. 5030.5.

Recommendations

The College of Pharmacy recommends establishing a Product Based Prior Authorization category for ophthalmic NSAIDs and ophthalmic corticosteroids to ensure appropriate cost-effective utilization in accordance with current treatment guidelines. The College of Pharmacy recommends the following tier list and criteria to the Drug Utilization Review Board based on cost and clinical effectiveness for approval before referral to the Oklahoma Health Care Authority.

In addition the College of Pharmacy will implement an educational initiative consisting of a targeted mailing to all prescribers of ophthalmic anti-inflammatory medications in the SoonerCare population in the previous 12 months. The mailing may include information regarding approval criteria of ophthalmic anti-inflammatory medications and a link to the OHCA web page which will contain the updated tier chart.

Ophthalmic Non-Steroidal Anti-Inflammatory Drug (NSAIDs) Tier-2 Approval Criteria:

1. Documented trials of all Tier-1 ophthalmic NSAIDs (from different product lines) in the last 30 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
2. Contraindication to all lower tiered medications; or
3. A unique indication for which the Tier-1 anti-inflammatories lack.

Ophthalmic NSAIDs (Non-Steroidal Anti-Inflammatory Drugs)	
Tier-1	**Tier-2**
Voltaren® (diclofenac) Solution 0.1%	Nevanac™ (nepafenac) 0.1% Suspension
Acular® (ketorolac) Solution 0.5%	Acuvail® (ketorolac) Solution 0.45%
Acular LS ® (ketorolac) Solution 0.4%	Ilevro™ (nepafenac) 0.3 % Suspension
Ocufen® (flurbiprofen) Solution 0.03%	Prolensa™ (bromfenac) 0.07% Solution
	Bromfenac 0.09% Solution

Ophthalmic Corticosteroid Tier-2 Approval Criteria:

1. Documented trials of all Tier-1 ophthalmic corticosteroids (from different product lines) in the last 30 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
2. Contraindication to all lower tiered medications; or
3. A unique indication for which the Tier-1 anti-inflammatories lack.

Ophthalmic Corticosteroids	
Tier-1	**Tier-2**
Dexamethasone Sodium Phosphate Solution 0.1%	Lotemax® (loteprednol) Gel 0.5%
Maxidex™ (dexamethasone) Suspension 0.1%	Lotemax® (loteprednol) Ointment 0.5%
FML Liquifilm® (fluorometholone) Suspension 0.1%	Pred Forte® (prednisolone Acetate) Suspension 1%
Flarex® (fluorometholone) Suspension 0.1%	FML Forte® (fluorometholone) Suspension 0.25%
Lotemax® (loteprednol) Suspension 0.5%	FML S.O.P® (fluorometholone) Ointment 0.1%
Omnipred® (prednisolone Acetate) Suspension 1%	
Durezol® (difluprednate) Emulsion 0.05%	
Pred Mild® (prednisolone Acetate) Suspension 0.12%	
Prednisolone Sodium Phosphate Solution 1%	
Vexol® (rimexolone) Suspension 1%	

Appendix E

Vote to Prior Authorize Lorzone™ (Chlorzoxazone)

Oklahoma Health Care Authority
May 2014

Recommendations

The College of Pharmacy recommends the addition of Lorzone™ (chlorzoxazone) to the special PA category of the Skeletal Muscle Relaxants Product Based Prior Authorization category. The following criteria will apply:

Lorzone ™ (Chlorzoxazone) Approval Criteria:

1. Generic chlorzoxazone 500mg tablets must be tried prior to consideration of Lorzone™; and
2. A patient-specific, clinically significant reason why the member cannot use generic chlorzoxazone 500mg tablets must be provided; and
3. The following quantity limits apply:
    a. Lorzone™ 375mg tablets: 120 tablets for 30 days
    b. Lorzone™ 750mg tablets: 120 tablets for 30 days

Skeletal Muscle Relaxants		
Tier-1	**Tier-2**	**Special PA**
Cyclobenzaprine (Flexeril®)	Metaxalone (Skelaxin®)	Carisoprodol (Soma®) 350mg
Baclofen (Lioresal®)		Carisoprodol w Aspirin
Tizanidine (Zanaflex®)		Carisoprodol, ASA, Codeine
Methocarbamol (Robaxin®)		Carisoprodol (Soma®) 250mg
Chlorzoxazone (Parafon Forte®)		Tizanidine Capsules (Zanaflex®)
Orphenadrine (Norflex®)		Cyclobenzaprine ER (Amrix®)
		Cyclobenzaprine 7.5mg (Fexmid®)
		Chlorzoxazone (Lorzone™)

Appendix F

Vote to Prior Authorize Farxiga™ (Dapagliflozin) and Invokana™ (Canagliflozin)

Oklahoma Health Care Authority
May 2014

Recommendations

The College of Pharmacy recommends the addition of Invokana™ and Farxiga™ to Tier-3 of the Anti-Diabetic Product Based Prior Authorization category. The existing criteria for this category will apply. In addition, the College of Pharmacy recommends moving Avandia®, Avandamet®, and Avandaryl® to Tier-3 and Precose® to Tier-1 of the Anti-Diabetic Product Based Prior Authorization category.

Anti-Diabetic Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Biaguanides Metformin (Glucophage®) Metformin SR (Glucophage XR®) Metformin-Glyburide (Glucovance®) Metformin-Glipizide (Metaglip®) **Sulfonylureas** Glyburide (Diabeta®) Glyburide Micronized (Micronase®) Glipizide (Glucotrol®) Glipizide SR (Glucotrol XL®) Glimepiride (Amaryl®) **Miscellaneous** Chlorpropamide Tolbutamide **Alpha-Glucosidase Inhibitors** Acarbose (Precose®)	**DPP-4 Inhibitors** Linagliptin (Tradjenta®) Saxagliptin (Onglyza®) Saxagliptin-Metformin (Kombiglyze®) Sitagliptin (Januvia®) Sitagliptin-Metformin (Janumet®) Sitagliptin-Met ER (Janumet XR®) Sitagliptin-Simvastatin (Juvisync®) Alogliptin-Metformin (Kazano®)1/1/14 Alogliptin (Nesina®) Alogliptin-Pioglitazone (Oseni®) **Glinides** Repaglinide-Metformin (Prandimet®) Repaglinide (Prandin®) Nateglinide (Starlix®) **GLP-1 Agonists** Liraglutide (Victoza®) Exenatide (Byetta®) Exenatide Qweek (Bydureon®) **Thiazolidinediones** Pioglitazone (Actos®)	**DPP-4 Inhibitors** Linagliptin-Metformin (Jentadueto™) **Thiazolidinediones** Pioglitazone-Metformin (Actoplus Met®, Actoplus Met XR®) Pioglitazone-Glimepiride (Duetact®) **Alpha-Glucosidase Inhibitors** Miglitol (Glyset®) **SGLT 2 Inhibitor** Canagliflozin (Invokana™) Dapagliflozin (Farxiga™) **Thiazolidinediones** Rosiglitazone (Avandia®) Rosiglitazone-Metformin (Avandamet®) Rosiglitazone-Glimepiride (Avandaryl®)	**Biaguanides** Metformin solution (Riomet®) Metformin Long-Acting (Fortamet®, Glumetza®) **Amylinomimetic** Pramlintide (Symlin®)

*Tier structure based on supplemental rebate participation.

Appendix G

Vote to Prior Authorize Luzu® (Luliconazole)

Oklahoma Health Care Authority
May 2014

Recommendations

The College of Pharmacy recommends the placement of Luzu® (luliconazole) into Tier-2 of the Topical Antifungal Medications PBPA category. The existing criteria for this category will apply.

Tier-2 Approval Criteria:

1. Documented trials of at least two Tier-1 topical antifungal products within the last 30 days.
2. For treatment of onychomycosis, a trial of oral antifungals (6 weeks for fingernails and 12 weeks for toenails) will be required for consideration of approval of Penlac® (ciclopirox solution).

Topical Antifungal Medications	
Tier-1	**Tier-2**
ciclopirox 0.77% cream	ciclopirox solution, shampoo, & gel (Penlac® and Loprox®), and 0.77% Suspension
clotrimazole 1% Rx cream, solution	miconazole/zinc oxide/white petrolatum (Vusion®)
econazole 1% cream	oxiconazole (Oxistat®)
ketoconazole 2% cream, shampoo	sertaconazole nitrate (Ertaczo®)
nystatin cream, ointment	butenafine (Mentax®)
clotrimazole 1% cream (OTC)*	ketoconazole gel (Xolegel™)
terbinafine 1% cream (OTC)*	Naftifine 1% and 2% cream, 1% and 2% gel (Naftin®)
tolnaftate 1% cream (OTC)*	sulconazole (Exelderm®)
	ketoconazole foam 2% (Extina®)
	nystatin/triamcinolone cream, ointment
	clotrimazole/betamethasone 1% and 0.05% cream, lotion
	Luliconazole cream 1% (Luzu®)

*Over the counter antifungal products are covered for pediatric members 0-20 years of age without prior authorization.

Appendix H

Vote to Prior Authorize
Zorvolex™ (Diclofenac) and Tivorbex™ (Indomethacin)

Oklahoma Health Care Authority
May 2014

Recommendations

The College of Pharmacy recommends the addition of Tivorbex™, based on the placement of other available indomethacin products, and Zorvolex™ to the Special PA category of the NSAIDs Product Based Prior Authorization category. The existing criteria for this category will apply.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)		
Tier-1	**Tier-2**	**Special PA**
Diclofenac potassium (Cataflam®) Diclofenac sodium (Voltaren®) Diclofenac sodium ER (Voltaren® XR) Etodolac (Lodine®) Etodolac ER (Lodine® XL) Flurbiprofen (Ansaid®) Ibuprofen (Motrin®) Ketoprofen (Orudis®) Meclofenamate (Meclomen®) Meloxicam (Mobic®) Nabumetone (Relafen®) Naproxen (Naprosyn®) Naproxen EC (EC-Naprosyn®) Naproxen sodium (Anaprox®) Oxaprozin (Daypro®) Sulindac (Clinoril®) Tolmetin (Tolectin®)	Celecoxib (Celebrex®) Diclofenac /Misoprostol (Arthrotec®) Fenoprofen (Nalfon®)	Diclofenac (Zorvolex™) Diclofenac epolamine patches (Flector®) Diclofenac potassium (Zipsor®) Diclofenac potassium powder packets for oral soln (Cambia®) Diclofenac sodium topical gel (Voltaren® Gel) Diclofenac sodium topical solution (Pennsaid®) Ibuprofen/Famotidine (Duexis®) Indomethacin (Indocin®) Indomethacin (Tivorbex™) Ketoprofen ER (Oruvail®) Mefenamic acid (Ponstel®) Naproxen Sodium (Naprelan®) Naproxen/Esomeprazole (Vimovo®) Piroxicam (Feldene®)

Tier-2 Approval Criteria:

1. Previous use of at least two Tier-1 NSAID products (from different product lines) plus a PPI (proton pump inhibitor) within the last 120 days; or
2. For those with prior GI bleed who must have an NSAID, a Tier-2 product may be approved (Celebrex® should be taken with a PPI).

Special Prior Authorization Criteria:

1. A unique indication for which a Tier-1 or Tier-2 medication is not appropriate, such as the diagnosis of gout for indomethacin; or
2. Previous use of at least two Tier-1 NSAID products (from different product lines); and
3. A patient-specific, clinically significant reason why a special formulation is needed over a Tier-1 product.
4. Additionally, use of Tivorbex™ will require a patient-specific, clinically significant reason why member cannot use other available generic indomethacin products.

Appendix I

Fiscal Year 2013 Annual Review of Anticonvulsant Medications and 30-Day Notice to Prior Authorize Trokendi XR™ (Topiramate Extended-Release), Aptiom® (Eslicarbazepine Acetate), and Qudexy™ XR (Topiramate Extended-Release)

Oklahoma Health Care Authority
May 2014

Current Prior Authorization Criteria

1. Anticonvulsants are included in the current mandatory generic plan.
    a. All brand-name anticonvulsants (with a generic equivalent) require prior authorization.
        i. Brand-name medications (with a generic equivalent) will be approved for all members who are currently stable on these medications and have a seizure diagnosis.
2. Prior authorization is required for certain non-standard dosage forms of medications when the drug is available in standard dosage forms.
    a. Members 12 and older must have a documented medical reason demonstrating need for non-standard dosage forms.
    b. Criteria for approval of extended-release formulations:
        i. Previously stabilized on the short-acting formulation.
        ii. Dosing is not more than once daily.
        iii. A patient-specific, clinically significant reason why the short-acting formulation is not adequate.
    c. Dose packs are not approved if standard dosage forms are available.
3. Quantity limit restrictions have been placed on lower strength tablets and capsules. The highest strengths continue to have no quantity restrictions unless a maximum dose is specified for a particular medication. (Please see Attachment A for additional details)
4. **Felbamate® (Felbatol) Approval Criteria**:
    a. Initial prescription written by a neurologist.
    b. Member has failed therapy with at least three other medications commonly used for seizures.
5. **Onfi® (Clobazam) Approval Criteria:**
    a. Diagnosis of severe seizures or generalized tonic, atonic or myoclonic seizures; and
    b. Previous failure of at least two non-benzodiazepine anticonvulsants; and
    c. Previous failure of clonazepam.
    d. For continuation prescriber must include information regarding improved response/effectiveness of this medication.
6. **Sabril® (Vigabatrin) Approval Criteria:**
    a. FDA approved diagnosis of refractory complex seizures in adults and pediatric patients 10 years or older, or infantile spasms in children ages 1 month to 2 years of age; and

b. Members with refractory complex seizures must have previous trials of at least three other antiepileptic medications; or
c. Members with infantile spasms must have had a previous trial with adrenocorticotropic hormone (ACTH) OR have a diagnosis of infantile spasms with tuberous sclerosis; and
d. Prescription must be written by a neurologist; and
e. Member, prescriber, and pharmacy must all register in the SHARE program and maintain enrollment throughout therapy.

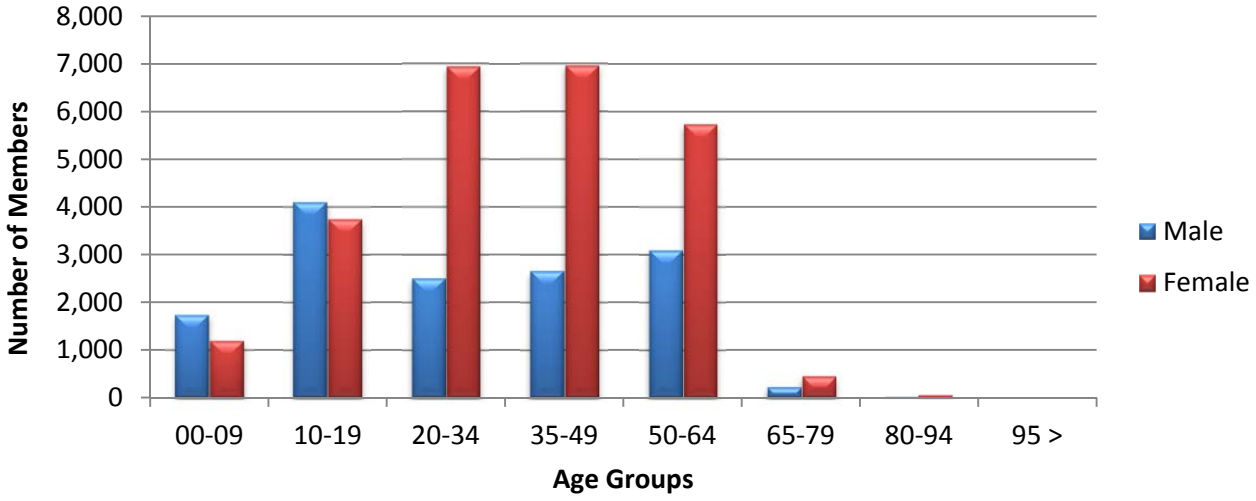
Utilization of Anticonvulsants

Comparison of Fiscal Years

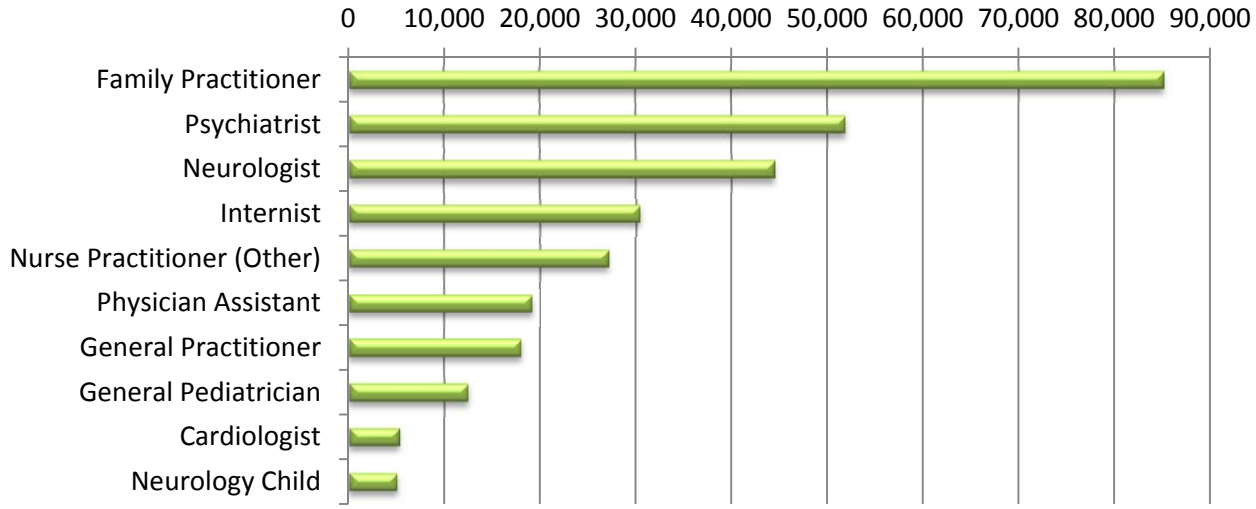
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2012	36,869	251,295	$13,976,962.12	$55.62	$1.84	25,502,085	7,579,181
2013	39,555	262,571	$15,034,382.62	$57.26	$1.88	26,496,724	7,993,301
% Change	**7.30%**	**4.50%**	**7.60%**	**2.90%**	**2.20%**	**3.90%**	**5.50%**
Change	**2,686**	**11,276**	**$1,057,420.50**	**$1.64**	**$0.04**	**994,639**	**414,120**

*Total number of unduplicated members

Demographics of Members Utilizing Anticonvulsants



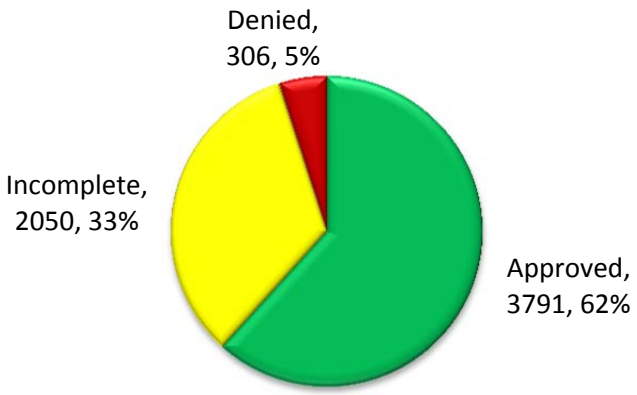
Top Prescriber Specialties of Anticonvulsants by Number of Claims



Prior Authorization of Anticonvulsants

There was a total of 6,147 petitions submitted for anticonvulsants during fiscal year 2013. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3,4,5]

Anticipated Patent Expirations:

- Sabril® (vigabatrin)- 08/2014
- Vimpat® (lacosamide)- 03/2017
- Onfi® (clobazam)-10/2018
- Lyrica® (pregabalin)-12/2018
- Banzel® (rufinamide)-11/2022

New Medications:
In October 2012, the FDA approved Fycompa™ (perampanel) as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ages 12 years and older. Fycompa™ has a novel mechanism of action compared to other available anticonvulsant medications, as it is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over-excitation. The precise mechanism by which Fycompa™ exerts its anticonvulsant effects in humans has not been fully elucidated. Fycompa™ is dosed once daily at bedtime, and is available as a 2, 4, 6, 8, 10, and 12mg tablet. It is dosed to efficacy, with a recommended dosage range of 8 to 12mg once daily at bedtime and the maximum dose being 12mg per day. Fycompa™ is a Schedule III controlled substance and has been available on the market since January 2014. Since its availability in January 2014, there have been 3 SoonerCare members utilizing Fycompa™.

The FDA recently approved two new topiramate products, both of which are once-daily topiramate extended-release capsules. Trokendi XR™ was approved by the FDA and became available on the market in August 2013. Qudexy™ XR was approved by the FDA in March 2014, and is not yet available on the market. Additionally, a new once-daily medication, Aptiom® (eslicarbazepine acetate), was approved by the FDA in November 2013 and became available on the market in February 2014. Trokendi XR™, Qudexy™ XR, and Aptiom® are discussed in more detail below.

Trokendi XR™ (Topiramate Extended-Release Capsules)[6,7]

- **FDA Approved:** August 2013
- **Indication:** Trokendi XR™ (topiramate extended-release) is an antiepileptic drug indicated as monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures and as adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures. Trokendi XR™ is also indicted as adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut Syndrome (LGS).
- **Dosage Forms:** 25mg, 50mg, 100mg, and 200mg oral, extended-release capsules
- **Dosing:**
    - **Monotherapy:**
        - **Partial onset or primary generalized tonic-clonic seizures:** 400mg by mouth once daily
    - **Adjunctive therapy:**
        - **LGS:** 200 to 400mg by mouth once daily
        - **Primary generalized tonic-clonic seizures:** 400mg by mouth once daily
        - **Pediatric patients (6 years of age and older):** 5-9mg/kg by mouth once daily

- **Mechanism of Action:** The precise mechanism of action of Trokendi XR™ is unknown. Evidence suggests that Trokendi XR™ may block voltage-dependent sodium channels, augment the activity of the neurotransmitter gamma-aminobutyrate at the GABA-A receptor, antagonize a subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme.

- **Efficacy:**
  - The efficacy of Trokendi XR™ was established based on the demonstration of pharmacokinetic equivalence of Trokendi XR™ to immediate-release topiramate through analysis of concentrations and cumulative area under the curve (AUCs) at multiple time points.
  - The clinical studies described in the package insert were conducted using immediate-release topiramate.

- **Utilization:**
  - There has been no utilization of Trokendi XR™ in the SoonerCare population since its approval in August 2013.
  - Generic topiramate immediate-release tablets and capsules were utilized by 7,894 members for a total of 35,983 claims during fiscal year 2013.

- **Cost:**

Topiramate Dosage Form	EAC Per Tablet or Capsule	EAC Per Day	EAC for 30 days of Therapy
Trokendi XR™ 200mg Capsules	$20.03	$40.06	$1,201.80
Topiramate 200mg Tablets	$0.18∞	$0.36	$10.80

EAC= estimated acquisition cost
∞ State maximum allowable cost (SMAC) pricing
Daily dosing based on an average daily dose of 400mg/day.

Aptiom® (Eslicarbazepine Acetate Tablets)[8,9,10,11]

- **FDA Approved:** November 2013

- **Indication:** Aptiom® (eslicarbazepine acetate) is an antiepileptic drug indicated as adjunctive treatment of partial onset seizures.

- **Dosage Forms:** 200mg, 400mg, 600mg, and 800mg oral tablets

- **Dosing:**
  - The recommended maintenance dose of Aptiom® is 800mg by mouth once daily.
  - Recommended dosing suggests starting at 400mg by mouth once daily and after one week, increase the dosage to 800mg once daily. The maximum recommended maintenance dosage is 1200mg once daily.

- **Mechanism of Action:** The precise mechanism by which Aptiom® exerts anticonvulsant activity is unknown, but is thought to involve inhibition of voltage-gated sodium channels.

- **Efficacy:** The efficacy of Aptiom® was established in three randomized, double-blind, placebo-controlled, trials in adult patients with epilepsy. Participants had partial-onset seizures with or without secondary generalized seizures and were not adequately controlled with 1 to 3 concomitant antiepileptic drugs (AEDs). During an 8-week baseline period, participants were required to have an average of ≥4 partial-onset seizures per 28 days with no seizure-free period exceeding 21 days. The most commonly used AEDs were carbamazepine (50%), lamotrigine (24%), valproic acid (21%), and levetiracetam (18%). Studies 1 and 2 compared dosages of Aptiom® 400mg, 800mg, and 1200mg once daily with placebo. Study 3 compared dosages of Aptiom® 800mg and 1200mg once daily with placebo. The standardized seizure frequency during the maintenance phase over 28 days was the primary efficacy endpoint in all three trials. The Aptiom® dose of 400 mg/day in studies 1 and 2 did not show a significant treatment effect. A statistically significant effect was observed with Aptiom® treatment at doses of 800 mg/day in Studies 1 and 2 but not in Study 3, and at doses of 1200 mg/day in all 3 studies.

- **Utilization:**
  - There has been no utilization of Aptiom® in the SoonerCare population since its approval in November 2013.

- **Cost:**

Medication and Dosage Form	EAC Per Tablet or Capsule	EAC Per Day	EAC for 30 days of Therapy
Aptiom® 800mg Tablets	$21.10	$21.10	$633.00
Oxcarbazepine 600mg Tablets	$0.49∞	$0.98	$29.40

EAC= estimated acquisition cost
∞ State maximum allowable cost (SMAC) pricing
Daily dosing based on recommended daily dose for indication of adjunctive therapy for partial seizure.

Qudexy™ XR (Topiramate Extended-Release Capsules)[12,13]

- **FDA Approved:** March 2014

- **Indication:** Qudexy™ XR (topiramate extended-release) is an antiepileptic drug indicated as monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures and as adjunctive therapy in patients 2 years of age and older. Qudexy™ XR is also indicated for the treatment of LGS as adjunctive therapy in patients 2 years of age and older.

- **Dosage Forms:** 25mg, 50mg, 100mg, 150mg, and 200mg oral, extended-release capsules

- **Dosing:**
  - **Monotherapy:**
    - **Partial onset or primary generalized tonic-clonic seizures:** 400mg by mouth once daily
  - **Adjunctive therapy:**
    - **LGS:** 200 to 400mg by mouth once daily
    - **Primary generalized tonic-clonic seizures:** 400mg by mouth once daily
    - **Pediatric patients (2 years and older):** 5-9mg/kg by mouth once daily

- **Mechanism of Action:** The precise mechanism of action of Qudexy™ XR is unknown. Evidence suggests that Qudexy™ XR may block voltage-dependent sodium channels, augment the activity of the neurotransmitter gamma-aminobutyrate at the GABA-A receptor, antagonize a subtype of the glutamate receptor, and inhibit the carbonic anhydrase enzyme.

- **Efficacy:** Although a controlled clinical trial was performed the basis for approval of Qudexy™ XR included studies using an immediate-release formulation and the demonstration of the pharmacokinetic equivalence of Qudexy™ XR to immediate-release topiramate through the analysis of concentrations and cumulative AUCs at multiple time points.

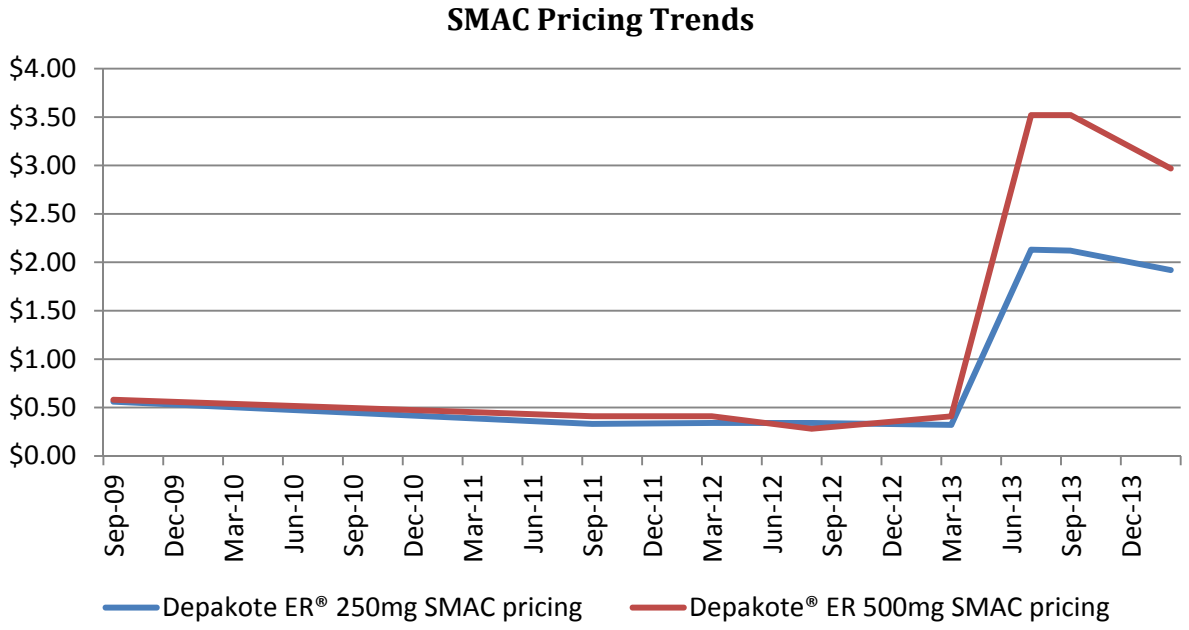
  The effectiveness of Qudexy™ XR as an adjunctive treatment for adults was evaluated in a randomized, double-blind, placebo-controlled trial in patients with a history of partial onset seizures. Patients with partial onset seizures on a stable dose of 1 to 3 AEDs entered into an 8 week baseline period. Patients who experienced at least 8 partial onset seizures, and no more than 21 consecutive seizure free days during the 8 week baseline phase were randomly assigned to placebo or Qudexy™ XR administered once daily in addition to their concomitant AEDs. Patients than entered the maintenance period at the assigned dose of 200 mg once daily, or its placebo equivalent. The percent reduction in the frequency of partial-onset seizures during the baseline period compared to the treatment phase was the primary endpoint. The median percent reduction in seizure rate was 39.5% in patients taking Qudexy™ XR (N=124) and 21.7% in patients taking placebo (N=125). This difference was statistically significant.

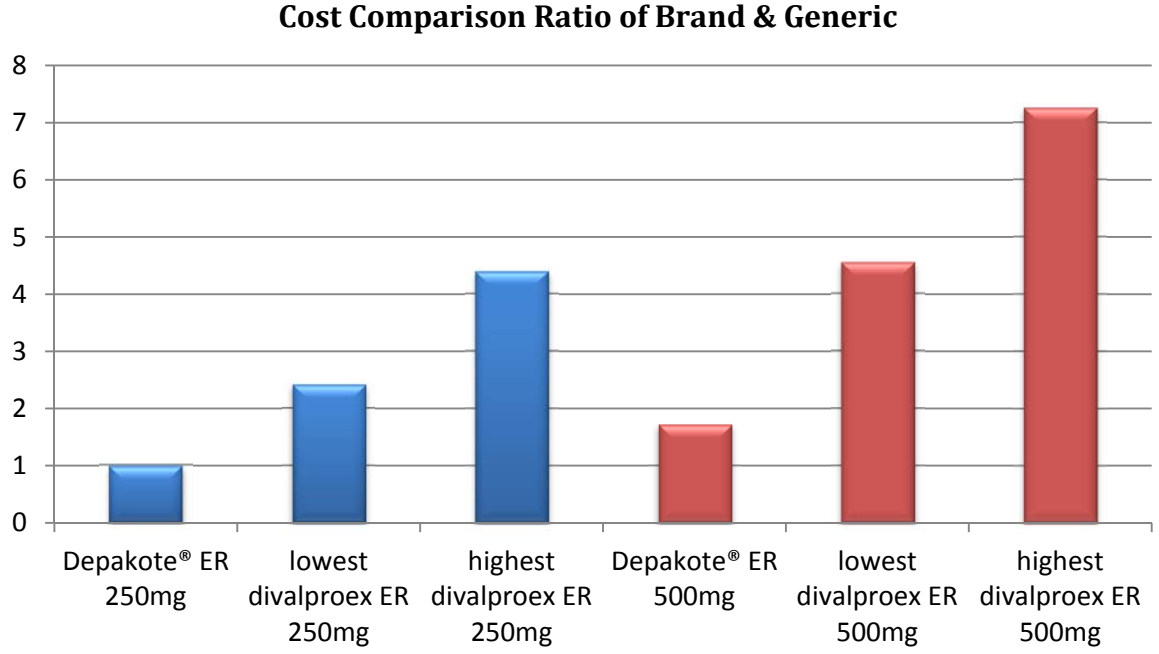
- **Utilization:**
  - There has been no utilization of Qudexy™ XR in the SoonerCare population since its approval in March 2014.
  - Generic topiramate immediate-release tablets and capsules were utilized by 7,894 members for a total of 35,983 claims during fiscal year 2013.

- **Cost:** The estimated acquisition cost of Qudexy™ XR is not yet available.

Discussion[14]

Depakote® ER is indicated in the treatment of adult patients and pediatric patients (10 years of age and older) as monotherapy or adjunctive therapy of complex partial seizures that occur either in isolation or in association with other types of seizures, as monotherapy or adjunctive therapy of simple and complex absence seizures, and as adjunctive therapy of multiple seizure types that include absence seizures. Depakote® ER is also indicated for the prophylaxis of migraine headaches and for the treatment of acute mania or mixed episodes associated with bipolar disorder, with or without psychotic features. In fiscal year 2013, there were 12,144 claims for Depakote® ER brand and generic products for all diagnoses. Depakote® ER is included in the current mandatory generic plan; therefore brand-name Depakote® ER requires prior authorization. As a result of the mandatory generic requirement, generic divalproex ER products comprised 11,882 (97.8%) of the total claims for Depakote® ER brand and generic usage during fiscal year 2013. In July 2013, the state maximum allowable cost (SMAC) pricing of generic divalproex ER products increased drastically. The SMAC pricing dropped slightly in February 2014, but is still significantly more expensive compared to brand name Depakote® ER after taking supplemental rebates into consideration. The utilization details for fiscal year 2013 in this report are not reflective of these changes in cost. Below is a trend chart of the Depakote® ER SMAC pricing, displaying the drastic cost increase, as well as a cost comparison ratio of the brand name and generic products after the inclusion of supplemental rebates.





The above graph shows a cost comparison ratio of brand name Depakote® ER and generic divalproex extended-release, after supplemental rebates. The chart displays ratios of costs and does not reflect actual dollar amounts.

Recommendations

The College of Pharmacy recommends the prior authorization of Trokendi XR™ (topiramate extended-release), Aptiom® (eslicarbazepine acetate), Qudexy™ XR (topiramate extended-release), and generic divalproex extended-release with the following criteria:

1. **Trokendi XR™ (Topiramate Extended-Release) Approval Criteria:**
    a. An FDA approved diagnosis of partial onset or primary generalized tonic-clonic seizures or as adjunctive therapy in seizures associated with Lennox-Gastaut syndrome; and
    b. A patient specific, clinically significant reason why member cannot use the short-acting formulation, Topamax® (topiramate).
    c. A quantity limit of 30 per 30 days will apply on the lower strength capsules (25mg, 50mg, and 100mg) and 60 per 30 days on the higher strength capsules (200mg).
2. **Aptiom® (Eslicarbazepine Acetate) Approval Criteria:**
    a. An FDA approved diagnosis of partial-onset seizures as adjunctive therapy; and
    b. Member must be on current antiepileptic drug therapy (Aptiom® is only indicated for adjunctive treatment); and
    c. Member must <u>not</u> currently be taking oxcarbazepine (concurrent use is contraindicated); and
    d. A patient specific, clinically significant reason why member cannot use oxcarbazepine.
    e. A quantity limit of 30 per 30 days will apply on the lower strength tablets (200mg and 400mg) and 60 per 30 days on the higher strength tablets (600mg and 800mg).

3. **Qudexy™ XR (Topiramate Extended-Release) Approval Criteria:**
    a. An FDA approved diagnosis of partial onset or primary generalized tonic-clonic seizures or as adjunctive therapy in seizures associated with Lennox-Gastaut syndrome; and
    b. A patient specific, clinically significant reason why member cannot use the short-acting formulation, Topamax® (topiramate).
    c. A quantity limit of 30 per 30 days will apply on the lower strength capsules (25mg, 50mg, and 100mg) and 60 per 30 days on the higher strength capsules (150mg and 200mg).
4. **Divalproex ER Approval Criteria:**
    a. Generic divalproex ER will require a patient-specific, clinically significant reason why member cannot use brand name Depakote® ER.
        i. Brand name Depakote® ER will be the preferred product and will not require prior authorization.
    b. Members with a seizure diagnosis currently stabilized on generic divalproex ER in the previous 90 days will be grandfathered.

Utilization Details of Anticonvulsants

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
GABAPENTIN PRODUCTS						
GABAPENTIN CAP 300MG	30,584	9,561	$498,466.55	$0.51	$16.30	3.32%
GABAPENTIN TAB 600MG	15,227	3,416	$540,741.71	$1.15	$35.51	3.60%
GABAPENTIN CAP 100MG	7,436	3,013	$69,689.12	$0.31	$9.37	0.46%
GABAPENTIN TAB 800MG	6,429	1,320	$361,220.53	$1.86	$56.19	2.40%
GABAPENTIN CAP 400MG	3,861	1,090	$58,488.09	$0.50	$15.15	0.39%
GABAPENTIN SOL 250/5ML	494	93	$49,725.93	$3.46	$100.66	0.33%
NEURONTIN CAP 300MG	14	2	$3,150.27	$5.08	$225.02	0.02%
NEURONTIN TAB 800MG	12	1	$5,881.32	$16.34	$490.11	0.04%
NEURONTIN TAB 600MG	4	1	$1,634.28	$4.54	$408.57	0.01%
SUBTOTAL	**64,061**	**15,468***	**$1,588,997.80**	**$0.79**	**$24.80**	**10.57%**
LAMOTRIGINE PRODUCTS						
LAMOTRIGINE TAB 100MG	10,345	2,418	$121,944.94	$0.39	$11.79	0.81%
LAMOTRIGINE TAB 200MG	7,249	1,354	$103,549.77	$0.44	$14.28	0.69%
LAMOTRIGINE TAB 25MG	7,074	2,701	$116,692.76	$0.55	$16.50	0.78%
LAMOTRIGINE TAB 150MG	3,809	821	$49,453.00	$0.42	$12.98	0.33%
LAMOTRIGINE CHW 25MG	448	80	$18,873.12	$1.41	$42.13	0.13%
LAMICTAL TAB 200MG	289	40	$136,644.65	$16.04	$472.82	0.91%
LAMICTAL XR TAB 200MG	266	44	$158,628.72	$20.08	$596.35	1.06%
LAMOTRIGINE CHW 5MG	186	65	$6,053.78	$1.13	$32.55	0.04%
LAMICTAL TAB 150MG	127	15	$66,400.24	$17.47	$522.84	0.44%
LAMICTAL ODT TAB 100MG	105	15	$46,029.87	$14.23	$438.38	0.31%
LAMICTAL TAB 100MG	99	16	$43,649.95	$14.94	$440.91	0.29%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
LAMICTAL XR TAB 100MG	80	16	$61,464.04	$25.77	$768.30	0.41%
LAMICTAL XR TAB 300MG	71	12	$43,024.10	$20.34	$605.97	0.29%
LAMICTAL ODT TAB 200MG	66	9	$31,566.20	$15.94	$478.28	0.21%
LAMICTAL ODT TAB 50MG	57	10	$19,286.40	$11.28	$338.36	0.13%
LAMICTAL XR TAB 50MG	50	16	$16,704.86	$11.53	$334.10	0.11%
LAMICTAL TAB 25MG	49	5	$27,026.16	$18.60	$551.55	0.18%
LAMICTAL ODT TAB 25MG	46	10	$22,782.54	$16.51	$495.27	0.15%
LAMOTRIGINE TAB 200MG ER	46	15	$25,277.81	$17.55	$549.52	0.17%
LAMOTRIGINE TAB 300MG ER	30	9	$18,055.92	$20.06	$601.86	0.12%
LAMICTAL CHW 25MG	24	2	$51,153.53	$71.05	$2,131.40	0.34%
LAMOTRIGINE TAB 50MG ER	19	7	$5,428.23	$9.52	$285.70	0.04%
LAMICTAL XR TAB 25MG	10	1	$3,210.29	$11.89	$321.03	0.02%
LAMICTAL XR TAB 250MG	10	4	$9,532.84	$31.88	$953.28	0.06%
LAMOTRIGINE TAB 100MG ER	9	5	$7,039.72	$26.07	$782.19	0.05%
LAMICTAL KIT START 49	5	5	$1,580.90	$10.61	$316.18	0.01%
LAMOTRIGINE TAB 250MG ER	4	2	$1,930.68	$16.09	$482.67	0.01%
LAMICTAL KIT START 35	1	1	$213.58	$7.63	$213.58	0.00%
SUBTOTAL	**30,574**	**5,466***	**$1,213,198.60**	**$1.29**	**$39.68**	**8.07%**
OXCARBAZAPINE PRODUCTS						
OXCARBAZEPIN TAB 300MG	8,911	2,025	$208,256.57	$0.78	$23.37	1.39%
OXCARBAZEPIN TAB 600MG	6,632	1,134	$284,016.85	$1.42	$42.83	1.89%
OXCARBAZEPIN TAB 150MG	5,758	1,679	$107,611.21	$0.63	$18.69	0.72%
TRILEPTAL SUS 300MG/5M	1,772	338	$592,954.42	$11.14	$334.62	3.94%
OXCARBAZEPIN SUS	1,182	281	$283,188.66	$8.06	$239.58	1.88%
TRILEPTAL TAB 600MG	80	11	$56,222.40	$23.28	$702.78	0.37%
TRILEPTAL TAB 300MG	62	9	$14,686.49	$7.68	$236.88	0.10%
TRILEPTAL TAB 150MG	12	2	$2,418.22	$6.72	$201.52	0.02%
OXTELLAR XR TAB 600MG	6	2	$2,425.46	$13.47	$404.24	0.02%
OXTELLAR XR TAB 300MG	1	1	$135.18	$4.51	$135.18	0.00%
SUBTOTAL	**24,416**	**4,422***	**$1,551,915.46**	**$2.12**	**$63.56**	**10.32%**
LEVETIRACETAM PRODUCTS						
LEVETIRACETA SOL	8,852	1,303	$321,990.00	$1.22	$36.37	2.14%
LEVETIRACETA TAB 500MG	8,728	1,864	$156,658.77	$0.59	$17.95	1.04%
LEVETIRACETA TAB 1000MG	3,653	565	$160,499.62	$1.49	$43.94	1.07%
LEVETIRACETA TAB 750MG	3,144	538	$138,559.12	$1.47	$44.07	0.92%
LEVETIRACETA TAB 250MG	1,328	332	$21,574.63	$0.55	$16.25	0.14%
LEVETIRACETA TAB 500MG ER	564	101	$22,700.21	$1.34	$40.25	0.15%
LEVETIRACETA TAB 750MG ER	294	57	$17,192.73	$1.90	$58.48	0.11%
KEPPRA TAB 500MG	156	24	$80,179.09	$17.61	$513.97	0.53%
KEPPRA SOL 100MG/ML	155	22	$59,153.35	$12.14	$381.63	0.39%
KEPPRA XR TAB 500MG	144	22	$81,398.01	$18.02	$565.26	0.54%
KEPPRA TAB 1000MG	134	19	$108,200.33	$27.20	$807.47	0.72%
KEPPRA XR TAB 750MG	131	15	$96,878.14	$24.61	$739.53	0.64%
KEPPRA TAB 750MG	69	11	$51,042.60	$24.31	$739.75	0.34%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
KEPPRA TAB 250MG	23	5	$5,944.66	$8.62	$258.46	0.04%
LEVETIRACETM INJ 500/5ML	5	4	$1,307.56	$100.58	$261.51	0.01%
SUBTOTAL	**27,380**	**4,243***	**$1,323,278.82**	**$1.61**	**$48.33**	**8.80%**
DIVALPROEX, VALPROATE, & VALPROIC ACID PRODUCTS						
DIVALPROEX TAB 500MG DR	8,440	1,621	$150,284.64	$0.59	$17.81	1.00%
DIVALPROEX TAB 500MG ER	8,201	1,567	$202,134.19	$0.81	$24.65	1.34%
DIVALPROEX TAB 250MG DR	6,376	1,555	$98,188.98	$0.51	$15.40	0.65%
DIVALPROEX TAB 250MG ER	3,681	881	$84,812.03	$0.76	$23.04	0.56%
DIVALPROEX CAP 125MG	2,756	434	$228,009.52	$2.85	$82.73	1.52%
VALPROIC ACD SYP 250/5ML	1,833	266	$25,439.92	$0.49	$13.88	0.17%
VALPROIC ACD CAP 250MG	1,599	318	$55,984.54	$1.18	$35.01	0.37%
DIVALPROEX TAB 125MG DR	1,497	343	$21,218.25	$0.47	$14.17	0.14%
VALPROIC ACD SOL 250/5ML	568	96	$6,453.70	$0.37	$11.36	0.04%
DEPAKOTE SPR CAP 125MG	420	53	$83,081.89	$6.62	$197.81	0.55%
DEPAKOTE ER TAB 500MG	160	22	$51,319.14	$10.63	$320.74	0.34%
DEPAKOTE TAB 500MG DR	142	20	$55,333.55	$13.07	$389.67	0.37%
DEPAKOTE TAB 250MG DR	121	31	$26,149.69	$6.78	$216.11	0.17%
DEPAKOTE ER TAB 250MG	102	15	$31,845.24	$10.16	$312.21	0.21%
DEPAKENE SYP 250/5ML	44	5	$2,099.97	$1.59	$47.73	0.01%
STAVZOR CAP 500MG	36	11	$10,798.38	$10.00	$299.96	0.07%
DEPAKOTE TAB 125MG DR	31	7	$2,324.82	$2.49	$74.99	0.02%
STAVZOR CAP 250MG	29	6	$5,646.73	$6.60	$194.71	0.04%
VALPROATE INJ 100MG/ML	17	4	$8,224.91	$16.13	$483.82	0.05%
STAVZOR CAP 125MG	16	4	$1,362.83	$2.84	$85.18	0.01%
VALPROATE INJ 500/5ML	7	2	$7,889.60	$47.53	$1,127.09	0.05%
SUBTOTAL	**36,076**	**5,617***	**$1,158,602.52**	**$1.07**	**$32.12**	**7.71%**
TOPIRAMATE PRODUCTS						
TOPIRAMATE TAB 50MG	8,234	2,572	$90,316.40	$0.36	$10.97	0.60%
TOPIRAMATE TAB 100MG	7,604	1,646	$97,715.46	$0.42	$12.85	0.65%
TOPIRAMATE TAB 25MG	6,734	2,837	$64,341.55	$0.32	$9.55	0.43%
TOPIRAMATE TAB 200MG	3,073	499	$54,667.04	$0.58	$17.79	0.36%
TOPIRAMATE CAP 25MG	403	93	$33,031.85	$2.73	$81.96	0.22%
TOPIRAMATE CAP 15MG	353	120	$19,950.07	$1.90	$56.52	0.13%
TOPAMAX TAB 100MG	89	12	$51,214.71	$19.67	$575.45	0.34%
TOPAMAX SPR CAP 25MG	46	4	$40,238.22	$29.16	$874.74	0.27%
TOPAMAX TAB 200MG	45	5	$25,678.25	$19.02	$570.63	0.17%
TOPAMAX TAB 25MG	27	3	$4,116.17	$5.08	$152.45	0.03%
TOPAMAX TAB 50MG	23	3	$14,067.92	$20.39	$611.65	0.09%
TOPAMAX SPR CAP 15MG	12	3	$7,280.68	$17.33	$606.72	0.05%
SUBTOTAL	**26,643**	**6,281***	**$502,618.32**	**$0.62**	**$18.86**	**3.34%**
PHENYTOIN PRODUCTS						
PHENYTOIN EX CAP 100MG	7,655	1,343	$180,501.56	$0.78	$23.58	1.20%
DILANTIN CAP 100MG	1,301	207	$92,391.70	$2.33	$71.02	0.61%
PHENYTOIN SUS 125/5ML	592	76	$24,459.71	$1.62	$41.32	0.16%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
DILANTIN CHW 50MG	465	88	$22,470.03	$1.60	$48.32	0.15%
PHENYTOIN CHW 50MG	183	56	$5,837.27	$1.05	$31.90	0.04%
PHENYTOIN EX CAP 300MG	150	48	$7,864.67	$1.60	$52.43	0.05%
DILANTIN CAP 30MG	115	20	$4,612.28	$1.31	$40.11	0.03%
PHENYTOIN EX CAP 200MG	96	33	$4,840.28	$1.54	$50.42	0.03%
DILANTIN-125 SUS 125/5ML	34	4	$2,504.72	$2.46	$73.67	0.02%
PHENYTEK CAP 300MG	25	6	$1,936.76	$1.87	$77.47	0.01%
PHENYTEK CAP 200MG	23	4	$1,466.26	$2.53	$63.75	0.01%
SUBTOTAL	**10,639**	**1,643***	**$348,885.24**	**$1.09**	**$32.79**	**2.32%**
CARBAMAZEPINE PRODUCTS						
CARBAMAZEPIN TAB 200MG	5,185	1,040	$45,367.60	$0.29	$8.75	0.30%
CARBAMAZEPIN CHW 100MG	1,370	271	$29,549.09	$0.72	$21.57	0.20%
EPITOL TAB 200MG	866	222	$4,899.52	$0.19	$5.66	0.03%
CARBAMAZEPIN TAB 200MG	709	176	$39,832.18	$1.87	$56.18	0.26%
CARBAMAZEPIN TAB 400MG	670	104	$66,113.13	$3.23	$98.68	0.44%
CARBAMAZEPIN CAP 300MG	574	87	$70,659.99	$4.08	$123.10	0.47%
CARBAMAZEPIN CAP 200MG	404	61	$59,734.42	$4.96	$147.86	0.40%
CARBAMAZEPIN SUS 100/5ML	369	50	$43,260.74	$4.15	$117.24	0.29%
TEGRETOL-XR TAB 100MG	231	47	$11,897.20	$1.62	$51.50	0.08%
TEGRETOL-XR TAB 200MG	188	23	$26,310.76	$4.53	$139.95	0.18%
TEGRETOL TAB 200MG	165	20	$33,935.29	$6.54	$205.67	0.23%
TEGRETOL-XR TAB 400MG	160	20	$28,279.81	$5.58	$176.75	0.19%
CARBATROL CAP 300MG	142	17	$20,115.22	$4.90	$141.66	0.13%
CARBATROL CAP 200MG	128	16	$27,993.97	$7.17	$218.70	0.19%
CARBAMAZEPIN CAP 100MG	115	27	$9,619.06	$2.75	$83.64	0.06%
TEGRETOL SUS 100/5ML	114	13	$20,305.21	$6.16	$178.12	0.14%
CARBATROL CAP 100MG	40	5	$7,030.50	$5.86	$175.76	0.05%
TEGRETOL CHW 100MG	1	1	$54.67	$1.82	$54.67	0.00%
SUBTOTAL	**11,431**	**1,880***	**$544,958.36**	**$1.58**	**$47.67**	**3.62%**
PREGABALIN PRODUCTS						
LYRICA CAP 150MG	3,225	611	$751,635.77	$7.81	$233.07	5.00%
LYRICA CAP 75MG	2,468	672	$542,701.87	$7.37	$219.90	3.61%
LYRICA CAP 100MG	1,986	438	$506,294.29	$8.54	$254.93	3.37%
LYRICA CAP 50MG	1,115	360	$266,746.35	$7.96	$239.23	1.77%
LYRICA CAP 300MG	784	130	$165,107.79	$6.79	$210.60	1.10%
LYRICA CAP 200MG	589	123	$124,013.89	$7.07	$210.55	0.82%
LYRICA CAP 225MG	251	53	$54,433.15	$7.22	$216.87	0.36%
LYRICA CAP 25MG	171	64	$33,552.83	$6.65	$196.22	0.22%
SUBTOTAL	**10,589**	**1,949***	**$2,444,485.94**	**$7.71**	**$230.85**	**16.26%**
ZONISAMIDE PRODUCTS						
ZONISAMIDE CAP 100MG	2,376	323	$56,031.01	$0.81	$23.58	0.37%
ZONISAMIDE CAP 50MG	824	143	$12,822.51	$0.52	$15.56	0.09%
ZONISAMIDE CAP 25MG	735	148	$12,292.41	$0.57	$16.72	0.08%
ZONEGRAN CAP 100MG	52	7	$26,643.07	$16.86	$512.37	0.18%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
ZONEGRAN CAP 25MG	6	1	$482.97	$2.68	$80.50	0.00%
SUBTOTAL	**3,993**	**472***	**$108,271.97**	**$0.92**	**$27.12**	**0.72%**
PHENOBARBITAL PRODUCTS						
PHENOBARB TAB 64.8MG	1,477	254	$18,197.30	$0.41	$12.32	0.12%
PHENOBARB TAB 32.4MG	1,311	235	$18,799.60	$0.48	$14.34	0.13%
PHENOBARB ELX 20MG/5ML	1,141	227	$34,716.07	$1.13	$30.43	0.23%
PHENOBARB TAB 30MG	935	178	$12,233.18	$0.44	$13.08	0.08%
PHENOBARB TAB 97.2MG	637	108	$8,450.89	$0.42	$13.27	0.06%
PHENOBARB SOL 20MG/5ML	598	116	$17,566.64	$1.04	$29.38	0.12%
PHENOBARB TAB 60MG	579	122	$4,787.42	$0.27	$8.27	0.03%
PHENOBARB TAB 15MG	240	43	$2,761.36	$0.39	$11.51	0.02%
PHENOBARB TAB 16.2MG	188	38	$2,584.97	$0.47	$13.75	0.02%
PHENOBARB TAB 100MG	57	13	$465.91	$0.27	$8.17	0.00%
PHENOBARB INJ 130MG/ML	4	2	$624.32	$5.20	$156.08	0.00%
SUBTOTAL	**7,167**	**1,074***	**$121,187.66**	**$0.57**	**$16.91**	**0.81%**
LACOSAMIDE PRODUCTS						
VIMPAT TAB 100MG	1,075	197	$500,858.92	$15.82	$465.92	3.33%
VIMPAT TAB 200MG	968	134	$495,399.17	$17.21	$511.78	3.30%
VIMPAT TAB 50MG	481	124	$130,920.69	$9.18	$272.18	0.87%
VIMPAT SOL 10MG/ML	460	61	$167,556.40	$13.02	$364.25	1.11%
VIMPAT TAB 150MG	381	74	$184,629.76	$16.36	$484.59	1.23%
VIMPAT INJ 200MG/20	1	1	$410.21	$82.04	$410.21	0.00%
SUBTOTAL	**3,366**	**426***	**$1,479,775.15**	**$14.97**	**$439.62**	**9.84%**
CLOBAZAM PRODUCTS						
ONFI TAB 10MG	800	116	$376,010.88	$16.22	$470.01	2.50%
ONFI TAB 20MG	465	72	$335,283.14	$24.41	$721.04	2.23%
ONFI TAB 5MG	224	60	$39,035.16	$6.02	$174.26	0.26%
SUBTOTAL	**1,489**	**182***	**$750,329.18**	**$17.29**	**$503.91**	**4.99%**
ETHOSUXIMIDE PRODUCTS						
ETHOSUXIMIDE CAP 250MG	702	112	$54,879.42	$2.62	$78.18	0.37%
ETHOSUXIMIDE SOL 250/5ML	631	113	$42,492.59	$2.27	$67.34	0.28%
ZARONTIN CAP 250MG	31	4	$5,411.05	$5.82	$174.55	0.04%
SUBTOTAL	**1,364**	**210***	**$102,783.06**	**$2.53**	**$75.35**	**0.68%**
PRIMIDONE PRODUCTS						
PRIMIDONE TAB 50MG	539	112	$9,807.51	$0.57	$18.20	0.07%
PRIMIDONE TAB 250MG	420	53	$9,566.06	$0.71	$22.78	0.06%
MYSOLINE TAB 250MG	19	2	$14,395.79	$20.28	$757.67	0.10%
SUBTOTAL	**978**	**160***	**$33,769.36**	**$1.07**	**$34.53**	**0.22%**
RUFINAMIDE PRODUCTS						
BANZEL TAB 400MG	473	49	$487,684.60	$34.42	$1,031.05	3.24%
BANZEL TAB 200MG	126	20	$26,031.06	$6.99	$206.60	0.17%
BANZEL SUS 40MG/ML	104	18	$71,672.23	$24.60	$689.16	0.48%
SUBTOTAL	**703**	**83***	**$585,387.89**	**$28.13**	**$832.70**	**3.89%**
ACETAZOLAMIDE PRODUCTS						

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
ACETAZOLAMID TAB 250MG	420	122	$18,288.39	$1.47	$43.54	0.12%
ACETAZOLAMID CAP 500MG	219	82	$32,421.98	$4.98	$148.05	0.22%
ACETAZOLAMID TAB 125MG	43	12	$1,317.03	$1.05	$30.63	0.01%
SUBTOTAL	**682**	**204***	**$52,027.40**	**$2.57**	**$76.29**	**0.35%**
FELBAMATE PRODUCTS						
FELBAMATE TAB 600MG	207	19	$100,652.45	$16.17	$486.24	0.67%
FELBATOL TAB 600MG	108	14	$74,483.45	$22.93	$689.66	0.50%
FELBAMATE SUS 600/5ML	86	8	$80,792.97	$35.88	$939.45	0.54%
FELBATOL TAB 400MG	72	9	$37,185.15	$15.35	$516.46	0.25%
FELBAMATE TAB 400MG	65	10	$21,380.44	$11.14	$328.93	0.14%
FELBATOL SUS 600/5ML	45	6	$45,213.27	$34.73	$1,004.74	0.30%
SUBTOTAL	**583**	**58***	**$359,707.73**	**$20.71**	**$616.99**	**2.39%**
METHSUXIMIDE PRODUCTS						
CELONTIN CAP 300MG	85	8	$12,181.29	$4.83	$143.31	0.08%
SUBTOTAL	**85**	**8***	**$12,181.29**	**$4.83**	**$143.31**	**0.08%**
VIGABATRIN PRODUCTS						
SABRIL POW 500MG	83	12	$420,388.40	$168.83	$5,064.92	2.80%
SABRIL TAB 500MG	25	4	$201,512.27	$268.68	$8,060.49	1.34%
SUBTOTAL	**108**	**14***	**$621,900.67**	**$191.94**	**$5,758.34**	**4.14%**
TIAGABINE PRODUCTS						
GABITRIL TAB 4MG	82	19	$53,162.26	$20.48	$648.32	0.35%
TIAGABINE TAB 4MG	61	16	$29,784.62	$16.23	$488.27	0.20%
GABITRIL TAB 12MG	22	7	$8,769.12	$12.44	$398.60	0.06%
GABITRIL TAB 16MG	16	4	$6,441.99	$13.42	$402.62	0.04%
GABITRIL TAB 2MG	2	2	$1,199.18	$19.66	$599.59	0.01%
SUBTOTAL	**183**	**33***	**$99,357.17**	**$17.50**	**$542.94**	**0.66%**
EZOGABINE PRODUCTS						
POTIGA TAB 50MG	26	7	$6,865.74	$8.31	$264.07	0.05%
POTIGA TAB 200MG	20	7	$16,146.67	$26.87	$807.33	0.11%
POTIGA TAB 300MG	8	3	$3,976.84	$16.57	$497.11	0.03%
POTIGA TAB 400MG	6	1	$3,766.68	$20.93	$627.78	0.03%
SUBTOTAL	**60**	**13***	**$30,755.93**	**$16.65**	**$512.60**	**0.20%**
FOSPHENYTOIN PRODUCTS						
FOSPHENYTOIN INJ 100/2ML	1	1	$7.10	$7.10	$7.10	0.00%
SUBTOTAL	**1**	**1***	**$7.10**	**$7.10**	**$7.10**	**0.00%**
TOTAL	**262,571**	**39,555***	**$15,034,382.62**	**$1.88**	**$57.26**	**100.00%**

*Total number of unduplicated members

PRODUCT DETAILS OF TROKENDI XR™ (TOPIRAMATE EXTENDED-RELEASE)

INDICATIONS AND USE: Trokendi XR™ (topiramate) is an anticonvulsant indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures, as adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures, and as adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome.

DOSAGE FORMS: Trokendi XR™ is available as 25mg, 50mg, 100mg, and 200mg extended-release capsules.

ADMINISTRATION:

- The recommended dose of Trokendi XR™ for monotherapy in adults and pediatric patients 10 years of age and older is 400mg orally once daily. Trokendi XR™ should be titrated, starting with 50mg once daily (week 1), followed by 100mg once daily (week 2), 150mg once daily (week 3), 200mg once daily (week 4), 300mg once daily (week 5), and finally to the recommended dose, 400mg once daily (week 6).
- The recommended total daily dose of Trokendi XR™ as adjunctive therapy in adults (17 years of age and older) with partial onset seizures or Lennox-Gastaut syndrome is 200-400mg orally once daily, with primary generalized tonic-clonic seizures is 400mg orally once daily. Initiate therapy at 25-50mg once daily followed by titration to an effective dose in increments of 25-50mg every week. Daily topiramate doses about 1600mg have not been studied.
- The recommended total daily dose of Trokendi XR™ as adjunctive therapy in pediatric patients (ages 6 years to 16 years) with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5-9mg/kg orally once daily. Begin titration at 25mg once daily (based on a range of 1-3mg/kg/day) given nightly for the first week. Subsequently, increase the dosage at 1- or 2-week intervals by increments of 1-3mg/kg to achieve optimal clinical response. Dose titration should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.
- Trokendi XR™ capsules should be swallowed whole and intact. Do not sprinkle on food, chew or crush.
- Trokendi XR™ can be taken without regard to meals.
- Alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR™ administration.
- In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose. Prior to dosing, obtain an estimated GFR measurement in patients at high risk for renal insufficiency (e.g., older patients, or those with diabetes mellitus, hypertension, or autoimmune disease).
- Trokendi XR™ is cleared by hemodialysis at a rate that is 4-6 times greater than in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause Trokendi XR™ concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in Trokendi XR™ plasma concentration during hemodialysis, a supplemental dose of Trokendi XR™ may be required. The actual

adjustment should take into account the duration of dialysis period, clearance rate of the dialysis system being used, and effective renal clearance of Trokendi XR™ in the patient being dialyzed.

- Measurement of baseline and periodic serum bicarbonate during Trokendi XR™ treatment is recommended.
- It is not necessary to monitor topiramate plasma concentrations to optimize Trokendi XR™ therapy.
- The co-administration of Trokendi XR™ with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with Trokendi XR™ may require adjustment of the dose of Trokendi XR™.

CONTRAINDICATIONS:

- Patients with recent alcohol use (i.e., within 6 hours prior to and 6 hours after Trokendi XR™ use).
- Patients with metabolic acidosis who are taking concomitant metformin.

SPECIAL POPULATIONS:

- **Pregnancy:** Trokendi XR™ can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have increased risk for cleft lip and/or cleft palate (oral clefts). Trokendi XR™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. (Category D).
- **Women of Childbearing Potential:** Consider the benefits and risks of Trokendi XR™ when prescribing this drug to women of childbearing potential, particularly when Trokendi XR™ is considered for a condition not usually associated with permanent injury or death. Because the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be apprised of the potential hazard to the fetus from exposure to topiramate. If the decision is made to use Trokendi XR™, women who are not planning a pregnancy should use effective contraception. Women who are planning a pregnancy should be counseled regarding the relative risks and benefits of Trokendi XR™ use during pregnancy, and alternative treatment options should be considered for these patients.
- **Labor and Delivery:** Although the effect of Trokendi XR™ on labor and delivery in humans has not been established, the development of Trokendi XR™ -induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor.
- **Nursing Mothers:** Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when Trokendi XR™ is administered to a nursing woman.

- **Pediatrics:** Because the capsule must be swallowed whole, and may not be sprinkled on food, crushed, or chewed, Trokendi XR™ is recommended only for children age 6 or older. The safety and effectiveness of Trokendi XR™ in pediatric patients is based on controlled trials with immediate-release topiramate. The safety and effectiveness of Trokendi XR™ in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures or seizures associated with Lennox-Gastaut syndrome.
- **Geriatrics:** Clinical studies of immediate-release topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment is necessary for elderly with creatinine clearance < 70 mL/min/1.73m^2. Estimated GFR should be measured prior to dosing.
- **Renal Impairment:** The clearance of Trokendi XR™ was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance less than 30 mL/min/1.73m^2). One-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment.
- **Patients Undergoing Hemodialysis:** Trokendi XR™ is cleared by hemodialysis at a rate that is 4-6 times greater than in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause the Trokendi XR™ concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in Trokendi XR™ plasma concentration during hemodialysis, a supplemental dose of Trokendi XR™ may be required. The actual adjustment should take into account the duration of dialysis period, clearance rate of the dialysis system being used, and effective renal clearance of Trokendi XR™ in the patient being dialyzed.
- **Hepatic Impairment:** In patients with hepatic impairment, the clearance of Trokendi XR™ may be decreased; however, the mechanism underlying the disease is not well understood.

WARNINGS AND PRECAUTIONS:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including Trokendi XR™, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Anyone considering prescribing Trokendi XR™ or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or

behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

- **Acute Myopia and Secondary Angle Closure Glaucoma:** A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber swallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary acute closure glaucoma. Symptoms typically occur within 1 month of initiating Trokendi XR™ therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of Trokendi XR™ as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of Trokendi XR™, may be helpful. Elevated intraocular pressure, if left untreated, can lead to serious sequelae including permanent vision loss.
- **Oligohydrosis and Hyperthermia:** Oligohydrosis (decreased sweating), resulting in hospitalization in some cases, has been reported in association with topiramate use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of reports have been in pediatric patients. Patients, especially pediatric patients, treated with Trokendi XR™ should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when Trokendi XR™ is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.
- **Metabolic Acidosis:** Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate, and can be expected with treatment with Trokendi XR™. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of topiramate. Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk for fractures. Chronic metabolic acidosis in pediatric patients may also

reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

- **Interaction with Alcohol:** In vitro data show that, in the presence of alcohol, the pattern of topiramate release from Trokendi XR™ capsules is significantly altered. As a result, plasma levels of topiramate with Trokendi XR™ may be markedly higher soon after dosing and subtherapeutic later in the day. Therefore, alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR™ administration.
- **Cognitive/Neuropsychiatric Adverse Reactions:** Adverse reactions most often associated with the use of topiramate, and therefore expected to be associated with the use of Trokendi XR™ were related to the central nervous system and were observed in the epilepsy population. In adults, the most frequent of these can be classified into three general categories: cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, or speech or language problems, particularly word-finding difficulties); psychiatric/behavioral disturbances (e.g. depression or mood problems); and somnolence or fatigue.
- **Fetal Toxicity:** Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Consider the benefits and risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.
- **Withdrawal of Antiepileptic Drugs:** In patients with or without a history of seizures or epilepsy, antiepileptic drugs including Trokendi XR™ should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In situations where rapid withdrawal of Trokendi XR™ is medically required, appropriate monitoring is recommended.
- **Hyperammonemia and Encephalopathy:** Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs in very young pediatric patients (1 month to 24 months) who were treated with adjunctive topiramate for partial onset epilepsy. Trokendi XR™ is not approved as adjunctive treatment of partial onset seizures in pediatric patients less than 6 years old. In some patients, ammonia was markedly increased (greater than 50% above the upper limit of normal). The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Concomitant administration of topiramate

and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. This adverse reaction is not due to a pharmacokinetic interaction. The hyperammonemia associated with topiramate treatment appears to be more common when used concomitantly with valproic acid. In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

- **Kidney Stones:** A total of 32/2086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. Trokendi XR™ would be expected to have the same effect as topiramate on the formation of kidney stones. An explanation for the association of topiramate and kidney stones may lay in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (e.g. zonisamide, acetazolamide, or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of Trokendi XR™ with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.
- **Hypothermia with Concomitant Valproic Acid Use:** Hypothermia, defined as an unintentional drop in body core temperature to less than 35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid both in the presence and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproic acid can occur after starting topiramate treatment or after increasing the daily dose of topiramate. Consideration should be given to stopping topiramate or valproic acid in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.
- **Paresthesia:** Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of topiramate. In the majority of instances, paresthesia did not lead to treatment discontinuation.
- **Interaction with Other CNS Depressants:** Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs can result in significant CNS depression. Patients should be watched carefully when Trokendi XR™ is co-administered with other CNS depressant drugs.

ADVERSE REACTIONS:

- Serious adverse reactions (discussed elsewhere in the labeling):
  - Suicidal behavior and ideation, acute myopia and secondary angle closure, oligohydrosis and hyperthermia, metabolic acidosis, cognitive/neuropsychiatric adverse reactions, fetal toxicity, withdrawal of antiepileptic drugs, hyperammonemia and encephalopathy (without and with concomitant valproic acid use), kidney stones, hypothermia with concomitant valproic acid use, and paresthesia.
- Common adverse reactions:
  - Paresthesia, weight decrease, somnolence, anorexia, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, diplopia, fatigue, asthenia, insomnia, anxiety, difficulty with concentration/attention, confusion, depression, nervousness, upper respiratory tract infection, diarrhea, difficulty with memory, aggressive reaction, aggravated convulsions, language problems, personality disorder, and mood problems.
- Laboratory abnormalities:
  - Decreased serum bicarbonate level, decreased serum phosphorus, increased serum alkaline phosphatase, decreased serum potassium, increased serum creatinine, and hyperammonemia (with or without encephalopathy).

DRUG INTERACTIONS:

- **Alcohol:** Alcohol use is contraindicated within 6 hours prior to and 6 hours after Trokendi XR™ administration. In vitro data show that, in the presence of alcohol, the pattern of topiramate release from Trokendi XR™ capsules is significantly altered. As a result, plasma levels of topiramate with Trokendi XR™ may be markedly higher soon after dosing and subtherapeutic later in the day. Therefore, alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR™ administration.
- **Oral Contraceptives:** Exposure to ethinyl estradiol was statistically significantly decreased when topiramate (at doses above 200mg) was given as adjunctive therapy in patients taking valproic acid. However, norethindrone exposure was not significantly affected. Another study with a concomitantly administered combination oral contraceptive product (norethindrone/ethinyl estradiol) and topiramate (given in the absence of other medications at doses of 50 to 200mg per day), did not show statistically significant changes in mean exposure to either component of the oral contraceptive. The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Trokendi XR™. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
- **Antiepileptic Drugs (AEDs):** Concomitant administration of phenytoin or carbamazepine with topiramate decreased plasma concentrations of topiramate. Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of valproic acid and topiramate has also been associated with hypothermia (with and

without hyperammonemia) in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported. Number AEDs are substrates of the CYP enzyme system. In vitro studies indicate that immediate-release topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes, but is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. The same drug interactions can be expected with the use of Trokendi XR™.

- **CNS Depressants:** Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs or alcohol can result in significant CNS depression.
- **Other Carbonic Anhydrase Inhibitors:** Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Patient should be monitored for the appearance or worsening of metabolic acidosis when Trokendi XR™ is given concomitantly with another carbonic anhydrase inhibitor.
- **Metformin:** Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated. The concomitant use of Trokendi XR™ and metformin is contraindicated in patients with metabolic acidosis.
- **Lithium:** There was an observed increase in systemic exposure of lithium in patients following topiramate doses of up to 600mg per day. Lithium levels should be monitored when co-administered with high-dose Trokendi XR™.

PATIENT COUNSELING INFORMATION:

1. Trokendi XR™ (topiramate) is an antiepileptic drug (AED) indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures, as adjunctive therapy in patients 6 years of age and older with partial onset or primary generalized tonic-clonic seizures, and as adjunctive therapy in patients 6 years of age and older with seizures associated with Lennox-Gastaut syndrome. Trokendi XR™ is not indicated in children under the age of 6 years.
2. Take Trokendi XR™ exactly as prescribed by your doctor. Trokendi XR™ can be taken with or without food, and capsules should be swallowed whole and intact. Trokendi XR™ should not be sprinkled on food, chewed, or crushed.
3. Before taking Trokendi XR™, talk to your doctor or healthcare provider about other medications you are currently taking. Trokendi XR™ has some possible drug-drug interactions that may result in adverse reactions. Do not stop taking Trokendi XR™ without talking to your doctor or healthcare provider. Trokendi XR™ should be gradually withdrawn to minimize the risk of increased seizure frequency.
4. Trokendi XR™ may decrease the effectiveness of hormonal contraceptives. Please report any change in your bleeding patterns or any unusual breakthrough bleeding. Talk to your doctor or healthcare provider for more information.
5. Before taking Trokendi XR™, talk to your doctor or healthcare provider if you are pregnant or plan to become pregnant. Topiramate, including Trokendi XR™, can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have an increased risk for cleft lip

and/or cleft palate (oral clefts). Trokendi XR™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential who are not planning a pregnancy should use effective contraception while taking Trokendi XR™. Pregnant patients taking Trokendi XR™ are encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry. Information on the registry can also be found at the website: http://www.aedpregnancyregistry.org/.

6. Before taking Trokendi XR™, talk to your doctor or healthcare provider if you are breastfeeding. There is limited data on whether Trokendi XR™ is excreted in human milk. The effects of exposure to Trokendi XR™ on infants are unknown. Caution should be exercised when Trokendi XR™ is administered to a nursing woman.
7. Trokendi XR™ should not be taken if you are allergic to topiramate. Talk to your doctor or healthcare provider for more information.
8. Alcohol use should be completely avoided within 6 hours prior to and 6 hours after Trokendi XR™ administration.
9. Patients with metabolic acidosis who are also taking metformin should not take Trokendi XR™.
10. AEDs, including Trokendi XR™, increase the risk of suicidal thoughts or behavior. Be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to your doctor or other healthcare providers.
11. Seek immediate medical attention if you experience blurred vision, visual disturbances, or periorbital pain while taking Trokendi XR™. This could be a serious adverse effect from taking Trokendi XR™.
12. Trokendi XR™ can cause decreased sweating and increased body temperature, especially in hot weather and especially in pediatric patients. Seek medical attention if these symptoms occur.
13. There is a potentially significant risk for metabolic acidosis with Trokendi XR™ that may be asymptomatic and may be associated with adverse effects on the kidneys, bones, growth (in pediatric patients), and on the fetus. Talk to your doctor or healthcare provider for more information.
14. Trokendi XR™ may cause hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. This can develop with Trokendi XR™ alone, or with Trokendi XR™ treatment taken with valproic acid. Contact your doctor or healthcare provider if you develop unexplained lethargy, vomiting, or changes in mental status.
15. Trokendi XR™ can cause a reduction in body temperature (hypothermia), which can lead to alterations in mental status. Patients also taking valproic acid are at greater risk of developing this adverse effect. If you note such changes, call your doctor or health care provider and measure your body temperature.

16. Trokendi XR™ may cause somnolence, dizziness, confusion, difficulty concentrating, and visual effects. Do not drive or operate machinery until you know how Trokendi XR™ affects your ability to drive or operate machinery.
17. Even when taking Trokendi XR™ or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Use caution when engaging in any activities where loss of consciousness could result in serious danger to yourself or those around you (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Talk to you doctor or healthcare provider for more information.
18. Trokendi XR™ may cause kidney stones. It is recommended to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation.
19. Trokendi XR™ can cause paresthesia. If you experience tingling in the arms and legs, contact your doctor or healthcare provider.
20. Common adverse effects of Trokendi XR™ include paresthesia (tingling of arms and legs), decreased appetite, nausea, a change in the way foods taste, diarrhea, weight loss, nervousness, and upper respiratory tract infection.

PRODUCT DETAILS OF APTIOM® (ESLICARBAZEPINE ACETATE)

INDICATIONS AND USE: Aptiom® (eslicarbazepine acetate) is an anticonvulsant indicated as adjunctive treatment of partial onset seizures in adults.

DOSAGE FORMS: Aptiom® (eslicarbazepine acetate) is available as200mg, 400mg, 600mg, and 800mg tablets.

ADMINISTRATION:

- The recommended starting dose of Aptiom® is 400mg orally once daily.
- After one week, increase dosage to 800mg orally once daily, which is the recommended maintenance dosage.
- Some patients may benefit from the maximum recommended maintenance dosage of 1200mg orally once daily, although this dosage is associated with an increase in adverse reactions. A maximum dose of 1200mg daily should only be initiated after the patient has tolerated 800mg daily for at least one week.
- For some patients, treatment may be initiated at 800mg once daily if the need for additional seizure reduction outweighs an increased risk of adverse reactions during initiation.
- Aptiom® tablets should be administered either as whole or as crushed tablets.
- Aptiom® can be taken with or without food.
- Aptiom® should not be taken as an adjunctive therapy with oxcarbazepine. Some adverse reactions occur more frequently when patients take Aptiom® with carbamazepine. However, carbamazepine reduces the plasma concentration of eslicarbazepine. When Aptiom® and carbamazepine are taken concomitantly, the dose of Aptiom® or carbamazepine may need to be adjusted based on efficacy and tolerability. For patients taking other enzyme-inducing antiepileptic drugs (AEDs) (i.e., phenobarbital, phenytoin, and Primidone), higher doses of Aptiom® may be needed.
- A dose reduction is recommended in patients with moderate and severe renal impairment (i.e., creatinine clearance < 50mL/min). Start treatment with 200mg orally once daily. After two weeks, increase dosage to 400mg orally once daily; 400mg once daily is the recommended maintenance dosage. Some patients may benefit from the maximum recommended maintenance dosage of 600mg orally once daily.
- When discontinuing Aptiom®, reduce the dosage gradually and avoid abrupt discontinuation in order to minimize the risk of increased seizure frequency and status epilepticus.

CONTRAINDICATIONS:

- Patients with a hypersensitivity to eslicarbazepine acetate or oxcarbazepine.

SPECIAL POPULATIONS:

- **Pregnancy:** There are no adequate or well-controlled studies of Aptiom® in pregnant women. In oral studies conducted in pregnant mice, rats, and rabbits, eslicarbazepine acetate demonstrated developmental toxicity, including teratogenicity, embryo lethality, and fetal growth retardation, at clinically relevant doses. Aptiom® should be

used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (Category C)

- **Nursing Mothers:** Eslicarbazepine is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Aptiom®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
- **Pediatrics:** The safety and effectiveness of Aptiom® in patients below 18 years of age have not been established.
- **Geriatrics:** There were insufficient numbers of patients ≥ 65 years old enrolled in the controlled epilepsy trials to determine the efficacy of Aptiom® in this patient population. The pharmacokinetics of Aptiom® were evaluated in elderly healthy subjects (N=12). Although the pharmacokinetics of Aptiom® are not affected by age independently, dose selection should take in consideration the greater frequency of renal impairment and other concomitant medical conditions and drug therapies in the elderly patient. Dose adjustment is necessary if CrCl is < 50mL/min.
- **Renal Impairment:** Clearance of Aptiom® is decreased in patients with impaired renal function and is correlated with creatinine clearance. Dosage adjustment is necessary in patients with CrCl < 50mL/min.
- **Hepatic Impairment:** Dose adjustments are not required in patients with mild to moderate hepatic impairment. Use of Aptiom® in patients with severe hepatic impairment has not been evaluated, and use in these patients is not recommended.

WARNINGS AND PRECAUTIONS:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including Aptiom®, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Anyone considering prescribing Aptiom® or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
- **Serious Dermatologic Reactions:** Serious dermatologic reactions including Stevens-Johnson Syndrome (SJS) have been reported in association with Aptiom® use. Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and SJS, have been reported in patients using oxcarbazepine or carbamazepine, which

are chemically related to Aptiom®. The reported rate of these reactions associated with oxcarbazepine use exceeds the background incidence rate estimates by a factor of 3- to 10-fold. Risk factors for development of serious dermatologic reactions with Aptiom® use have not been identified. If a patient develops a dermatologic reaction while taking Aptiom®, discontinue Aptiom® use, unless the reaction is clearly not drug-related. Patients with a prior dermatologic reaction with either oxcarbazepine or Aptiom® should not be treated with Aptiom®.

- **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Multi-organ Hypersensitivity:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), also known as Multi-organ Hypersensitivity, has been reported in patients taking Aptiom®. DRESS may be fatal or life-threatening. DRESS typically, although not exclusively, presents with fever, rash, and/or lymphadenopathy, in associated with other organ system involvement, such as hepatitis, nephritis, hematological abnormalities, myocarditis, or myositis sometimes resembling an acute viral infection. Eosinophilia is often present. Because this disorder is variable in its expression, other organ systems not noted here may be involved. It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Aptiom® should be discontinued and not be resumed if an alternative etiology for the signs or symptoms cannot be established. Patients with a prior DRESS reaction with either oxcarbazepine or Aptiom® should not be treated with Aptiom®.
- **Anaphylactic Reactions and Angioedema:** Rare cases of anaphylaxis and angioedema have been reported in patients taking Aptiom®. Anaphylaxis and angioedema associated with laryngeal edema can be fatal. If a patient develops any of these reactions after treatment with Aptiom®, the drug should be discontinued. Patients with a prior anaphylactic-type reaction with either oxcarbazepine or Aptiom® should not be treated with Aptiom®.
- **Hyponatremia:** Clinically significant hyponatremia (sodium < 125 mEq/L) can develop in patients taking Aptiom®. In the controlled epilepsy trials, 4/415 patients (1.0%) treated with 800mg and 6/410 patients (1.5%) treated with 1200mg of Aptiom® had at least one serum sodium value less than 125 mEq/L, compared to none of the patients assigned to placebo. A higher percentage of Aptiom®-treated patients (5.1%) than placebo-treated patients (0.7%) experienced decreases in sodium values of more than 10 mEq/L. These effects were dose-related and generally appeared within the first 8 weeks of treatment (as early as after 3 days). Serious, life-threatening complications were reported with Aptiom®-associated hyponatremia (as low as 112 mEq/L) including seizures, severe nausea/vomiting leading to dehydration, severe gait instability, and injury. Some patients required hospitalization and discontinuation of Aptiom®. Concurrent hypochloremia was also present in patients with hyponatremia. Depending on the severity of hyponatremia, the dose of Aptiom® may need to be reduced or discontinued. Measurement of serum sodium and chloride levels should be considered during maintenance treatment with Aptiom®, particularly if the patient is receiving other medications known to decrease serum sodium levels and should be performed if symptoms of hyponatremia develop (e.g., nausea/vomiting, malaise, headache,

lethargy, confusion, irritability, muscle weakness/spasms, obtundation, or increase in seizure frequency or severity).

- **Neurological Adverse Reactions:**
  - **Dizziness and Disturbance in Gait and Coordination:** Aptiom® causes dose-related increases in adverse reactions related to dizziness and disturbance in gait and coordination (dizziness, ataxia, vertigo, balance disorder, gait disturbance, nystagmus, and abnormal coordination). There was an increased risk of these adverse reactions during the titration period (compared to the maintenance period) and there also may be an increased risk of these adverse reactions in patients 60 years of age and older compared to younger adults. Nausea and vomiting also occurred with these events. The incidence of dizziness was greater with the concomitant use of Aptiom® and carbamazepine compared to the use of Aptiom® without carbamazepine. Therefore, consider dosage modifications of both Aptiom® and carbamazepine if these drugs are used concomitantly. In the controlled epilepsy trials, events related to dizziness and disturbance in gait and coordination were serious in 2% of Aptiom®-treated patients and led to discontinuation in 9% of Aptiom®-treated patients.
  - **Somnolence and Fatigue:** Aptiom® causes dose-dependent increases in somnolence and fatigue-related adverse reactions (fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy. In the controlled epilepsy trials, somnolence and fatigue-related events were serious in 0.3% of Aptiom®-treated patients and led to discontinuation in 3% of Aptiom®-treated patients.
  - **Cognitive Dysfunction:** Aptiom® causes dose-dependent increases in cognitive dysfunction-related events (memory impairment, disturbance in attention, amnesia, confusional state, aphasia, speech disorder, slowness of thought, disorientation, and psychomotor retardation). In the controlled epilepsy trials, cognitive dysfunction-related events were serious in 0.2% of Aptiom®-treated patients and led to discontinuation in 1% of Aptiom®-treated patients.
  - **Visual Changes:** Aptiom® causes dose-dependent increases in events related to visual changes including diplopia, blurred vision, and impaired vision. There was an increased risk of these adverse reactions during the titration period (compared to the maintenance period) and there also may be an increased risk of these adverse reactions in patients 60 years of age and older compared to younger adults. The incidence of diplopia was greater with the concomitant use of Aptiom® and carbamazepine compared to the use of Aptiom® without carbamazepine. In the controlled epilepsy trials, visual adverse events were serious in 0.7% of Aptiom®-treated patients and led to discontinuation in 4% of Aptiom®-treated patients.
  - **Hazardous Activities:** Prescribers should advise patients against engaging in hazardous activities requiring mental alertness, such as operating motor vehicles or dangerous machinery, until the effect of Aptiom® is known.
- **Withdrawal of AEDs:** As with all antiepileptic drugs, Aptiom® should be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus.
- **Drug Induced Liver Injury:** Hepatic events, ranging from mild to moderate elevations in transaminases (> 3 times the upper limit of normal) to rare cases with concomitant

elevations of total bilirubin (> 2 times the upper limit of normal) have been reported with Aptiom® use. Baseline evaluations of liver laboratory tests are recommended. The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury. Aptiom® should be discontinued in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence).

- **Abnormal Thyroid Function Tests:** Dose-dependent decreases in serum T3 and T4 (free and total) values have been observed in patients taking Aptiom®. These changes were not associated with other abnormal thyroid function tests suggesting hypothyroidism. Abnormal thyroid function tests should be clinically evaluated.

ADVERSE REACTIONS:

- **Serious adverse reactions** (discussed elsewhere in the labeling): Suicidal behavior and ideation, serious dermatologic reactions, drug reaction with eosinophilia and systemic symptoms (DRESS)/multi-organ hypersensitivity, anaphylactic reactions and angioedema, hyponatremia, neurological adverse reactions, drug induced liver injury, and abnormal thyroid function tests.
- **Adverse reactions leading to discontinuation** (observed in clinical trials): Dizziness, nausea, vomiting, ataxia, diplopia, somnolence, headache, blurred vision, vertigo, asthenia, fatigue, rash, dysarthria, and tremor.
- **Common adverse reactions** (observed in clinical trials): Dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor.
- **Other adverse reactions** (associated with slightly higher frequency with Aptiom® than placebo): Decreases in hemoglobin and hematocrit; increases in total cholesterol, triglycerides, and LDL; and increases in creatine phosphokinase.

DRUG INTERACTIONS:

- **General Information:** Several AEDs (e.g., carbamazepine, phenobarbital, phenytoin, and Primidone) can induce enzymes that metabolize Aptiom® and can cause decreased plasma concentrations of eslicarbazepine. Aptiom® can inhibit CYP2C19, which can cause increased plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., phenytoin, clobazam, and omeprazole). In vivo studies suggest that Aptiom® can induce CYP3A4, decreasing plasma concentrations of drugs that are metabolized by this isoenzyme (e.g., simvastatin).
- **Potential for Other AEDs to Affect Eslicarbazepine:** Other AEDs may impact the systemic exposure (area under the curve, AUC) of eslicarbazepine, the active metabolite of Aptiom®, and dose adjustments may be necessary. Aptiom® should not be taken as an adjunctive therapy with oxcarbazepine. Some adverse reactions occur more frequently when patients take Aptiom® with carbamazepine. However, carbamazepine reduces the plasma concentration of eslicarbazepine. When Aptiom® and carbamazepine are taken concomitantly, the dose of Aptiom® or carbamazepine may need to be adjusted based on efficacy and tolerability. For patients taking other enzyme-inducing antiepileptic drugs (AEDs) (i.e., phenobarbital, phenytoin, and Primidone), higher doses of Aptiom® may be needed.

- **Potential for Eslicarbazepine to Affect Other AEDs:**
    - **Carbamazepine:** May need a dose adjustment of carbamazepine or Aptiom® (see above).
    - **Phenytoin:** Aptiom® may increase the plasma concentration of phenytoin. Monitor plasma phenytoin concentration; in epilepsy, dose adjustment may be needed based on response and serum levels of phenytoin.
- **Potential for Eslicarbazepine to Affect Other AEDs:**
    - **Simvastatin/Rosuvastatin:** Aptiom® may decrease the plasma concentration of simvastatin and rosuvastatin. Adjust the dose of simvastatin or rosuvastatin if a clinically significant change in lipids is noted.
    - **Warfarin:** Aptiom® may decrease the plasma concentration of warfarin. Patients taking warfarin should be monitored to maintain INR.
    - **Oral Contraceptives:** Because concomitant use of Aptiom® and ethinyl estradiol and levonorgestrel is associated with lower plasma levels of these hormones, females of reproductive potential should use additional or alternative non-hormonal birth control.

PATIENT COUNSELING INFORMATION:

1. Aptiom® (eslicarbazepine) is an antiepileptic drug (AED) indicated for the adjunctive treatment of partial onset seizures. Aptiom® has not been studied in children (under the age of 18 years).
2. Take Aptiom® exactly as prescribed by your doctor. Aptiom® can be taken with or without food, and can be taken as whole or as crushed tablets.
3. Before taking Aptiom®, talk to your doctor or healthcare provider about other medications you are currently taking. Aptiom® has some possible drug-drug interactions that may result in adverse reactions. Aptiom® should not be taken as an adjunctive therapy with oxcarbazepine. Do not stop taking Aptiom® without talking to your doctor or healthcare provider. Aptiom® should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus.
4. Aptiom® can significantly decrease the effectiveness of hormonal contraceptives. It is recommended that female patients of childbearing potential use additional or alternative non-hormonal forms of contraception during treatment with Aptiom® and after treatment has been discontinued for at least one menstrual cycle or until otherwise instructed by your healthcare provider.
5. Before taking Aptiom®, talk to your doctor or healthcare provider if you are pregnant or plan to become pregnant, or are breastfeeding. Aptiom® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Based on the available data, Aptiom® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Aptiom®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
6. Aptiom® should not be taken if you are allergic to eslicarbazepine or oxcarbazepine. Talk to your doctor or healthcare provider for more information.
7. AEDs, including Aptiom®, increase the risk of suicidal thoughts or behavior. Be alert for the emergence or worsening of the signs and symptoms of depression, any unusual

changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to your doctor or other healthcare providers.

8. There is a risk of potentially fatal skin reactions with Aptiom®. Consult your doctor or healthcare provider immediately if a skin reaction occurs during treatment with Aptiom®.
9. Fever associated with signs of other organ system involvement (e.g., rash, lymphadenopathy, hepatic dysfunction) may be drug-related and should be reported to your doctor or healthcare provider immediately.
10. Anaphylactoid reactions may occur with Aptiom®. Symptoms of anaphylactoid reactions include difficulty breathing or swallowing and swelling of the face, eyes, lips, tongue or throat. If these symptoms occur, stop taking Aptiom® and seek immediate emergency help.
11. Aptiom® may reduce serum sodium concentrations, especially if you are taking other medications that can lower sodium. Report symptoms of low sodium such as nausea, tiredness, lack of energy, irritability, confusion, muscle weakness/spasms, or more frequent or more severe seizures to your doctor or healthcare provider.
12. Aptiom® may cause dizziness, gait disturbance, somnolence/fatigue, cognitive dysfunction, and visual changes. These adverse reactions, if observed, are more likely to occur during the titration period compared to the maintenance period. Do not drive or operate machinery until you know how Aptiom® affects your ability to drive or operate machinery.
13. Common adverse effects of Aptiom® include dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor.

PRODUCT DETAILS OF QUDEXY™ XR (TOPIRAMATE EXTENDED-RELASE)

INDICATIONS AND USE: Qudexy™ XR (topiramate) is an anticonvulsant indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures, as adjunctive therapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures, and as adjunctive therapy in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome.

DOSAGE FORMS: Qudexy™ XR is available as 25mg, 50mg, 100mg, 150mg, and 200mg extended-release capsules.

ADMINISTRATION:

- The recommended dose of Qudexy™ XR for monotherapy in adults and pediatric patients 10 years of age and older is 400mg orally once daily. Qudexy™ XR should be titrated, starting with 50mg once daily (week 1), followed by 100mg once daily (week 2), 150mg once daily (week 3), 200mg once daily (week 4), 300mg once daily (week 5), and finally to the recommended dose, 400mg once daily (week 6).
- The recommended total daily dose of Qudexy™ XR as adjunctive therapy in adults (17 years of age and older) with partial onset seizures or Lennox-Gastaut syndrome is 200-400mg orally once daily, with primary generalized tonic-clonic seizures is 400mg orally once daily. Initiate therapy at 25-50mg once daily followed by titration to an effective dose in increments of 25-50mg every week. Daily topiramate doses about 1600mg have not been studied.
- The recommended total daily dose of Qudexy™ XR as adjunctive therapy in pediatric patients (ages 2 years to 16 years) with partial onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome is approximately 5-9mg/kg orally once daily. Begin titration at 25mg once daily (based on a range of 1-3mg/kg/day) given nightly for the first week. Subsequently, increase the dosage at 1- or 2-week intervals by increments of 1-3mg/kg to achieve optimal clinical response. Dose titration should be guided by clinical outcome. If required, longer intervals between dose adjustments can be used.
- Qudexy™ XR capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. The drug/food mixture should be swallowed immediately and not chewed or crushed. Do not store drug/food mixture for further use.
- Qudexy™ XR can be taken without regard to meals.
- In patients with renal impairment (creatinine clearance less than 70 mL/min/1.73m^2), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose. Prior to dosing, obtain an estimated GFR measurement in patients at high risk for renal insufficiency (e.g., older patients, or those with diabetes mellitus, hypertension, or autoimmune disease).
- Topiramate is cleared by hemodialysis at a rate that is 4-6 times greater than in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take

into account the duration of dialysis period, clearance rate of the dialysis system being used, and effective renal clearance of topiramate in the patient being dialyzed.

- Measurement of baseline and periodic serum bicarbonate during Qudexy™ XR treatment is recommended.
- It is not necessary to monitor topiramate plasma concentrations to optimize Qudexy™ XR therapy.
- The co-administration of Qudexy™ XR with phenytoin may require an adjustment of the dose of phenytoin to achieve optimal clinical outcome. Addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with Qudexy™ XR may require adjustment of the dose of Qudexy™ XR.

CONTRAINDICATIONS:

- Patients with metabolic acidosis who are taking concomitant metformin.

SPECIAL POPULATIONS:

- **Pregnancy:** Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. (Category D)
- **Women of Childbearing Potential:** Data from pregnancy registries indicated that infants exposed to topiramate in utero have increased risk for cleft lip and/or cleft palate (oral clefts). Consider the benefits and risks of topiramate when prescribing this drug to women of childbearing potential, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. Because the risk of oral clefts to the fetus, which occur in the first trimester of pregnancy before many women know they are pregnant, all women of childbearing potential should be apprised of the potential hazard to the fetus from exposure to topiramate. If the decision is made to use topiramate, women who are not planning a pregnancy would use effective contraception. Women who are planning a pregnancy would be counseled regarding the relative risks and benefits of topiramate use during pregnancy, and alternative treatment options should be considered for these patients.
- **Labor and Delivery:** Although the effect of topiramate on labor and delivery in humans has not been established, the development of topiramate-induced metabolic acidosis in the mother and/or in the fetus might affect the fetus' ability to tolerate labor.
- **Nursing Mothers:** Limited data on 5 breastfeeding infants exposed to topiramate showed infant plasma topiramate levels equal to 10-20% of the maternal plasma level. The effects of this exposure on infants are unknown. Caution should be exercised when Qudexy™ XR is administered to a nursing woman.
- **Pediatrics:** The safety and effectiveness of Qudexy™ XR in pediatric patients is based on controlled trials with immediate-release topiramate. The safety and effectiveness of

Trokendi XR™ in patients below the age of 2 years have not been established for the adjunctive therapy treatment of partial onset seizures or seizures associated with Lennox-Gastaut syndrome.

- **Geriatrics:** Clinical studies of immediate-release topiramate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Dosage adjustment is necessary for elderly with creatinine clearance less than 70 mL/min/1.73m^2. Estimate creatinine clearance prior to dosing.
- **Renal Impairment:** The clearance of topiramate was reduced by 42% in moderately renally impaired (creatinine clearance 30-69 mL/min/1.73m^2) and by 54% in severely renally impaired subjects (creatinine clearance less than 30 mL/min/1.73m^2). One-half the usual starting and maintenance dose is recommended in patients with moderate or severe renal impairment.
- **Patients Undergoing Hemodialysis:** Topiramate is cleared by hemodialysis at a rate that is 4-6 times greater than in patients with normal renal function. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an anti-seizure effect. To avoid rapid drops in topiramate plasma concentration during hemodialysis, a supplemental dose of topiramate may be required. The actual adjustment should take into account the duration of dialysis period, clearance rate of the dialysis system being used, and effective renal clearance of topiramate in the patient being dialyzed.
- **Hepatic Impairment:** In patients with hepatic impairment, the clearance of topiramate may be decreased; however, the mechanism underlying the disease is not well understood.

WARNINGS AND PRECAUTIONS:

- **Suicidal Behavior and Ideation:** Antiepileptic drugs (AEDs), including Qudexy™ XR, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting treatment with AEDs and persisted for the duration of treatment assessed. Anyone considering prescribing Qudexy™ XR or any other AED must balance this risk with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated. Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.
- **Acute Myopia and Secondary Angle Closure Glaucoma:** A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients

receiving topiramate. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber swallowing, ocular hyperemia (redness), and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary acute closure glaucoma. Symptoms typically occur within 1 month of initiating topiramate therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of Qudexy™ XR as rapidly as possible, according to the judgment of the treating physician. Other measures, in conjunction with discontinuation of Qudexy™ XR, may be helpful. Elevated intraocular pressure, if left untreated, can lead to serious sequelae including permanent vision loss.

- **Visual Field Defects:** Visual field defects have been reported in patients receiving topiramate independent of elevated intraocular pressure. In clinical trials, most of these events were reversible after topiramate discontinuation. If visual problems occur at any time during topiramate treatment, consideration should be given to discontinuing the drug.
- **Oligohydrosis and Hyperthermia:** Oligohydrosis (decreased sweating), resulting in hospitalization in some cases, has been reported in association with topiramate use. Decreased sweating and an elevation in body temperature above normal characterized these cases. Some of the cases were reported after exposure to elevated environmental temperatures. The majority of reports have been in pediatric patients. Patients, especially pediatric patients, treated with Qudexy™ XR should be monitored closely for evidence of decreased sweating and increased body temperature, especially in hot weather. Caution should be used when Qudexy™ XR is prescribed with other drugs that predispose patients to heat-related disorders; these drugs include, but are not limited to, other carbonic anhydrase inhibitors and drugs with anticholinergic activity.
- **Metabolic Acidosis:** Hyperchloremic, non-anion gap, metabolic acidosis (i.e., decreased serum bicarbonate below the normal reference range in the absence of chronic respiratory alkalosis) is associated with topiramate, and can be expected with treatment with Qudexy™ XR. This metabolic acidosis is caused by renal bicarbonate loss due to the inhibitory effect of topiramate on carbonic anhydrase. Generally, topiramate-induced metabolic acidosis occurs early in treatment although cases can occur at any time during treatment. Bicarbonate decrements are usually mild-moderate (average decrease of 4 mEq/L at daily doses of 400mg in adults and at approximately 6 mg/kg/day in pediatric patients); rarely, patients can experience severe decrements to values below 10 mEq/L. Conditions or therapies that predispose patients to acidosis (such as renal disease, severe respiratory disorders, status epilepticus, diarrhea, ketogenic diet, or specific drugs) may be additive to the bicarbonate lowering effects of topiramate. Some manifestations of acute or chronic metabolic acidosis may include hyperventilation, nonspecific symptoms such as fatigue and anorexia, or more severe sequelae including cardiac arrhythmias or stupor. Chronic, untreated metabolic acidosis may increase the risk for nephrolithiasis or nephrocalcinosis, and may also result in osteomalacia (referred to as rickets in pediatric patients) and/or osteoporosis with an increased risk

for fractures. Chronic metabolic acidosis in pediatric patients may also reduce growth rates. A reduction in growth rate may eventually decrease the maximal height achieved. Measurement of baseline and periodic serum bicarbonate during topiramate treatment is recommended. If metabolic acidosis develops and persists, consideration should be given to reducing the dose or discontinuing topiramate (using dose tapering). If the decision is made to continue patients on topiramate in the face of persistent acidosis, alkali treatment should be considered.

- **Cognitive/Neuropsychiatric Adverse Reactions:** Adverse reactions most often associated with the use of topiramate, and therefore expected to be associated with the use of Qudexy™ XR, were related to the central nervous system and were observed in the epilepsy population. In adults, the most frequent of these can be classified into three general categories: cognitive-related dysfunction (e.g., confusion, psychomotor slowing, difficulty with concentration/attention, difficulty with memory, or speech or language problems, particularly word-finding difficulties); psychiatric/behavioral disturbances (e.g. depression or mood problems); and somnolence or fatigue.
- **Fetal Toxicity:** Qudexy™ XR can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). When multiple species of pregnant animals received topiramate at clinically relevant doses, structural malformations, including craniofacial defects, and reduced fetal weights occurred in offspring. Consider the benefits and risks of Qudexy™ XR when prescribing this drug to women of childbearing potential, particularly when Qudexy™ XR is considered for a condition not usually associated with permanent injury or death. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.
- **Withdrawal of Antiepileptic Drugs:** In patients with or without a history of seizures or epilepsy, antiepileptic drugs including Qudexy™ XR should be gradually withdrawn to minimize the potential for seizures or increased seizure frequency. In situations where rapid withdrawal of Qudexy™ XR is medically required, appropriate monitoring is recommended.
- **Hyperammonemia and Encephalopathy:** Topiramate treatment has produced hyperammonemia (in some instances dose-related) in clinical investigational programs in very young pediatric patients (1 month to 24 months) who were treated with adjunctive topiramate for partial onset epilepsy. Qudexy™ XR is not approved as adjunctive treatment of partial onset seizures in pediatric patients less than 2 years old. In some patients, ammonia was markedly increased (greater than 50% above the upper limit of normal). The hyperammonemia associated with topiramate treatment occurred with and without encephalopathy. Clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. Concomitant administration of topiramate and valproic acid has been associated with hyperammonemia with or without encephalopathy in patients who have tolerated either drug alone based upon post-marketing reports. This adverse reaction is not due to a pharmacokinetic interaction. The hyperammonemia associated with topiramate treatment appears to be more

common when used concomitantly with valproic acid. In patients who develop unexplained lethargy, vomiting, or changes in mental status associated with any topiramate treatment, hyperammonemic encephalopathy should be considered and an ammonia level should be measured.

- **Kidney Stones:** A total of 32/2086 (1.5%) of adults exposed to topiramate during its adjunctive epilepsy therapy development reported the occurrence of kidney stones, an incidence about 2-4 times greater than expected in a similar, untreated population. As in the general population, the incidence of stone formation among topiramate treated patients was higher in men. Kidney stones have also been reported in pediatric patients. Qudexy™ XR would be expected to have the same effect as topiramate on the formation of kidney stones. An explanation for the association of topiramate and kidney stones may lay in the fact that topiramate is a carbonic anhydrase inhibitor. Carbonic anhydrase inhibitors (e.g. zonisamide, acetazolamide, or dichlorphenamide) can promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. The concomitant use of Qudexy™ XR with any other drug producing metabolic acidosis, or potentially in patients on a ketogenic diet may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Hydration is recommended to reduce new stone formation.
- **Hypothermia with Concomitant Valproic Acid Use:** Hypothermia, defined as an unintentional drop in body core temperature to less than 35°C (95°F), has been reported in association with topiramate use with concomitant valproic acid both in the presence and in the absence of hyperammonemia. This adverse reaction in patients using concomitant topiramate and valproic acid can occur after starting topiramate treatment or after increasing the daily dose of topiramate. Consideration should be given to stopping topiramate or valproic acid in patients who develop hypothermia, which may be manifested by a variety of clinical abnormalities including lethargy, confusion, coma, and significant alterations in other major organ systems such as the cardiovascular and respiratory systems. Clinical management and assessment should include examination of blood ammonia levels.
- **Paresthesia:** Paresthesia (usually tingling of the extremities), an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of topiramate. In the majority of instances, paresthesia did not lead to treatment discontinuation.
- **Interaction with Other CNS Depressants:** Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs or alcohol can result in significant CNS depression. Patients should be watched carefully when Qudexy™ XR is co-administered with other CNS depressant drugs.

ADVERSE REACTIONS:

- **Serious adverse reactions** (discussed elsewhere in the labeling): Suicidal behavior and ideation, acute myopia and secondary angle closure, visual field effects, oligohydrosis and hyperthermia, metabolic acidosis, cognitive/neuropsychiatric adverse reactions, fetal toxicity, withdrawal of antiepileptic drugs, hyperammonemia and encephalopathy

(without and with concomitant valproic acid use), kidney stones, hypothermia with concomitant valproic acid use, and paresthesia.

- **Common adverse reactions:** Paresthesia, weight decrease, somnolence, anorexia, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, abnormal vision, diplopia, fatigue, asthenia, insomnia, anxiety, difficulty with concentration/attention, confusion, depression, nervousness, upper respiratory tract infection, diarrhea, difficulty with memory, aggressive reaction, aggravated convulsions, language problems, personality disorder, and mood problems.
- **Laboratory abnormalities:** Decreased serum bicarbonate level, decreased serum phosphorus, increased serum alkaline phosphatase, decreased serum potassium, increased serum creatinine, and hyperammonemia (with or without encephalopathy).

DRUG INTERACTIONS:

- **Oral Contraceptives:** The possibility of decreased contraceptive efficacy and increased breakthrough bleeding should be considered in patients taking combination oral contraceptive products with Qudexy™ XR. Patients taking estrogen-containing contraceptives should be asked to report any change in their bleeding patterns. Contraceptive efficacy can be decreased even in the absence of breakthrough bleeding.
- **Antiepileptic Drugs (AEDs):** Concomitant administration of phenytoin or carbamazepine with topiramate decreased plasma concentrations of topiramate. Concomitant administration of valproic acid and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of valproic acid and topiramate has also been associated with hypothermia (with and without hyperammonemia) in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported. Number AEDs are substrates of the CYP enzyme system. In vitro studies indicate that immediate-release topiramate does not inhibit enzyme activity for CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes, but is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4. The same drug interactions can be expected with the use of Qudexy™ XR.
- **CNS Depressants and Alcohol:** Topiramate is a CNS depressant. Concomitant administration of topiramate with other CNS depressant drugs or alcohol can result in significant CNS depression. Concomitant use of alcohol should be avoided.
- **Other Carbonic Anhydrase Inhibitors:** Concomitant use of topiramate, a carbonic anhydrase inhibitor, with any other carbonic anhydrase inhibitor (e.g., zonisamide, acetazolamide, or dichlorphenamide), may increase the severity of metabolic acidosis and may also increase the risk of kidney stone formation. Patient should be monitored for the appearance or worsening of metabolic acidosis when Qudexy™ XR is given concomitantly with another carbonic anhydrase inhibitor.
- **Metformin:** Topiramate treatment can frequently cause metabolic acidosis, a condition for which the use of metformin is contraindicated. The concomitant use of Qudexy™ XR and metformin is contraindicated in patients with metabolic acidosis.
- **Lithium:** There was an observed increase in systemic exposure of lithium in patients following topiramate doses of up to 600mg per day. Lithium levels should be monitored when co-administered with high-dose Qudexy™ XR.

PATIENT COUNSELING INFORMATION:

1. Qudexy™ XR (topiramate) is an antiepileptic drug (AED) indicated as initial monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures, as adjunctive therapy in patients 2 years of age and older with partial onset or primary generalized tonic-clonic seizures, and as adjunctive therapy in patients 2 years of age and older with seizures associated with Lennox-Gastaut syndrome. Qudexy™ XR is not indicated in children under the age of 2 years.
2. Take Qudexy™ XR exactly as prescribed by your doctor. Qudexy™ XR capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. The drug/food mixture should be swallowed immediately and not chewed or crushed. Do not store drug/food mixture for further use. Qudexy™ XR can be taken with or without food.
3. Before taking Qudexy™ XR , talk to your doctor or healthcare provider about other medications you are currently taking. Qudexy™ XR has some possible drug-drug interactions that may result in adverse reactions. Do not stop taking Qudexy™ XR without talking to your doctor or healthcare provider. Qudexy™ XR should be gradually withdrawn to minimize the risk of increased seizure frequency.
4. Qudexy™ XR may decrease the effectiveness of hormonal contraceptives. Please report any change in your bleeding patterns or any unusual breakthrough bleeding. Talk to your doctor or healthcare provider for more information.
5. Before taking Qudexy™ XR, talk to your doctor or healthcare provider if you are pregnant or plan to become pregnant. Topiramate, including Qudexy™ XR, can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicated that infants exposed to topiramate in utero have an increased risk for cleft lip and/or cleft palate (oral clefts). Qudexy™ XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. Women of childbearing potential who are not planning a pregnancy should use effective contraception while taking Qudexy™ XR.
6. Before taking Qudexy™ XR, talk to your doctor or healthcare provider if you are breastfeeding. There is limited data on whether Qudexy™ XR is excreted in human milk. The effects of exposure to Qudexy™ XR on infants are unknown. Caution should be exercised when Qudexy™ XR is administered to a nursing woman.
7. Qudexy™ XR should not be taken if you are allergic to topiramate. Talk to your doctor or healthcare provider for more information.
8. Alcohol use should be avoided while taking Qudexy™ XR.
9. Patients with metabolic acidosis who are also taking metformin should not take Qudexy™ XR.
10. AEDs, including Qudexy™ XR, increase the risk of suicidal thoughts or behavior. Be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to your doctor or other healthcare providers.

11. Seek immediate medical attention if you experience blurred vision, visual disturbances, or periorbital pain while taking Qudexy™ XR. This could be a serious adverse effect from taking Qudexy™ XR.
12. Qudexy™ XR can cause decreased sweating and increased body temperature, especially in hot weather and especially in pediatric patients. Seek medical attention if these symptoms occur.
13. There is a potentially significant risk for metabolic acidosis with Qudexy™ XR that may be asymptomatic and may be associated with adverse effects on the kidneys, bones, growth (in pediatric patients), and on the fetus. Talk to your doctor or healthcare provider for more information.
14. Qudexy™ XR may cause hyperammonemia with or without encephalopathy. Although hyperammonemia may be asymptomatic, clinical symptoms of hyperammonemic encephalopathy often include acute alterations in level of consciousness and/or cognitive function with lethargy or vomiting. This can develop with Qudexy™ XR alone, or with Qudexy™ XR treatment taken with valproic acid. Contact your doctor or healthcare provider if you develop unexplained lethargy, vomiting, or changes in mental status.
15. Qudexy™ XR can cause a reduction in body temperature (hypothermia), which can lead to alterations in mental status. Patients also taking valproic acid are at greater risk of developing this adverse effect. If you note such changes, call your doctor or health care provider and measure your body temperature.
16. Qudexy™ XR may cause somnolence, dizziness, confusion, difficulty concentrating, and visual effects. Do not drive or operate machinery until you know how Qudexy™ XR affects your ability to drive or operate machinery.
17. Even when taking Qudexy™ XR or other anticonvulsants, some patients with epilepsy will continue to have unpredictable seizures. Use caution when engaging in any activities where loss of consciousness could result in serious danger to yourself or those around you (including swimming, driving a car, climbing in high places, etc.). Some patients with refractory epilepsy will need to avoid such activities altogether. Talk to you doctor or healthcare provider for more information.
18. Qudexy™ XR may cause kidney stones. It is recommended to maintain an adequate fluid intake in order to minimize the risk of kidney stone formation.
19. Qudexy™ XR can cause paresthesia. If you experience tingling in the arms and legs, contact your doctor or healthcare provider.
20. Common adverse effects of Qudexy™ XR include paresthesia (tingling of arms and legs), decreased appetite, nausea, a change in the way foods taste, diarrhea, weight loss, nervousness, and upper respiratory tract infection.

Attachment A

Anticonvulsant Dosing and Restrictions				
Drug name	**How Supplied**	**Normal daily dosing**	**Max dose**	**Restrictions**
Barbiturates				
Mephobarbital (Mebaral)	32, 50, 100mg tablet	400-600mg div TID-QID, or given HS	600 mg/day	Discontinued production
Phenobarbital (Luminal)	15, 16.2, 30, 32.4, 60, 64.8, 97.2, 100 mg tablet	Adult: 50-100mg BID-TID, Ped: 15-50mg BID-TID		
Phenobarbital elixir	20 mg/mL oral elixir	Adult: 60-200mg/day, Ped: 3-6mg/kg/day		
Phenobarbital injection	65 mg/mL, 130mg/mL injection	100 -320mg slow IV or IM		
Hydantoins				
Fosphenytoin (Cerebyx)	100mg PE/2mL, 500mg PE/10mL injections	LD: 10-20mg PE/kg IV or IM, MD: 4-6mg PE/kg/day	Max IV rate 150mg PE/min	
Phenytoin (Dilantin)	50 mg chew tablet	Adults: ID: 100mg TID, MD: 300-400mg, Ped: 4-8mg/kg/day div BID-TID	Adult:600mg/day Ped: 300mg/day	180/30
	100 mg/4mL, 125 mg/5mL oral suspension	Adult: 125mg TID, Ped: 4-8mg/kg/day div BID-TID	Adult:625mg/day Ped: 300mg/day	360mL/30
	50 mg/mL injection	LD: 15-20 mg/kg, MD: 2 mL IV Q 6-8 hrs	Adult:600mg/day Ped: 300mg/day	
	100 mg ER capsule	Adult: 100 mg TID-QID or 300mg QD, Ped: 4-8mg/kg/day div BID-TID		180/30
	200 mg ER capsule			90/30
	300 mg ER capsule			
Succinimides				
Ethosuximide (Zarontin)	250 mg capsule	Individualized, Adults: ID 500 mg/day & Ped: ID 250mg/day	1500 mg/day	180/30
	250mg/5mL oral syrup			
Methsuximide (Celontin)	300 mg capsule	300 mg QD	1200mg/day	
Valproic acid and derivatives				
Valproic acid (Depakene)	250 mg/5 mL oral syrup	ID: 10-15 mg/kg/day, doses >250 mg/day should be given in divided doses	60 mg/kg/day 75 kg= 4,500mg/day 25 kg= 1,500mg/day	1020mL/34
	250mg capsule			
Valproic acid (Stavzor)	125 mg DR capsule			120/30
	250 mg DR capsule			120/30
	500 mg DR capsule			
Divalproex sodium (Depakote)	125 mg sprinkle capsule			Age ≤11yo, 360/30
	125 mg DR tablet			90/30
	250 mg DR tablet			90/30
	500 mg DR tablet			
	250 mg ER tablet			90/30
	500 mg ER tablet			
Valproate inj (Depacon)	100 mg/mL injection			1350mL/30

Drug name	How Supplied	Normal daily dosing	Max dose	Restrictions
Carbamazepine Derivatives				
Carbamazepine (Tegretol)	100 mg chew tablet	Adults: 400mg/day (BID for ER, TID-QID for others), Ped: ≤6yo: 10-20mg/kg/day div QID 6-12yo: 400-800mg div QID (div BID for ER)	Adult: 1,600mg/day, PED: 35mg/kg or 1,000mg/day	
	100 mg/5 mL oral suspension			1500mL/30
	200 mg tablet			
	100 mg XR tablet			90/30
	200 mg XR tablet			90/30
	400 mg XR tablet			
Carbamazepine (Carbatrol)	100 mg ER capsule			150/30
	200 mg ER capsule			150/30
	300 mg ER capsule			150/30
Oxcarbazepine (Trileptal)	300 mg/5 mL oral suspension	Adults: 1,200mg/day, given BID, Ped:2-4yo 60mg/kg/day div BID 4-16yo: 600- 2100mg/day	Ped: 2100mg/day Adult: 2,400mg/day	1200mL/30
	150 mg tablet			90/30
	300 mg tablet			90/30
	600 mg tablet			
Oxcarbazepine (Oxtellar XR)	150mg ER tablet	Adults:1200-2400mg/QD, Ped: 8-10mg/kg QD	Adult: 2,400mg/day, Ped: 600mg/day	30/30
	300mg ER tablet			30/30
	600mg ER tablet			120/30
Eslicarbazepine (Aptiom)	200mg tablet	Adults: 800-1200mg/QD	Adult: 1200mg/day	30/30
	400mg tablet			30/30
	600mg tablet			60/30
	800mg tablet			60/30
Lamotrigine				
Lamotrigine (Lamictal)	5 mg chew tablet	Ranges from 100-600mg/day in divided doses		Age ≤11yo 240/30
	25 mg chew tablet			Age ≤11yo 120/30
	25 mg tablet			180/30
	100 mg tablet			60/30
	150 mg tablet			120/30
	200 mg tablet			
	25 mg ODT tablet			Age ≤11yo 90/30
	50 mg ODT tablet			Age ≤11yo 90/30
	100 mg ODT tablet			Age ≤11yo 90/30
	200 mg ODT tablet			Age ≤11yo
	25 mg XR tablet			Dosage form 30/30
	50 mg XR tablet			Dosage form 30/30

Drug name	How Supplied	Normal daily dosing	Max dose	Restrictions
	100 mg XR tablet			Dosage form 30/30
	200 mg XR tablet			Dosage form 60/30
	250 mg XR tablet			Dosage form 60/30
	300 mg XR tablet			Dosage form 90/30
Levetiracetam				
Levetiracetam (Keppra)	100 mg/mL oral solution	Adults: 3000mg/day, Ped: 6mos-4yo: 50mg/kg/day div BID, 4-16yo: 60mg/kg/day div BID	Adults: 3000mg/day, Ped: 6mos-4yo: 50mg/kg/day, 4-16yo: 60mg/kg/day	900mL/30
	500 mg/5mL oral solution			
	250 mg tablet			60/30
	500 mg tablet			120/30
	750 mg tablet			120/30
	1000 mg tablet			
	500 mg XR tablet			60/30
	750 mg XR tablet			
Topiramate				
Topiramate (Topamax)	15 mg sprinkle capsule	Adults: 200-400 mg/day divided BID, Ped: 2-16 yo: 5-9mg/kg/day	400mg/day	Age ≤11yo 120/30
	25 mg sprinkle capsule			Age ≤11yo 120/30
	25 mg tablet			90/30
	50 mg tablet			90/30
	100 mg tablet			90/30
	200 mg tablet			
Topiramate ER (Trokendi XR)	25mg ER capsule	Adults: Monotherapy: 400mg once daily Adjunctive: 200-400mg QD Ped: 5-9mg/kg QD	1600mg/day	30/30
	50mg ER capsule			30/30
	100mg ER capsule			30/30
	200mg ER capsule			60/30
Topiramate ER (Qudexy XR)	25mg ER capsule	Adults: Monotherapy: 400mg once daily Adjunctive: 200-400mg QD Ped: 5-9mg/kg QD	1600mg/day	30/30
	50mg ER capsule			30/30
	100mg ER capsule			30/30
	150mg ER capsule			60/30
	200mg ER capsule			60/30
Other anticonvulsants				
Felbamate (Felbatol)	400 mg tablet	Adult: 1200-3600mg/day div TID-QID, Ped: 15-45mg/kg/day div TID-QID	Adults: 3600mg/day Ped: 45mg/kg/day	PA & 240/30
	600 mg tablet			PA
	600mg/5mL oral suspension			PA
Gabapentin (Neurontin)	250mg/5mL oral solution	Adult: 900-1800mg/day div TID, Ped: 5-12yo: 25-35mg/kg/day div TID	3600mg/day	2,250mL/30
	100 mg capsule			150/30
	300 mg capsule			300/30
	400 mg capsule			90/30

Drug name	How Supplied	Normal daily dosing	Max dose	Restrictions
	600 mg tablet			180/30
	800 mg tablet			
Lacosamide (Vimpat)	50 mg tablet	Adult: 200-400mg/day div BID, Ped: Not FDA approved	400 mg/day	60/30
	100 mg tablet			60/30
	150 mg tablet			60/30
	200 mg tablet			
	10mg/mL oral solution			
Primidone (Mysoline)	50 mg tablet	Adult:250 mg TID-QID Ped: 10-25mg/kg TID	2000 mg/day	120/30
	250 mg tablet			
Rufinamide (Banzel)	200 mg tablet	Adult: 3200mg/day div BID, Ped: 45mg/kg/day div BID	3200 mg/day	90/30
	400 mg tablet			
	40mg/mL oral suspension			
Zonisamide (Zonegran)	25 mg capsule	Adult:100-600mg/day div QD-BID, Ped: Not approved <16 yo	600 mg/day	90/30
	50 mg capsule			90/30
	100 mg capsule			
Pregabalin (Lyrica)	25 mg capsule	Adult:150-600 mg/day, div BID-TID, Ped: Not FDA approved	600 mg/day	90/30
	50 mg capsule			90/30
	75 mg capsule			90/30
	100 mg capsule			90/30
	150 mg capsule			90/30
	200 mg capsule			60/30
	225 mg capsule			
	300 mg capsule			
Acetazolamide (Diamox)	125 and 250mg tablets	8-30mg/kg/day div, range 375-1000 mg/day	1000mg/day	
Ezogabine (Potiga)	50, 200, 300, 400mg tablets	Adult: 200-400mg TID, Ped: Not FDA approved		90/30
Tiagabine (Gabitril)	2,4 mg tablets	Adult: 4-56mg/day div BID-QID Ped:2-32mg/day div BID-QID	Adult:56mg/day Ped: 32mg/day	
Vigabatrin (Sabril)	500 mg tablet, 500 mg oral powder for solution	Adult & >16 yo: 500-1500mg BID	1500mg BID	
Clobazam (Onfi)	5mg tablet	Patients ≤30kg: 5mg QD to 20mg div BID Patients >30kg: 10mg to 40mg div BID	40mg/day div BID	60/30
	10mg tablet			60/30
	20mg tablet			60/30
	2.5mg/mL oral solution			480mL/30
Perampanel (Fycompa)	2mg tablet	2mg-12mg QD HS	12mg QD HS	30/30
	4mg tablet			30/30
	6mg tablet			30/30
	8 mg tablet			30/30
	10mg tablet			30/30
	12mg tablet			30/30

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Appendix J

30-Day Notice to Prior Authorize Sovaldi™ (Sofosbuvir), Olysio™ (Simeprevir), Victrelis® (Boceprevir), and Incivek® (Telaprevir)

Oklahoma Health Care Authority
May 2014

Introduction[1, 2, 3, 4, 5, 6]

Pathophysiology

Hepatitis C is a contagious liver disease caused by the hepatitis C virus (HCV); HCV is a bloodborne virus that is spread through contact with the blood of an infected person. The most common mode of infection is through unsafe injection practices, particularly sharing needles to inject illicit drugs. Before 1992, when widespread screening of the blood supply began in the United States, hepatitis C was also commonly spread through blood transfusions and organ transplants. HCV can also be transmitted sexually, and can be passed from an infected mother to her baby; however these modes are less common.

Prevalence

Approximately 140 million people globally have chronic hepatitis C (CHC) infection. A significant number of those who are chronically infected will develop liver cirrhosis or liver cancer. The Center for Disease Control (CDC) estimates 3.2 million persons in the United States have CHC. Most people do not know they are infected because they don't look or feel sick. HIV and HCV coinfection is more common in persons who inject illicit drugs. An estimated 50%–90% of HIV-infected persons who inject illicit drugs are also infected with HCV.

HCV can cause both acute and chronic hepatitis infection. Acute HCV infection is a short-term illness that occurs within the first 6 months after exposure to HCV. Acute HCV infection is usually asymptomatic, and is only very rarely associated with life-threatening disease. About 15–25% of infected persons spontaneously clear the virus within 6 months of infection without any treatment. The remaining 75–85% will develop CHC. Of those with CHC, the risk of cirrhosis of the liver is 15–30% within 20 years. CHC can last a lifetime and lead to serious liver problems, including cirrhosis or liver cancer.

Symptoms

The incubation period for the hepatitis C virus is 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. If symptoms do occur, the average time is 6–7 weeks after exposure. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-colored feces, joint pain, and jaundice. Due to the fact that acute HCV infection is usually asymptomatic, early diagnosis of the HCV infection is rare. In those who go on to develop CHC, the infection may remain undiagnosed, often until serious liver damage has developed. HCV is the leading cause of cirrhosis and liver cancer and the most common reason for liver

transplantation in the United States. In many cases, there are no symptoms of the disease until liver problems have developed. In persons without symptoms, Hepatitis C is often detected during routine blood tests to measure liver function and liver enzyme levels.

Diagnosis and Assessment
After being diagnosed with CHC infection the degree of liver damage should be assessed. This can be done by liver biopsy or through a variety of non-invasive tests. The most widely used systems for grading activity and staging fibrosis are the Ishak and METAVIR systems. Biopsy results are obtained and evaluated with the five point METAVIR system where fibrosis is described as follows: chronic hepatitis without fibrosis (F0); portal fibrosis without septae (F1); portal fibrosis with a few septae (F2); septal fibrosis without cirrhosis (F3) and complete cirrhosis (F4). It is advisable to delay treatment for patients with a documented early fibrosis stage if the patient is not ready to commit to treatment.

Newer therapies, including Sovaldi™ (sofosbuvir) and Olysio™ (simeprevir), are not recommended in patients with decompensated hepatic disease. Current guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) define decompensated hepatic disease by Child Turcotte Pugh (CTP) class. CTP classes determine the severity of cirrhosis and are categorized by the following parameters: total bilirubin, serum albumin, prothrombin time/international normalized ratio (INR), ascites, and degree of hepatic encephalopathy. See attachment A for further details regarding CTP classes.

Prior to initiation of HCV therapy quantitative HCV-RNA testing is necessary to document the baseline level of viremia (viral load), because the degree of initial viral decline is a crucial marker of effectiveness of treatment. HCV-RNA levels should be monitored as clinically indicated. Use of a sensitive assay with a lower limit of quantification of at least 25 IU/mL for monitoring HCV-RNA levels during treatment is recommended.

Genotype
Laboratory testing to identify the genotype of the hepatitis C strain should be performed. There are at least 6 known genotypes of the HCV and more than 50 subtypes. Subtypes can also have unique polymorphisms which further determine response to treatment. Genotype information is not only helpful in defining the epidemiology of the HCV but necessary for making treatment recommendations. Knowing the genotype can help predict the likelihood of treatment response and, in many cases, determine the duration of treatment.The degree of liver damage and virus genotype are used to guide treatment decisions and management of the disease.

Treatment
In the recent past, the only treatment for hepatitis C was a combination of interferon (IFN) and ribavirin (RBV), which are effective against all the genotypes of HCV. With the introduction of the protease inhibitors Incivek® (telaprevir) and Victrelis® (boceprevir) in 2011 new treatment combinations were developed. The more recent introduction of Sovaldi™ (sofosbuvir) and Olysio™ (simeprevir) have overtaken the current treatment guidelines.

The cure rate depends on several factors including the genotype of the virus and the type of treatment given. Guidelines from the AASLD and the IDSA recommend the following regimens:

Patient Type	Treatment Regimen	Treatment Duration	FDA Approved Regimen
Genotype 1 (treatment naïve, all subtypes, IFN eligible)	Sovaldi™ 400mg QD + weight-based RBV + weekly PEG-IFN	12 weeks	✓
Genotype 1 (treatment naïve, all subtypes, IFN **in**-eligible)	Sovaldi™ 400mg QD + Olysio™ with or without weight-based RBV	12 weeks	No
Genotype 2 (treatment naïve, regardless of IFN eligibility)	Sovaldi™ 400mg QD + weight-based RBV	12 weeks	✓
Genotype 3 (treatment naïve, regardless of IFN eligibility)	Sovaldi™ 400mg QD + weight-based RBV	24 weeks	✓
Genotype 4 (treatment naïve, IFN eligible)	Sovaldi™ 400mg QD + weight-based RBV + weekly PEG-IFN	12 weeks	✓
Genotype 4 (treatment naïve, IFN **in**-eligible)	Sovaldi™ 400mg QD + weight-based RBV	24 weeks	No
Genotype 5 and 6 (treatment naïve, IFN eligible)	Sovaldi™ 400mg QD + weight-based RBV + weekly PEG-IFN	12 weeks	No

Prevalence in USA: Genotype 1: 74%, Genotype 2: 15%, Genotype 3: 6%, Genotype 4: 1%

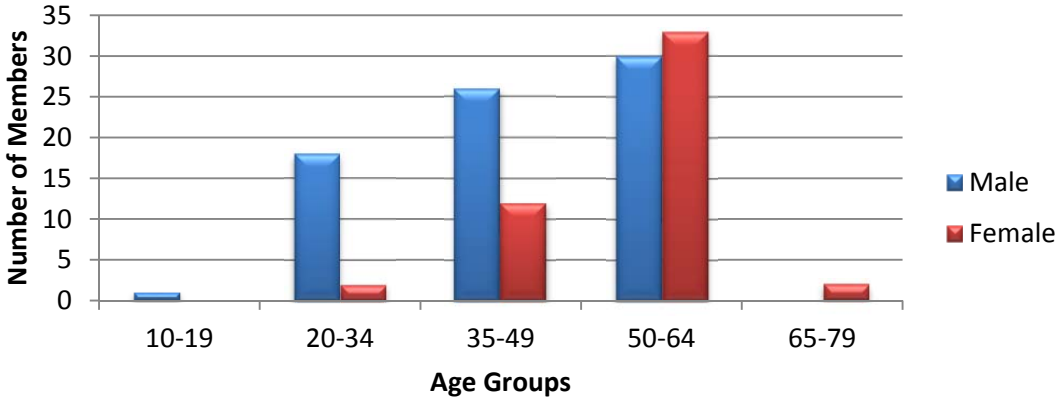
Utilization of Sovaldi™ and Olysio™

Utilization Details of Sovaldi™ and Olysio™: January 2014 - April 2014

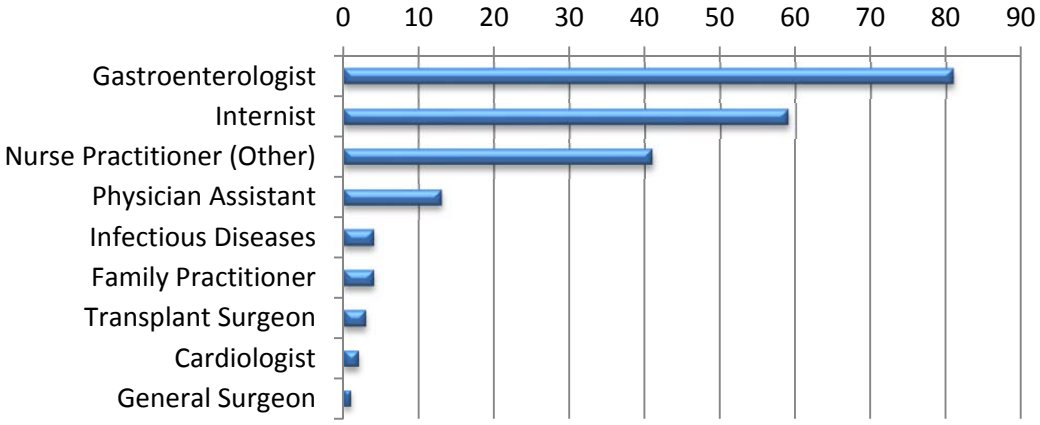
Medication	Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
Sovaldi™	124	252	$7,446,247.82	$29,548.60	$1,055.31	7,056	7,056
Olysio™	5	7	$163,518.18	$23,359.74	$834.28	196	196
Total	**125***	**259**	**$7,609,766.00**	**$29,385.34**	**$1,049.33**	**7,252**	**7,252**

*Total number of unduplicated members

Demographics of Members Utilizing Sovaldi™ and Olysio™: January 2014 - April 2014



Top Prescriber Specialties of Sovaldi™ and Olysio™ by Number of Claims: January 2014 - April 2014



Market News and Updates[7]

Anticipated Patent Expirations:

- Victrelis® (boceprevir)- 11/2027
- Incivek® (Telaprevir)- 02/2025

Sovaldi™ (Sofosbuvir) Oral Tablets Summary[8]

- **FDA Approved:** December 2013
- **Indication:**
  - Sovaldi™ (sofosbuvir) is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of CHC infection as a component of a combination antiretroviral treatment regimen.
  - Sovaldi™ efficacy has been established in subjects with HCV genotype 1, 2, 3, or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplant) and those with HCV/HIV-1 co-infection.
  - Treatment with Sovaldi™ is not recommended in patients with decompensated hepatic disease (CTP class B or C).
- **Dosage Forms:** 400mg oral tablet
- **Dosing:**
  - 400mg by mouth once daily with or without food
  - Treatment duration:
    - Genotype 1 or 4: Sovaldi™ + PEG-IFN + RBV for 12 weeks
    - Genotype 2: Sovaldi™ + RBV for 12 weeks
    - Genotype 3: Sovaldi™ + RBV for 24 weeks

- **Mechanism of Action:** Sovaldi™ is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sovaldi™ is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate, which can be incorporated into HCV-RNA by the NS5B polymerase and acts as a chain terminator.

- **Efficacy:** The safety and efficacy of Sovaldi™ was evaluated in five Phase 3 trials in a total of 1,724 HCV mono-infected subjects with genotypes 1 to 6 CHC and one Phase 3 trial in 223 HCV/HIV-1 co-infected subjects with genotype 1, 2, or 3 CHC. Among the five trials in mono-infected subjects, one was conducted in treatment-naïve subjects with genotype 1, 4, 5 or 6 CHC in combination with PEG-IFN 2a and RBV and the other four were conducted in subjects with genotype 2 or 3 CHC in combination with RBV, including one in treatment-naïve subjects, one in IFN intolerant, ineligible or unwilling subjects, one in subjects previously treated with an IFN-based regimen, and one in all subjects irrespective of prior treatment history or ability to take IFN. The trial in HCV/HIV-1 co-infected subjects was conducted in combination with RBV in treatment-naïve subjects with genotype 1 CHC and all subjects with genotype 2 or 3 CHC irrespective of prior treatment history or ability to take IFN. Subjects in these trials had compensated liver disease including cirrhosis. Sovaldi™ was administered at a dose of 400 mg once daily. The RBV dose was weight-based at 1000-1200 mg daily administered in two divided doses when used in combination with Sovaldi™, and the PEG-IFN 2a dose, where applicable, was 180 micrograms per week. Treatment duration was fixed in each trial and was not guided by subjects' HCV-RNA levels (no response guided algorithm). Plasma HCV-RNA values were measured during the clinical trials. Sustained virologic response (SVR) was the primary endpoint which was defined as HCV-RNA less than the lower limit of quantification at 12 weeks after the end of treatment.
  - NEUTRINO was an open-label, single-arm trial that evaluated 12 weeks of treatment with Sovaldi™ in combination with PEG-IFN and RBV in treatment-naïve subjects with genotype 1, 4, 5 or 6 HCV infection compared to pre-specified historical controls. The overall SVR rate for all genotypes was 90%. Only 7 subjects had genotype 5 or 6 leading to insufficient data for dosing recommendations in this population.
  - FISSION was a randomized, active-controlled trial that evaluated 12 weeks of treatment with Sovaldi™ and RBV compared to 24 weeks of treatment with PEG-IFN and RBV in treatment-naïve subjects with genotype 2 and 3 HCV. The SVR rate for genotype 2 was 95% in the Sovaldi™ and RBV treatment group and 78% in the PEG-IFN and RBV group. The SVR rate for genotype 3 was 56% in the Sovaldi™ and RBV treatment group and 63% in the PEG-IFN and RBV group.

- **Utilization/Cost:** Sovaldi™ has been used by 124 members for a total of 252 claims since January 2014.

Medication	EAC Per Tablet	EAC Per Day	EAC for 12 Weeks of Therapy
Sovaldi™ (sofosbuvir)	$1,056.00	$1,056.00	$88,704.00

EAC= estimated acquisition cost

Olysio™ (Simeprevir) Oral Capsules Summary[9]

- **FDA Approved:** November 2013
- **Indication:**
  - Olysio™ (simeprevir) is a HCV NS3/4A protease inhibitor indicated for the treatment of CHC infection as a component of a combination antiviral treatment regimen.
  - Olysio™ efficacy has been established in combination with PEG-IFN and RBV in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis). Olysio™ must not be used as monotherapy.
  - Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.
  - Treatment with Olysio™ is not recommended in patients with decompensated hepatic disease (CTP class B or C).
  - It is unlikely that patients with inadequate on-treatment virologic response will achieve a SVR, therefore discontinuation of treatment is recommended in these patients. The following treatment stopping rules in any patient with inadequate on-treatment virologic response apply:

HCV RNA	
Treatment Week 4: ≥ 25 IU/mL	Discontinue Olysio™, PEG-IFN, & RBV
Treatment Week 12: ≥ 25 IU/mL	Discontinue PEG-IFN & RBV (treatment with Olysio™ is complete at Week 12)
Treatment Week 24: ≥ 25 IU/mL	Discontinue PEG-IFN & RBV

* If PEG-IFN or RBV is discontinued for any reason, Olysio™ must also be discontinued.

- **Dosage Forms:** 150mg oral capsule
- **Dosing:**
  - 150mg by mouth once daily with food
  - The recommended treatment duration of Olysio™ with PEG-IFN and RBV is 12 weeks, followed by either 12 or 36 additional weeks of PEG-IFN and RBV depending on prior response status.
- **Mechanism of Action:** Olysio™ is an inhibitor of the HCV NS3/4A protease which is essential for viral replication. In a biochemical assay Olysio™ inhibited the proteolytic activity of recombinant genotype 1a and 1b HCV NS3/4A proteases.
- **Efficacy:** The efficacy of Olysio™ in patients with HCV genotype 1 infection was evaluated in two Phase 3 trials in treatment-naïve subjects, one Phase 3 trial in subjects who relapsed after prior INF-based therapy and one Phase 2b trial in subjects who failed prior therapy with PEG-IFN and RBV (including prior relapsers, partial and null responders). Subjects in these trials had compensated liver disease (including cirrhosis), HCV-RNA of at least 10,000 IU/mL, and liver histopathology consistent with CHC. In subjects who were treatment-naïve

and prior relapsers, the overall duration of treatment with PEG‑IFN and RBV in the Phase 3 trials was response-guided. In these subjects, the planned total duration of HCV treatment was 24 weeks if the following on-treatment protocol-defined response-guided therapy (RGT) criteria were met: HCV-RNA lower than 25 IU/mL (detectable or undetectable) at Week 4 and undetectable HCV-RNA at Week 12. Plasma HCV-RNA levels were measured. Treatment stopping rules for HCV therapy were used to ensure that subjects with inadequate on-treatment virologic response discontinued treatment in a timely manner. SVR was defined as undetectable HCV-RNA 24 weeks after planned end of treatment (SVR24) in the Phase 2b trial and was defined as HCV-RNA lower than 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment (SVR12) in the Phase 3 trials.
  - QUEST 1 and QUEST 2 evaluated the efficacy of Olysio™ in treatment-naïve patients with HCV genotype 1 infection. All subjects received 12 weeks of once daily treatment with 150 mg Olysio™ or placebo, plus PEG-IFN or PEG-IFN and RBV, followed by 12 or 36 weeks of therapy with PEG-IFN and RBV in accordance with the on-treatment protocol-defined RGT criteria. Subjects in the control groups received 48 weeks of PEG-IFN and RBV. In the pooled analysis for QUEST 1 and QUEST 2, 17% of the overall population and 34% of the subjects with genotype 1a virus had the NS3 Q80K polymorphism at baseline. In the Olysio™ treatment group, SVR12 rates were lower in subjects with genotype 1a virus with the NS3 Q80K polymorphism at baseline compared to subjects infected with genotype 1a virus without the Q80K polymorphism. The SVR rate for genotype 1a without Q80K was 84% in the Olysio™ treatment group and 43% in the PEG-IFN and RBV group. The SVR rate for genotype 1a with Q80K was 58% in the Olysio™ treatment group and 52% in the PEG-IFN and RBV group.

- **Utilization/Cost:** Olysio™ has been used by 5 members for a total of 7 claims since January 2014.

Medication	EAC Per Capsule	EAC Per Day	EAC for 12 Weeks of Therapy
Olysio™ (simeprevir)	$834.24	$834.24	$88,704.00

EAC= estimated acquisition cost

Victrelis® (Boceprevir) Oral Capsules Summary[10]

- **FDA Approved:** May 2011
- **Indication:**
  - Victrelis® (Boceprevir) is a HCV NS3/4A protease inhibitor indicated for the treatment of CHC genotype 1 infection, in combination with PEG-IFN and RBV, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous IFN and RBV therapy, including prior null responders, partial responders, and relapsers.
  - Victrelis® must not be used as monotherapy and should only be used in combination with PEG-IFN and RBV.
- **Dosage Forms:** 200mg oral capsule

- **Dosing:**
  - 800mg by mouth three times daily with food
  - Victrelis® must be administered in combination with PEG-IFN and RBV. Initiate therapy with PEG-IFN for 4 weeks, then add Victrelis® to PEG-IFN and RBV regimen. The duration of treatment is based on viral response, prior response status, and presence of cirrhosis.
  - Discontinuation of therapy is recommended in all patients with HCV-RNA levels ≥ 1,000 IU per mL at treatment week 8, or HCV-RNA levels ≥ 100 IU per mL at treatment week 12, or confirmed detectable HCV-RNA levels at treatment week 24.

- **Mechanism of Action:** Victrelis® is an inhibitor of the HCV NS3/4A protease that is necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins. Victrelis® covalently, yet reversibly, binds to the NS3 protease active site serine to inhibit viral replication in HCV-infected host cells. In a biochemical assay, Victrelis® inhibited the activity of recombinant HCV genotype 1a and 1b NS3/4A protease enzymes.

- **Efficacy:** The efficacy of Victrelis® as a treatment for CHC (genotype 1) infection was assessed in approximately 1,500 adult subjects who were previously untreated or who had failed previous PEG-IFN and RBV therapy in Phase 3 clinical studies. Previously untreated subjects were evaluated in a randomized, double-blind, placebo-controlled study comparing two therapeutic regimens of Victrelis® 800 mg orally three times daily in combination with PEG-IFN 1.5 micrograms per kg per week and weight-based RBV (600-1400 mg per day orally divided twice daily) to PEG-IFN alone. Participants were stratified by HCV genotype (1a or 1b) and by HCV-RNA viral load to one of the following three treatment arms:
  - PEG-IFN + RBV for 48 weeks
  - PEG-IFN + RBV for 4 weeks followed by Victrelis® 800 mg three times daily + PEG-IFN + RBV for 24 weeks. The subjects were then continued on different regimens based on Treatment Week (TW) 8 through TW24 response-guided therapy. All subjects in this treatment arm were limited to 24 weeks of therapy with Victrelis®.
  - PEG-IFN + RBV for 4 weeks followed by Victrelis® 800 mg three times daily + PEG-IFN + RBV for 44 weeks.

All subjects with detectable HCV-RNA in plasma at TW24 were discontinued from treatment. SVR was defined as plasma HCV-RNA less than 25 IU/mL at follow-up week 24. The addition of Victrelis® to PEG-IFN and RBV significantly increased the SVR rates compared to PEG-IFN and RBV alone in the combined cohort (63% to 66% in arms containing Victrelis® vs. 38% PEG-IFN and RBV for 48 weeks).

- **Utilization/Cost:** Victrelis® has been used by 33 members for a total of 115 claims since April 2013.

Medication	EAC Per Capsule	EAC Per Day	EAC for 28 Weeks of Therapy
Victrelis® (boceprevir)	$21.02	$252.24	$49,439.04

EAC= estimated acquisition cost

Incivek® (Telaprevir) Oral Tablets Summary[11]

- **FDA Approved:** May 2011

- **Indication:**
  - Incivek® (telaprevir) is a HCV NS3/4A protease inhibitor indicated, in combination with PEG-IFN and RBV, for the treatment of genotype 1 CHC in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with IFN-based treatment, including prior null responders, partial responders, and relapsers.
  - Incivek® must not be used as monotherapy and should only be used in combination with PEG-IFN and RBV.
- **Dosage Forms:** 375mg oral tablet

- **Dosing:**
  - 1,125mg by mouth twice daily with food
  - Incivek® must be administered with both PEG-IFN and RBV for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of PEG-IFN and RBV depending on viral response and prior response status.
  - HCV-RNA levels should be monitored at weeks 4 and 12 to determine combination treatment duration and assess for treatment futility.
  - Discontinuation of therapy is recommended in all patients with HCV-RNA levels ≥ 1,000 IU per mL at treatment week 4 or 12, or confirmed detectable HCV-RNA levels at treatment week 24.

- **Mechanism of Action:** Incivek® is an inhibitor of the HCV NS3/4A serine protease, necessary for the proteolytic cleavage of the HCV encoded polyprotein into mature forms of the NS4A, NS4B, NS5A and NS5B proteins and essential for viral replication. In a biochemical assay, Incivek® inhibited the proteolytic activity of the recombinant HCV NS3 protease domain.

- **Efficacy:** The efficacy and safety of Incivek® in subjects with genotype 1 CHC were evaluated in 4 controlled clinical trials: 3 in treatment-naïve subjects and one in previously treated subjects (relapsers, partial responders, and null responders). ADVANCE was a randomized, double-blind, parallel-group, placebo-controlled trial conducted in treatment-naïve subjects. Incivek® was given for the first 8 weeks or the first 12 weeks of treatment in combination with Peg-IFN and RBV for either 24 or 48 weeks. Subjects who had undetectable HCV-RNA at weeks 4 and 12 received 24 weeks of Peg-IFN and RBV, and subjects who did not have undetectable HCV-RNA at weeks 4 and 12 received 48 weeks of Peg-IFN and RBV. The control regimen had a fixed treatment duration, with Incivek®-matching placebo for the first 12 weeks and Peg-IFN and RBV for 48 weeks. The 8 week group had an overall SVR rate of 72%. More subjects in the 8 week group experienced virologic failure after week 12 while receiving PEG-IFN and RBV alone, 7% compared to 4% in 12 week group. SVR rates were higher (absolute difference of at least 22%) for the 12 week group than for the control group across subgroups by sex, age, race, ethnicity, body mass index, HCV genotype subtype, baseline HCV-RNA, and extent of liver fibrosis.

- **Utilization/Cost:** Incivek® has been used by 39 members for a total of 90 claims since April 2013.

Medication	EAC Per Tablet	EAC Per Day	EAC for 12 Weeks of Therapy
Incivek® (telaprevir)	$138.61	$831.66	$69,859.44

EAC= estimated acquisition cost

Recommendations

The College of Pharmacy recommends the prior authorization of Sovaldi™ (sofosbuvir), Olysio™ (simeprevir), Victrelis® (boceprevir), and Incivek® (telaprevir) with the following criteria:

Sovaldi™ (Sofosbuvir) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic hepatitis C (CHC) with a METAVIR fibrosis score of F2 or greater; and
3. Sovaldi™ must be prescribed by a gastroenterologist or infectious disease specialist or the member must be evaluated by a gastroenterologist or infectious disease specialist within the last six months; and
4. Sovaldi™ must be used as a component of a combination regimen; and
5. Member must be eligible for ribavirin (RBV) therapy. Approvals will not be granted for regimens without RBV; and
6. Hepatitis C Virus (HCV) genotype testing must be confirmed and indicted on prior authorization request; and
7. The following regimens and requirements based on genotype will apply:
    a. Genotype 1:
        i. Triple therapy: Sovaldi™ + Pegylated Interferon (PEG-IFN) + RBV x 12 weeks
        ii. Members who are PEG-IFN ineligible may be approved for total treatment duration of 24 weeks with a patient-specific, clinically significant reason why member cannot use PEG-IFN.
    b. Genotype 2:
        i. Dual therapy: Sovaldi™ + RBV x 12 weeks
    c. Genotype 3:
        i. Dual therapy: Sovaldi™ + RBV x 24 weeks
    d. Genotype 4:
        i. Triple therapy: Sovaldi™ + PEG-IFN + RBV x 12 weeks
    e. Hepatocellular Carcinoma:
        i. Dual therapy: Sovaldi™ + RBV x 48 weeks or until time of liver transplant (whichever occurs first)
        ii. Approvals will only be granted for HCV infected members (regardless of genotype) with hepatocellular carcinoma meeting the MILAN criteria (MILAN criteria defined as presence of a tumor 5cm or less in diameter in patients with single hepatocellular carcinomas and not more than three tumor nodules, each 3cm or

less in diameter in patients with multiple tumors and no extrahepatic manifestations of the cancer or evidence of vascular invasion of tumor).

8. Member must sign consent/intent to treat contract; and
9. Member must have no illicit IV drug use or alcohol abuse in the last 6 months and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
10. Must have documentation of immunization with the hepatitis A and B vaccines; and
11. Member must not have decompensated hepatic disease (Child Turcotte Pugh (CTP) class B or C); and
12. Female members must have a pregnancy test immediately prior to therapy initiation. Female partners of male patients should also be checked for pregnancy for informational purposes. Male and female members must be willing to use 2 forms of non-hormonal birth control while on therapy and for 6 months after therapy completion; and
13. Member must not be taking the following medications: rifampin, rifabutin, rifapentine, carbamazepine, phenytoin, oxcarbazepine, tipranavir/ritonavir, didanosine or St. John's wort; and
14. All other clinically significant issues must be addressed prior to starting therapy including but not limited to the following: neutropenia, anemia, thrombocytopenia, surgery, depression, psychosis, epilepsy, obesity, weight management, severe concurrent medical diseases, such as but not limited to, retinal disease or autoimmune thyroid disease.
15. Members must be adherent for continued approval. Treatment gaps of therapy longer than 7 days will result in denial of subsequent requests for continued therapy.
16. Combination therapy will be considered on a case by case basis. The coverage of hepatitis C treatments will be updated as new medications and clinical guidelines become available.

Olysio™ (Simeprevir) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic Hepatitis C (genotype 1) with a METAVIR fibrosis score of F2 or greater; and
3. HCV genotype testing must be confirmed and indicted on prior authorization request; and
4. Members with genotype 1a must be screened for the NS3 Q80K polymorphism prior to initiation of therapy. Approvals will not be granted for members with this polymorphism; and
5. Olysio™ must be prescribed by a gastroenterologist or infectious disease specialist or the member must be evaluated by a gastroenterologist or infectious disease specialist within the last six months; and
6. Olysio™ must be used as a component of a combination regimen.
    a. Olysio™ will be approved for combination therapy only.
    b. Triple therapy: Olysio™ + RBV + PEG-IFN x 12 weeks
    c. After completion of Olysio™ therapy member must continue on RBV and PEG-IFN therapy for
        i. an additional 12 weeks for treatment naïve patients
        ii. an additional 36 weeks for previously treated, now relapsed members, including those with cirrhosis

7. Member must not have previously failed treatment with a hepatitis C protease inhibitor (non-responder or relapser); and
8. Member must not have decompensated hepatic disease (CTP class B or C); and
9. Member must sign consent/intent to treat contract; and
10. Member must have no illicit IV drug use or alcohol abuse in the last 6 months and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
11. Must have documentation of immunization with the hepatitis A and B vaccines; and
12. Female members must have a pregnancy test immediately prior to therapy initiation. Female partners of male patients should also be checked for pregnancy for informational purposes. Male and female members must be willing to use 2 forms of non-hormonal birth control while on therapy and for 6 months after therapy completion; and
13. Member must not be taking the following medications: efavirenz, delavirdine, etravirine, nevirapine, ritanovir and any HIV protease inhibitor (boosted or not by ritanovir), rifampin, rifabutin, rifapentine, erythromycin, clarithromycin, telithromycin, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole, dexamethasone, cisapride, didanosine, milk thistle, or St. John's wort; and
14. All other clinically significant issues must be addressed prior to starting therapy including but not limited to the following: neutropenia, anemia, thrombocytopenia, surgery, depression, psychosis, epilepsy, obesity weight management, severe concurrent medical diseases such as but not limited to retinal disease or autoimmune thyroid disease.
15. Members must be adherent for continued approval. Treatment gaps of therapy longer than 7 days will result in denial of subsequent requests for continued therapy.
16. Combination therapy will be considered on a case by case basis. The coverage of hepatitis C treatments will be updated as new medications and clinical guidelines become available.

Victrelis® (Boceprevir) and Incivek® (Telaprevir) Approval Criteria:

1. Use of Victrelis® or Incivek® requires a patient-specific, clinically significant reason why the member cannot use Olysio™ (simeprevir).
2. Combination therapy will be considered on a case by case basis. The coverage of hepatitis C treatments will be updated as new medications and clinical guidelines become available.

Utilization Details of Hepatitis C Medications: April 2013 - April 2014

Product Utilized	Total Claims	Total Members	Total Cost	Claims/ Member	Cost/ Day	Cost/ Claim	Percent Cost
Peginterferon Products							
PEGASYS INJ PROCLICK 180MCG	374	92	$1,152766.25	4.07	$109.12	$3,082.26	8.70%
PEGASYS INJ 180MCG	211	64	$681,264.39	3.30	$112.16	$3,228.74	5.14%
PEG-INTRON KIT 120 MCG	136	36	$419,764.42	3.78	$109.43	$3,086.50	3.17%
PEG-INTRON KIT 150 MCG	114	28	$362,615.64	4.07	$113.25	$3,180.84	2.74%
PEG-INTRON KIT 80MCG	23	7	$65,598.73	3.29	$101.86	$2,852.12	0.49%
PEGASYS INJ PROCLICK 135MCG	10	4	$31,119.34	2.5	$111.14	$3,111.93	0.23%
PEG-INTRON KIT 50MCG	11	2	$30,626.91	5.5	$99.44	$2,784.26	0.23%
PEG-INTRON KIT 120MCG	2	1	$253.00	2	$4.52	$126.50	0.00%
PEG-INTRON KIT 150MCG	2	1	$6,866.52	2	$122.62	$3,433.26	0.05%
PEGASYS KIT 180MCG	1	1	$3045.18	1	$108.76	$3,045.18	0.02%
Subtotal	**884**	**227**	**$2,753,920.38**	**3.89**	**$109.95**	**$3,115.29**	**20.77%**
Ribavirin Products							
RIBASPHERE TAB 200MG	338	102	$38,511.56	3.31	$4.07	$113.94	0.29%
RIBAVIRIN TAB 200MG	324	103	$35,710.54	3.15	$3.81	$110.22	0.27%
RIBASPHERE CAP 200MG	196	55	$17,760.51	3.56	$3.24	$90.61	0.13%
RIBAVIRIN CAP 200MG	80	32	$7,419.77	2.5	$3.20	$92.75	0.06%
MODERIBA TAB 200MG	2	2	$210.94	1	$3.77	$105.47	0.00%
Subtotal	**940**	**280**	**$99,613.32**	**3.36**	**$3.73**	**$105.97**	**0.75%**
Sofosbuvir Products+							
SOVALDI 400MG	255	124	$7,534,953.38	2.06	$1,055.32	$29,548.84	51.75%
Subtotal	**255**	**124**	**$7,534,953.38**	**2.06**	**$1,055.32**	**$29,548.84**	**56.85%**
Boceprevir Products							
VICTRELIS CAP 200MG	116	33	$723,944.73	3.52	$220.85	$6,240.90	5.46
Subtotal	**116**	**33**	**$723,944.73**	**3.52**	**$220.85**	**$6,240.90**	**5.46%**
Telaprevir Products							
INCIVEK TAB 375MG	90	39	$1,977,707.85	2.31	$784.80	$21,974.53	14.92%
Subtotal	**90**	**39**	**$1,977,707.85**	**2.31**	**$784.80**	**$21,974.53**	**14.92%**
Simeprevir Products+							
OLYSIO CAP 150MG	7	5	$163,518.18	1.4	$834.28	$23,359.74	1.23%
Subtotal	**7**	**5**	**$163,518.18**	**1.4**	**$834.28**	**$23,359.74**	**1.23%**
Total	**2,292**	**289***	**$13,253,657.84**	**7.93**	**$204.28**	**$5,782.57**	**100%**

*Total number of unduplicated members.

+ Reflects utilization from December 2013 to April 2014.

PRODUCT DETAILS OF SOVALDI™ (SOFOSBUVIR)[8]

INDICATIONS AND USE:

- Sovaldi™ is a HCV nucleotide analog NS5B polymerase inhibitor indicated for the treatment of CHC infection as a component of a combination antiviral treatment regimen. Sovaldi™ efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

DOSAGE FORMS:

- Sovaldi™ is available as a 400mg tablet.

ADMISTRATION:

- The recommended dose of Sovaldi™ is 400mg by mouth once daily with or without food
- Duration of treatment depends on HCV genotype:
  - Genotype 1 or 4: Sovaldi™ + PEG-IFN + RBV for 12 weeks
  - Genotype 2: Sovaldi™ + RBV for 12 weeks
  - Genotype 3: Sovalid™ + RBV for 24 weeks

CONTRAINDICATIONS:

- Sovaldi™ is used in combination with RBV or PEG-IFN/RBV, and the contraindications applicable to those agents are applicable to combination therapies. Contraindications to these therapies include the following:
  - Known hypersensitivity to any of the 3 agents
  - Autoimmune hepatitis
  - Hepatic decompensation (CTP greater than 6: class B and C) in cirrhotic CHC patients
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Creatinine clearance less than 50mL/min
  - Coadministration with didanosine

SPECIAL POPULATIONS:

- **Pregnancy:** Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive RBV unless they are using two forms of effective contraception during treatment with RBV and for 6 months after treatment has concluded. There is no data on the effectiveness of systemic hormonal contraceptives in women taking Sovaldi™. Therefore, two effective non-hormonal methods of contraception should be used during treatment with Sovaldi™ and concomitant RBV. There are no adequate and well-controlled studies with Sovaldi™ in pregnant women.
- **Nursing Mothers:** It is not known whether Sovaldi™ is present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment, taking into account the importance of the therapy to the mother.

- **Pediatric Use:** The safety and effectiveness of Sovaldi™ in children less than 18 years of age have not been established.
- **Geriatric Use:** Sovaldi™ was administered to 90 subjects aged 65 and over. The response rates observed for subjects older than 65 years of age were similar to that of younger subjects**.** No dose adjustment of Sovaldi™ is warranted in geriatric patients
- **Renal Impairment:** No dose adjustment of Sovaldi™ is required for patients with mild or moderate renal impairment. The safety and efficacy of Sovaldi™ have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis.
- **Hepatic Impairment:** No dose adjustment of Sovaldi™ is required for patients with mild, moderate or severe hepatic impairment. Safety and efficacy of Sovaldi™ have not been established in patients with decompensated cirrhosis.
- **Patients with HCV/HIV-1 Co-Infection:** The safety and efficacy of Sovaldi™ was assessed in 223 HCV/HIV-1 co-infected subjects. The safety profile in HCV/HIV-1 co-infected subjects was similar to that observed in HCV mono-infected subjects. Elevated total bilirubin (grade 3 or 4) was observed in 30/32 (94%) subjects receiving atazanavir as part of the antiretroviral regimen. None of the subjects had concomitant transaminase increases. Among subjects not taking atazanavir, grade 3 or 4 elevated total bilirubin was observed in 2 (1.5%) subjects, similar to the rate observed with HCV mono-infected subjects receiving Sovaldi™ and RBV in Phase 3 trials.
- **Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation:** Sovaldi™ was studied in HCV-infected subjects with hepatocellular carcinoma prior to undergoing liver transplantation in an open-label clinical trial evaluating the safety and efficacy of Sovaldi™ and RBV administered pre-transplant to prevent post-transplant HCV reinfection. The primary endpoint of the trial was post-transplant virologic response. HCV-infected subjects, regardless of genotype, with hepatocellular carcinoma meeting the MILAN criteria received 400 mg Sovaldi™ and weight-based 1000-1200 mg RBV daily for 24-48 weeks or until the time of liver transplantation, whichever occurred first. Of the 37 subjects, the post-transplant virologic response rate was 64% (23/36) in the 36 evaluable subjects who reached the 12 week post-transplant time point. The safety profile of Sovaldi™ and RBV in HCV-infected subjects prior to liver transplantation was comparable to that observed in subjects treated with Sovaldi™ and RBV in Phase 3 clinical trials.
- **Post-Liver Transplant Patients:** The safety and efficacy of Sovaldi™ have not been established in post-liver transplant patients.
- **CHC Patients with Genotype 5 or 6 HCV Infection:** Available data on subjects with genotype 5 or 6 HCV infection is insufficient for dosing recommendations.

WARNINGS AND PRECAUTIONS:

- Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RBV therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy.
- When Sovaldi™ is used in combination with RBV or PEG-IFN/RBV, women of childbearing potential and their male partners must use two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly

pregnancy tests must be performed during this time. There are no data on the effectiveness of systemic hormonal contraceptives in women taking Sovaldi™, therefore, two non-hormonal methods of contraception should be used during treatment with Sovaldi™ and concomitant RBV.

ADVERSE REACTIONS:

- The proportion of subjects who permanently discontinued treatment due to adverse events was 4% for subjects receiving placebo, 1% for subjects receiving Sovaldi™ + RBV for 12 weeks, <1% for subjects receiving Sovaldi™ + RBV for 24 weeks, 11% for subjects receiving PEG-IFN + RBV for 24 weeks and 2% for subjects receiving Sovaldi™ + PEG-IFN + RBV for 12 weeks.
- The most common adverse events (≥ 20%) for Sovaldi™ + RBV combination therapy were fatigue and headache. The most common adverse events (≥ 20%) for Sovaldi™ + PEG-IFN + RBV combination therapy were fatigue, headache, nausea, insomnia and anemia.

DRUG INTERACTIONS:

- Coadministration of Sovaldi™ with carbamazepine, phenytoin, phenobarbital or oxcarbazepine is expected to decrease the concentration of Sovaldi™, leading to reduced therapeutic effect of Sovaldi™. Coadministration is not recommended.
- Coadministration of Sovaldi™ with rifabutin or rifapentine is expected to decrease the concentration of Sovaldi™, leading to reduced therapeutic effect of Sovaldi™.
- Sovaldi™ should not be used with St. John's wort or rifampin, both of which are potent intestinal P-gp inducers that reduce the plasma concentrations of Sovaldi™ and may lead to a reduced therapeutic effect of Sovaldi™.
- Coadministration of Sovaldi™ with tipranavir/ritonavir is expected to decrease the concentration of Sovaldi™, leading to reduced therapeutic effect of Sovaldi™. Coadministration is not recommended.

PATIENT COUNSELING INFORMATION:

1. Sovaldi™ is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C infection in adults.
2. You should not take Sovaldi™ alone. Sovaldi™ should be used together with RBV or in combination with PEG-IFN and RBV.
3. Females must have a negative pregnancy test before starting treatment with Sovaldi™ and RBV or in combination with PEG-IFN and RBV, every month while being treated, and for 6 months after your treatment ends.
4. Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with Sovaldi™ and RBV or in combination with PEG-IFN and RBV.
5. Before taking Sovaldi™, tell your healthcare provider if you:
    a. Have liver problems other than hepatitis C infection
    b. Have had a liver transplant
    c. Have severe kidney problems or you are on dialysis
    d. Have HIV
    e. Have any other medical condition
    f. Are breastfeeding or plan to breastfeed

6. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you take any of the following medicines:
    a. carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
    b. oxcarbazepine (Trileptal®, Oxtellar XR™)
    c. phenytoin (Dilantin®, Phenytek®)
    d. phenobarbital (Luminal®)
    e. rifabutin (Mycobutin®)
    f. rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
    g. rifapentine (Priftin®)
    h. St. John's wort
    i. tipranavir (Aptivus®)
7. Take Sovaldi™ exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
8. Do not stop taking Sovaldi™ without first talking with your healthcare provider
9. Take Sovaldi™ once daily with or without food.
10. If you miss a dose of Sovaldi™, take the missed dose as soon as you remember the same day. Do not take more than 1 tablet (400 mg) of Sovaldi™ in a day.
11. If you take too much Sovaldi™, call your healthcare provider or go to the nearest hospital emergency room right away.
12. The most common side effects of Sovaldi™ when used in combination with RBV include: fatigue and headache. The most common side effects of Sovaldi™ when used in combination with PEG-IFN and RBV include: tiredness, headache, nausea, difficulty sleeping, and low red blood cell count.

PRODUCT DETAILS OF OLYSIO™ (SIMEPREVIR)[9]

INDICATIONS AND USE:

- Olysio™ is a HCV NS3/4A protease inhibitor indicated for the treatment of CHC infection as a component of a combination antiviral treatment regimen. Olysio™ efficacy has been established in combination with PEG-IFN and RBV, in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis).
- Olysio™ must not be used as monotherapy
- Olysio™ efficacy in combination with PEG-IFN and RBV is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with HCV genotype 1a without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.
- Olysio™ efficacy has not been studied in patients who have previously failed therapy with a treatment regimen that includes Olysio™ or other HCV protease inhibitors.

DOSAGE FORMS:

- Olysio™ is available as a 150mg oral capsule.

ADMISTRATION:

- The recommended dose of Olysio™ is 150mg by mouth once daily with food.
- The recommended duration of treatment with Olysio™ is 12 weeks in combination with PEG-IFN and RBV.
    - All treatment-naïve and prior relapse patients, including those with cirrhosis should receive an additional 12 weeks of PEG-IFN and RBV after completing 12 weeks of treatment with Olysio™, PEG-IFN, and RBV (total treatment duration of 24 weeks).
    - All prior non-responder patients (including partial and null-responders), including those with cirrhosis, should receive an additional 36 weeks of PEG-IFN and RBV after completing 12 weeks of treatment with Olysio™, PEG-IFN, and RBV (total treatment duration of 48 weeks).

CONTRAINDICATIONS:

- Olysio™ is used in combination with RBV or PEG-IFN/RBV, and the contraindications applicable to those agents are applicable to combination therapies. Contraindications to these therapies include the following:
    - Known hypersensitivity to any of the 3 agents
    - Autoimmune hepatitis
    - Hepatic decompensation (CTP greater than 6: class B and C) in cirrhotic CHC patients
    - Pregnant women and men whose female partners are pregnant
    - Hemoglobinopathies
    - Creatinine clearance less than 50mL/min
    - Coadministration with didanosine

SPECIAL POPULATIONS:

- **Pregnancy:** Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive RBV unless they are using two forms of effective contraception during treatment with RBV and for 6 months after treatment has concluded. There are no adequate and well-controlled studies with Olysio™ in pregnant women.
- **Nursing Mothers:** It is not known whether Olysio™ is present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment, taking into account the importance of the therapy to the mother.
- **Pediatric Use:** The safety and effectiveness of Olysio™ in children less than 18 years of age have not been established.
- **Geriatric Use:** Clinical studies of Olysio™ did not include sufficient numbers of patients older than 65 years to determine whether they respond differently from younger patients. No dose adjustment of Olysio™ is warranted in geriatric patients
- **Race:** Patients of East Asian ancestry exhibit higher Olysio™ exposures. In clinical trials, higher Olysio™ exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity. There are insufficient safety data to recommend an appropriate dose for patients of East Asian ancestry. The potential risks and benefits of Olysio™ should be carefully considered prior to use in patients with East Asian ancestry.
- **Renal Impairment:** No dose adjustment of Olysio™ is required for patients with mild, moderate, or severe renal impairment. The safety and efficacy of Olysio™ have not been established in patients with severe renal impairment (CrCl <30 mL/min) or end stage renal disease (ESRD) requiring hemodialysis.
- **Hepatic Impairment:** No dose adjustment of Olysio™ is required for patients with mild, hepatic impairment (Child-Pugh Class A). No dose recommendation can be given for patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) due to higher Olysio™ exposures. The safety and efficacy of Olysio™ have not been studied in patients with moderate or severe hepatic impairment .The combination of PEG-IFN and RBV is contraindicated in patients with decompensated cirrhosis.
- **Other HCV Genotypes:** The safety and efficacy of Olysio™ in combination with PEG-IFN and RBV has not been established in patients with other HCV genotypes.
- **Liver Transplantation:** The safety and efficacy of Olysio™ in combination with PEG-IFN and RBV has not been established in liver transplant patients.

WARNINGS AND PRECAUTIONS:

- Olysio™ must not be used as monotherapy. Olysio™ should be used in combination with both PEG-IFN and RBV. Therefore the prescribing information for PEG-IFN and RBV must be consulted before starting therapy with Olysio™. Contraindications and Warnings and Precautions related to PEG-IFN and RBV also apply to Olysio™ combination treatment with PEG-IFN and RBV.

- RBV may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RBV therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners, as well as male patients and their female partners, must use two effective contraceptive methods during treatment and for 6 months after completion of treatment. Routine monthly pregnancy tests must be performed during this time.
- Photosensitivity reactions have been observed with Olysio™, including serious reactions which resulted in hospitalization. Photosensitivity reactions occurred most frequently in the first 4 weeks of treatment with Olysio™, but can occur at any time during treatment. During treatment sun protective measures and limiting sun exposure should be implemented.
- Rash has been observed in subjects receiving Olysio™. Rash occurred most frequently in the first 4 weeks of treatment with Olysio™ in, but can occur at any time during treatment.
- Olysio™ contains a sulfonamide moiety. In subjects with a history of sulfa allergy, no increased incidence of rash or photosensitivity reactions has been observed. However, there are insufficient data to exclude an association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of Olysio™.

ADVERSE REACTIONS:

- Discontinuation of Olysio™ or placebo due to adverse reactions occurred in 2% and 1% of subjects receiving Olysio™ with PEG-IFN and RBV and subjects receiving placebo with PEG-IFN and RBV, respectively.
- The following adverse reactions occurred with at least 3% higher frequency among subjects receiving Olysio™ 150 mg once daily in combination with PEG-IFN and RBV compared to subjects receiving placebo in combination with PEG-IFN and RBV during the first 12 weeks of treatment in the pooled Phase 3 trials:
    - Rash
    - Pruritus
    - Nausea
    - Myalgia
    - Dyspnea

DRUG INTERACTIONS:

- Concomitant use of Olysio™ with carbamazepine, oxcarbazepine, phenobarbital or phenytoin may result in significantly decreased plasma concentrations of Olysio™ due to strong CYP3A induction by these anticonvulsants. It is not recommended to co-administer Olysio™ with these anticonvulsants.
- Concomitant use of Olysio™ with erythromycin resulted in significantly increased plasma concentrations of both erythromycin and Olysio™ due to inhibition of CYP3A and P-gp by both erythromycin and Olysio™. It is not recommended to co-administer Olysio™ with erythromycin.
- Concomitant use of Olysio™ with clarithromycin or telithromycin may result in increased plasma concentrations of Olysio™ due to CYP3A inhibition by these antibiotics. It is not recommended to co-administer Olysio™ with clarithromycin or telithromycin.

- Concomitant use of Olysio™ with systemic itraconazole, ketoconazole, fluconazole, voriconazole, or posaconazole may result in significantly increased plasma concentrations of Olysio™ due to CYP3A inhibition by these antifungals. Co-administration of Olysio™ with these antifungals is not recommended.
- Concomitant use of Olysio™ with rifampin, rifabutin or rifapentine may result in significantly decreased plasma concentrations of Olysio™ due to CYP3A4 induction by these antimycobacterials. It is not recommended to co-administer Olysio™ with rifampin, rifabutin or rifapentine.
- Concomitant use of Olysio™ with systemic dexamethasone may result in decreased plasma concentrations of Olysio™ due to moderate induction of CYP3A4 by dexamethasone. It is not recommended to co-administer Olysio™ with systemic dexamethasone.
- Cisapride has the potential to cause cardiac arrhythmias. Concomitant use of Olysio™ with cisapride may result in increased plasma concentrations of cisapride due to intestinal CYP3A4 inhibition by Olysio™. It is not recommended to co-administer Olysio™ with cisapride.
- Concomitant use of Olysio™ with milk thistle may result in increased plasma concentrations of Olysio™ due to CYP3A inhibition by milk thistle. It is not recommended to co-administer Olysio™ with milk thistle.
- Concomitant use of Olysio™ with products containing St. John's wort may result in significantly decreased plasma concentrations of Olysio™ due to CYP3A induction by St. John's wort. It is not recommended to co-administer Olysio™ with products containing St. John's wort.
- Concomitant use of Olysio™ and a cobicistat‑containing product (elvitegravir/cobicistat/emtricitabine/ tenofovir disoproxil fumarate) may result in significantly increased plasma concentrations of Olysio™ due to strong CYP3A inhibition by cobicistat. It is not recommended to co‑administer Olysio™ with an acobicistat‑containing product.
- Concomitant use of Olysio™ with efavirenz resulted in significantly decreased plasma concentrations of Olysio™ due to CYP3A induction by efavirenz. It is not recommended to co-administer Olysio™ with efavirenz.
- Concomitant use of Olysio™ with delavirdine, etravirine, or nevirapine may result in altered plasma concentrations of Olysio™ due to CYP3A inhibition (delavirdine) or induction (etravirine and nevirapine) by these drugs. It is not recommended to co-administer Olysio™ with delavirdine, etravirine or nevirapine.
- Concomitant use of Olysio™ with darunavir/ritonavir resulted in increased plasma concentrations of Olysio™ due to CYP3A inhibition by darunavir/ritonavir. It is not recommended to co-administer darunavir/ritonavir and Olysio™.
- Concomitant use of Olysio™ with ritonavir resulted in significantly increased plasma concentrations of Olysio™ due to strong CYP3A inhibition by ritonavir. It is not recommended to co-administer Olysio™ with ritonavir.
- Concomitant use of Olysio™ with ritonavir-boosted or unboosted HIV protease inhibitors (PIs) may result in altered plasma concentrations of Olysio™ due toCYP3A inhibition or induction by these HIV PIs. It is not recommended to co-administer Olysio™ with any HIV PI, with or without ritonavir.

PATIENT COUNSELING INFORMATION:

1. Olysio™ is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C infection in adults.
2. You should not take Olysio™ alone. Olysio™ should be used together with PEG-IFN and RBV.
3. Females must have a negative pregnancy test before starting treatment with Olysio™ in combination with PEG-IFN and RBV, every month while being treated, and for 6 months after your treatment ends.
4. Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with Olysio™ in combination with PEG-IFN and RBV.
5. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
6. Take Olysio™ exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
7. Do not stop taking Olysio™ without first talking with your healthcare provider
8. Take Olysio™ once daily with food.
9. If you miss a dose of Olysio™ and remember within 12 hours of the usual dosing time, take the missed dose with food as soon as possible and then take the next dose of Olysio™ at the regularly scheduled time. If you miss a dose and it has been longer than 12 hours after the usual dosing time, you should skip the missed dose and resume the usual dosing of Olysio™ at the regularly scheduled time.
10. You should use sun protection measures (such as a hat, sunglasses, protective clothing, sunscreen) during treatment with Olysio™. You should limit exposure to natural sunlight and avoid artificial sunlight (tanning beds or phototherapy) during treatment with Olysio™.
11. You should be aware of the risk of rash related to the use of Olysio™ in combination with PEG-IFN and RBV; that rash may become severe.

PRODUCT DETAILS OF VICTRELIS® (BOCEPREVIR)[10]

INDICATIONS AND USE:

- Victrelis® is a HCV NS3/4A protease inhibitor indicated for the treatment of CHC genotype 1 infection, in combination with PEG-IFN and RBV, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous IFN and RBV therapy, including prior null responders, partial responders, and relapsers.
- Victrelis® must not be used as monotherapy and should only be used in combination with PEG-IFN and RBV.
- The efficacy of Victrelis® has not been studied in patients who have previously failed therapy with a treatment regimen that includes Victrelis® or other HCV NS3/4A protease inhibitors.

DOSAGE FORMS:

- Victrelis® is available as a 200mg oral capsule.

ADMISTRATION:

- The recommended dose of Victrelis® is 800mg by mouth three times daily with food.
- Therapy with PEG-IFN and RBV should be initiated for 4 weeks prior to starting Victrelis®. Victrelis® 800mg three times daily should be added to the PEG-IFN and RBV regimen after 4 weeks of treatment. Based on the patients HCV-RNA levels at treatment week (TW)8, TW12, and TW24, use the following guidelines to determine duration of treatment.

Patient Type	HCV-RNA Results TW8	HCV-RNA Results TW24	Recommendation
Previously Untreated	Not Detected	Not Detected	Complete 3-medicine regimen at TW28
	Detected	Not Detected	1) Continue 3-medicines and finish through TW36; and then 2) Administer PEG-IFN and RBV and finish through TW48
Previous Partial Responders or Relapsers	Not Detected	Not Detected	Complete 3-medicine regimen at TW36
	Detected	Not Detected	1) Continue 3-medicines and finish through TW36; and then 2) Administer PEG-IFN and RBV and finish through TW48
Previous Null Responders	Detected or Not Detected	Not Detected	Continue 3-medicines and finish through TW48

***TREATMENT FUTILITY**

If the patient has HCV-RNA results greater than or equal to 1,000 IU/mL at TW8, then discontinue three-medicine regimen.
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

CONTRAINDICATIONS:

- Victrelis® is used in combination with RBV or PEG-IFN/RBV, and the contraindications applicable to those agents are applicable to combination therapies. Contraindications to these therapies include the following:

- Known hypersensitivity to any of the 3 agents
- Autoimmune hepatitis
- Hepatic decompensation (CTP greater than 6: class B and C) in cirrhotic CHC patients
- Pregnant women and men whose female partners are pregnant
- Hemoglobinopathies
- Creatinine clearance less than 50mL/min
- Coadministration with didanosine

- Concomitant use of Vitrelis® is contraindicated with the following medications: Alfuzosin, doxazosin, silodosin, tamsulosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort, lovastatin, simvastatin, drospirenone, sildenafil, tadalafil, pimozide, triazolam, and oral midazolam

SPECIAL POPULATIONS:

- **Pregnancy:** Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive RBV unless they are using two forms of effective contraception during treatment with RBV and for 6 months after treatment has concluded. There are no adequate and well-controlled studies with Victrelis® in pregnant women.
- **Nursing Mothers:** It is not known whether Victrelis® is present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment, taking into account the importance of the therapy to the mother.
- **Pediatric Use:** The safety and effectiveness of Victrelis® in children less than 18 years of age have not been established.
- **Geriatric Use:** Clinical studies of Victrelis® did not include sufficient numbers of patients older than 65 years to determine whether they respond differently from younger patients.
- **Renal Impairment:** No dose adjustment of Victrelis® is required for patients with any degree of renal impairment.
- **Hepatic Impairment:** No dose adjustment of Victrelis® is required for patients with mild, moderate, or severe hepatic impairment. The safety and efficacy of Victrelis® have not been studied in patients with decompensated cirrhosis.

WARNINGS AND PRECAUTIONS:

- Victrelis® must not be used as monotherapy. Victrelis® should be used in combination with both PEG-IFN and RBV. Therefore the prescribing information for PEG-IFN and RBV must be consulted before starting therapy with Victrelis®. Contraindications and Warnings and Precautions related to PEG-IFN and RBV also apply to Victrelis® combination treatment with PEG-IFN and RBV.
- RBV may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RBV therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and

their male partners, as well as male patients and their female partners, must use two effective contraceptive methods during treatment and for 6 months after completion of treatment. Routine monthly pregnancy tests must be performed during this time.

- Anemia has been reported with PEG-IFN and RBV therapy. The addition of Victrelis® to PEG-IFN and RBV is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be obtained pretreatment, and at treatment weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. If hgb < 10 g per dL, a decrease in dosage of RBV is recommended; and if hbg < 8.5 g per dL, discontinuation of RBV is recommended. If RBV is permanently discontinued for management of anemia, then PEG-IFN and Victrelis® must also be discontinued.

ADVERSE REACTIONS: The most commonly reported adverse reactions (more than 35% of subjects regardless of investigator's causality assessment) in subjects were fatigue, anemia, nausea, headache, and dysgeusia when Victrelis® was used in combination with PEG-IFN and RBV.

DRUG INTERACTIONS: See contraindications section for a list of medications that are contraindicated for use with Victrelis®.

PATIENT COUNSELING INFORMATION:

1. Victrelis® is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C infection in adults.
2. You should not take Victrelis® alone. Victrelis® should be used together with PEG-IFN and RBV.
3. Females must have a negative pregnancy test before starting treatment with Victrelis® in combination with PEG-IFN and RBV, every month while being treated, and for 6 months after your treatment ends.
4. Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with Victrelis® in combination with PEG-IFN and RBV.
5. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
6. Take Victrelis® exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.
7. Do not stop taking Victrelis® without first talking with your healthcare provider
8. Take four capsules of Victrelis® three times daily with food.
9. If you miss a dose of Victrelis® and it is less than 2 hours before the next dose is due, the missed dose should be skipped. If you miss a dose and it is 2 or more hours before the next dose is due, you should take the missed dose with food and resume the normal dosing schedule.

PRODUCT DETAILS OF INCIVEK® (TELAPREVIR)[11]

INDICATIONS AND USE:

- Incivek® is a HCV NS3/4A protease inhibitor indicated, in combination with PEG-IFN and RBV, for the treatment of genotype 1 CHC in adult patients with compensated liver disease, including cirrhosis, who are treatment-naïve or who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.
- Incivek® must not be used as monotherapy and must only be used in combination with PEG-IFN and RBV.
- Incivek® efficacy has not been established for patients who have previously failed therapy with a treatment regimen that includes Incivek® or other HCV NS3/4A protease inhibitors.

DOSAGE FORMS:

- Incivek® is available as a 375mg oral tablet.

ADMISTRATION:

- The recommended dose of Incivek® is 1,125mg by mouth twice daily with food.
- The recommended duration of treatment with Incivek®is 12 weeks in combination with PEG-IFN and RBV. HCV-RNA levels should be monitored at weeks 4 and 12 to determine combination treatment duration and assess for treatment futility.

Treatment-Naïve and Prior Relapse Patients			
HCV RNA	**Triple Therapy** (Incivek®, PEG-IFN, RBV)	**Dual Therapy** (PEG-IFN, RBV)	**Total Treatment Duration**
Undetectable (target not detected) at Weeks 4 and 12	First 12 weeks	Additional 12 weeks	24 weeks
Detectable (1000IU/mL or less) at Weeks 4 and/or 12	First 12 weeks	Additional 36 weeks	48 weeks
Prior Partial and Null Responder Patients			
All Patients	First 12 weeks	Additional 36 weeks	48 weeks

- Discontinuation of therapy is recommended in all patients with HCV RNA levels of greater than 1,000 IU/mL at Treatment Week 4 or 12; or confirmed detectable HCV RNA levels at Treatment Week 24.

CONTRAINDICATIONS:

- Incivek® is used in combination with RBV or PEG-IFN/RBV, and the contraindications applicable to those agents are applicable to combination therapies. Contraindications to these therapies include the following:
  - Known hypersensitivity to any of the 3 agents
  - Autoimmune hepatitis
  - Hepatic decompensation (CTP greater than 6: class B and C) in cirrhotic CHC patients
  - Pregnant women and men whose female partners are pregnant
  - Hemoglobinopathies
  - Creatinine clearance less than 50ml/min
  - Coadministration with didanosine

- Concomitant use of Incivek® is contraindicated with the following medications: Alfuzosin, carbamazepine, phenobarbital, phenytoin, rifampin, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, St. John's wort, lovastatin, simvastatin, sildenafil, tadalafil, pimozide, oral triazolam, and oral midazolam

SPECIAL POPULATIONS:

- **Pregnancy:** Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while taking this combination. Women of childbearing potential and their male partners should not receive RBV unless they are using two forms of effective contraception during treatment with RBV and for 6 months after treatment has concluded. There are no adequate and well-controlled studies with Incivek® in pregnant women.
- **Nursing Mothers:** It is not known whether Incivek® is present in human breast milk. Because of the potential for adverse reactions from the drug in nursing infants, a decision must be made whether to discontinue nursing or discontinue treatment, taking into account the importance of the therapy to the mother.
- **Pediatric Use:** The safety and effectiveness of Incivek®in children less than 18 years of age have not been established.
- **Geriatric Use:** Clinical studies of Incivek® did not include sufficient numbers of patients older than 65 years to determine whether they respond differently from younger patients.
- **Renal Impairment:** No dose adjustment of Incivek® is required for patients with mild, moderate, or severe renal impairment. Incivek® has not been studied in patients with a CrCl ≤ 50mL per minute.
- **Hepatic Impairment:** Incivek® is not recommended for use in patients with moderate or severe hepatic impairment (CTP B or C) because appropriate doses have not been established. No dose adjustment of Incivek® is necessary for patients with mild hepatic impairment (CTP A).

WARNINGS AND PRECAUTIONS:

Black Box Warning: Serious Skin Reactions

- Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with Incivek® combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive Incivek® combination treatment after a serious skin reaction was identified.
- For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, Incivek®, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.

- Incivek® must not be used as monotherapy. Incivek® should be used in combination with both PEG-IFN and RBV. Therefore the prescribing information for PEG-IFN and RBV must be consulted before starting therapy with Incivek®. Contraindications and Warnings and Precautions related to PEG-IFN and RBV also apply to Incivek® combination treatment with PEG-IFN and RBV.

- RBV may cause birth defects and/or death of the exposed fetus and animal studies have shown that interferons have abortifacient effects. Therefore, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. RBV therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Female patients of childbearing potential and their male partners, as well as male patients and their female partners, must use two effective contraceptive methods during treatment and for 6 months after completion of treatment. Routine monthly pregnancy tests must be performed during this time.
- Anemia has been reported with PEG-IFN and RBV therapy. The addition of Incivek® to PEG-IFN and RBV is associated with an additional decrease in hemoglobin concentrations. Complete blood counts should be obtained pretreatment, and at treatment weeks 2, 4, 8, and 12, and should be monitored closely at other time points, as clinically appropriate. For the management of anemia, RBV dose reductions should be used (refer to the prescribing information for RBV for its dose reduction guidelines). If RBV dose reductions are inadequate, discontinuation of Incivek® should be considered. If RBV is permanently discontinued for the management of anemia, Incivek® must also be permanently discontinued. RBV may be restarted per the dosing modification guidelines for RBV. The dose of Incivek® must not be reduced and Incivek®must not be restarted if discontinued.

ADVERSE REACTIONS: Incivek® was administered in combination with PEG-IFN and RBV. The following adverse drug reactions occurred in subjects treated with Incivek® with an incidence at least 5% greater than in subjects receiving PEG-IFN and RBV alone:

- Rash
- Fatigue
- Pruritus
- Nausea
- Anemia
- Diarrhea
- Vomiting
- Hemorrhoids
- Anorectal discomfort
- Dysgeusia
- Anal pruritus

DRUG INTERACTIONS: See contraindications section for a list of medications that are contraindicated for use with Incivek®.

PATIENT COUNSELING INFORMATION:

1. Incivek® is a prescription medicine used with other antiviral medicines to treat chronic (lasting a long time) hepatitis C infection in adults.
2. You should not take Incivek® alone. Incivek® should be used together with PEG-IFN and RBV.
3. Females must have a negative pregnancy test before starting treatment with Incivek® in combination with PEG-IFN and RBV, every month while being treated, and for 6 months after your treatment ends.
4. Females and males must use 2 effective forms of birth control during treatment and for the 6 months after treatment with Incivek® in combination with PEG-IFN and RBV.
5. Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
6. Take Incivek® exactly as your healthcare provider tells you to take it. Do not change your dose unless your healthcare provider tells you to.

7. Do not stop taking Incivek® without first talking with your healthcare provider.
8. Take three capsules of Incivek® two times daily with food.
9. If you miss a dose of Incivek® and it is within 6 hours of when you usually take it, take your dose with food as soon as possible. If you miss a dose and it is more than 6 hours after the time you usuall take it, skip that dose only and take the next dose at your normal dosing schedule.
10. Incivek® can cause serious skin reactions. Sometimes these skin rashes and other reactions can be serious, require treatment in a hospital, and may lead to death. Call your healthcare provider right away if you develop any skin changes or itching during treatment with Incivek®.

Attachment A

Child Turcotte Pugh (CTP) Classification of the Severity of Cirrhosis

	Class A	Class B	Class C
Total Points	5-6	7-9	10-15
Factor	**1 point**	**2 points**	**3 points**
Total Bilirubin (µmol/L)	<34	34-50	>50
Serum Albumin (g/L)	>35	28-35	<28
Prothrombin Time/INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic Encephalopathy	None	Grade I-II (or suppressed)	Grade III-IV (or refractory)

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[4] Center for Disease Control. Hepatitis C. Available online at: www.cdc.gov/heptatits/c/cfaq.htm. Last revised: 02/10/2014. Last accessed: 05/01/2014.

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[6] Mahaney K, et al. Genotype Analysis of Hepatitis C Virus in American Patients. Hepatology. December 1994; 20(6); 1405-1411.

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[10] Victrelis® Product Information. Merk & C., INC. Available online at: http://www.merck.com/product/usa/pi_circulars/v/victrelis/victrelis_pi.pdf. Last revised: 04/2014. Last accessed 05/01/2014.

[11] Incivek® Product Information. Vertex Pharmaceuticals, Inc. Available online at: http://pi.vrtx.com/files/uspi_telaprevir.pdf. Last revised: 10/2013. Last accessed 05/01/2014.

Appendix K

FDA & DEA Updates (additional information can be found at http://www.fda.gov/Drugs/default.htm)

FDA NEWS RELEASE

For Immediate Release: April 29, 2014

FDA approves Zykadia for late-stage lung cancer

Breakthrough therapy drug approved four months ahead of review completion goal date

The U.S. Food and Drug Administration today granted accelerated approval to Zykadia (ceritinib) for patients with a certain type of late-stage (metastatic) non-small cell lung cancer (NSCLC).

Zykadia is an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor that blocks proteins that promote the development of cancerous cells. It is intended for patients with metastatic ALK-positive NSCLC who were previously treated with crizotinib, the only other approved ALK tyrosine kinase inhibitor.

Lung cancer is the leading cause of cancer-related deaths among men and women. According to the National Cancer Institute, an estimated 224,210 Americans will be diagnosed with lung cancer, and 159,260 will die from the disease this year. About 85 percent of lung cancers are NSCLC, making it the most common type of lung cancer. However, only 2-7 percent of patients with NSCLC are ALK-positive.

Zykadia is the fourth drug with breakthrough therapy designation to receive FDA approval. It is being approved four months ahead of the product's prescription drug user fee goal date of Aug. 24, 2014, the date the agency was scheduled to complete review of the drug application.

The FDA granted Zykadia breakthrough therapy designation, priority review and orphan product designation because the sponsor demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies; the drug had the potential, at the time of the application was submitted, to be a significant improvement in safety or effectiveness in the treatment of a serious condition; and the drug is intended to treat a rare disease, respectively.

The FDA is approving Zykadia under the agency's accelerated approval program, which allows approval of a drug to treat a serious or life-threatening disease based on clinical data showing the drug has an effect on a surrogate endpoint reasonably likely to predict clinical benefit to patients. This program provides earlier patient access to promising new drugs while the company conducts confirmatory clinical trials.

Zykadia's safety and effectiveness were established in a clinical trial of 163 participants with metastatic ALK-positive NSCLC. All participants were treated with Zykadia. Results showed that about half of the participants had their tumors shrink, and this effect lasted an average of about seven months.

Common side effects of Zykadia include gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain. Laboratory abnormalities such as increased liver enzymes, pancreatic enzymes and increased glucose levels were also observed.

Zykadia is marketed by Novartis, based in East Hanover, N.J.

FDA NEWS RELEASE

FDA Provides Facts About Zohydro

[04-30-2014] FDA has prepared this fact sheet to answer the many questions we have received about the drug Zohydro.

About FDA's Approval of Zohydro ER

- Zohydro ER (hydrocodone bitartrate) is a new treatment option for the management of pain severe enough to require daily, around-the-clock, long-term treatment and for which alternative treatments

options are inadequate. This type of debilitating pain negatively impacts patients' ability to live normal daily lives.

- As a single-entity hydrocodone, Zohydro ER can be taken without the threat of severe liver damage, which can occur with hydrocodone combination products that contain acetaminophen.
- The FDA makes its approval decisions based on science and by carefully evaluating the safety and effectiveness of every pain medication. In the case of Zohydro ER, we determined that the benefits of the product outweigh its risks.
- Hydrocodone is a Schedule II opioid analgesic with abuse risk similar to other drugs in its class, the Extended-Release/Long-Acting Opioid Analgesics. It is therefore subject to certain controls including a requirement that patients have a written prescription from their doctor instead of one provided to the pharmacist over the phone (other than in emergency situations, in which case the prescriber must follow up an oral prescription with a written prescription to the dispensing pharmacist within 7 days), and the prohibition of refills.
- Zohydro ER is the first ER/LA opioid analgesic to include the new safety labeling changes now required for all of the drugs in its class. These include a revised indication designed to enable a more careful and thorough approach to determining whether the drug should be prescribed for a particular patient as well as additional, more pointed, warnings regarding the potential for abuse, misuse, and addiction. The new safety labeling changes also include the need for prescribers to assess individual patient risk before prescribing the medication and to monitor and follow up with patients. These labeling changes were required to balance the public health risks associated with abuse and misuse while maintaining access to these important medications for those who are in need of them.
- Zohydro ER is subject to the ER/LA Opioid Analgesic REMS (Risk Evaluation and Management Strategy), which requires that manufacturers make training available to those who prescribe ER/LA opioids and to distribute an updated Medication Guide with each prescription filled.
- As part of the REMS, companies will report periodically on actions taken to implement the REMS, including the number of prescribers trained and other relevant information. If FDA determines that the REMS is not meeting its goals, the Agency will re-evaluate the program.
- Like all other sponsors of ER/LA opioids, Zohydro's sponsor, Zogenix, must conduct post-market studies to assess the risks of misuse, abuse, addiction, overdose, and death associated with long-term use of the product. This information will be used to further inform FDA's benefit-risk assessment of Zohydro ER and other ER/LA Opioids.
- We expect that many of the patients prescribed Zohydro ER will be those who are already prescribed an opioid – either extended-release or immediate-release. So, rather than increase the number of patients treated with opioids, Zohydro ER represents another choice for prescribers. Therefore, we anticipate Zohydro ER will, for the most part, take a slice of the market away from other opioids.
- FDA intends to monitor the utilization of all opioids to identify any emerging abuse issues.

Correcting Misinformation about Zohydro ER

- There have been many misperceptions about the potency of Zohydro ER in the press.
    - Zohydro ER is available in strengths ranging from 10 mg to 50 mg of hydrocodone and designed to be released over a 12-hour period. While this is a larger amount of hydrocodone compared to most immediate-release hydrocodone combination products (strengths ranging from 2.5 mg to 10 mg of hydrocodone), Zohydro ER is in fact less potent than certain strengths of other currently marketed ER/LA opioids such as morphine sulfate, hydromorphone, oxymorphone, and oxycodone.
    - In addition, it is misleading to say that Zohydro ER is stronger than anything currently on the market. While Zohydro ER has a higher available strength compared to immediate-release products with the same active ingredient, Zohydro ER can deliver the same amount of medication per day with fewer doses (e.g., two doses of Zohydro ER compared to 4 to 6 doses for immediate-release products with the same active ingredient).
- There has also been misinformation about the development of opioid analgesics with abuse-deterrent properties. Development of abuse-deterrent technologies is a priority for FDA, and we are strongly

encouraging companies to continue innovating in this area. However, the relevant science is still in its early stages and has not been fully tested in actual market conditions or use.

- Even the abuse-deterrent properties of Oxycontin, which are described in its labeling, are limited. We expect that people intent on abusing these medications will be able to circumvent many of the abuse-deterrent formulations currently on the market or in development. For example, the abuse-deterrent properties of Oxycontin do not prevent addiction; do not prevent oral abuse, which is the most common form of abuse for opioid analgesics; and will not prevent addiction or overdose in people who take too much orally.
- Abuse-deterrent Oxycontin does not meet the medical needs of all people in severe pain. We are encouraging development of other opioids with abuse-deterrent features, and development of Oxycontin with more robust abuse-deterrent properties.

Summary

- Both appropriate pain management and the prevention of prescription opioid abuse are top public health priorities at FDA. Actions to advance one should not impede the other; we must balance our efforts and apply sound science as we move forward.
- FDA shares the concerns about safe and appropriate use of all ER/LA opioid analgesics and the public health consequences associated with misuse and abuse of these drugs. We believe the steps we have taken for Zohydro ER, including revised labeling with a boxed warning about the known serious risks of addiction, abuse, and misuse (among others), a requirement that manufacturers provide prescriber training, and postmarketing study requirements, will help to support its safe and appropriate use.
- Our nation's front-line health professionals – especially physicians and other prescribers – must play a key role and have a responsibility to ensure that they are treating patients based on their individual needs. It is critically important that these health care professionals receive adequate, proper, training and education and that they practice responsible opioid prescribing in order to improve pain management and minimize prescription drug misuse and abuse.
- The complex public health challenge of opioid abuse and misuse requires a comprehensive and science-based approach involving federal and state governments, public health experts, opioid prescribers, addiction experts, patient groups and industry.

FDA NEWS RELEASE

FDA reminds health care professionals to stop dispensing prescription combination drug products with more than 325 mg of acetaminophen

FDA is reminding health care professionals to stop prescribing and pharmacists to stop dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen per tablet, capsule, or other dosage unit. If a pharmacist receives a prescription for a combination product with more than 325 mg of acetaminophen per dosage unit, FDA recommends that they contact the prescriber to discuss a product with a lower dose of acetaminophen. These products are no longer considered safe by FDA and have been voluntarily withdrawn. We encourage pharmacists to return them to the wholesaler or manufacturer.

These products were voluntarily withdrawn by the manufacturers at FDA's request to protect consumers from the risk of severe liver damage, which can result from taking too much acetaminophen.

FDA also asks wholesalers to remove the product codes for all prescription combination drug products containing more than 325 mg of acetaminophen per dosage unit from their ordering systems and return all products to the manufacturers.

Health care professionals who have questions are encouraged to contact the Division of Drug Information at 888.INFO.FDA (888-463-6332) or druginfo@fda.hhs.gov

Safety Announcements

FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain

[04-23-2014] The U.S. Food and Drug Administration (FDA) is warning that injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. We are requiring the addition of a *Warning* to the drug labels of injectable corticosteroids to describe these risks. Patients should discuss the benefits and risks of epidural corticosteroid injections with their health care professionals, along with the benefits and risks associated with other possible treatments.

Injectable corticosteroids are commonly used to reduce swelling or inflammation. Injecting corticosteroids into the epidural space of the spine has been a widespread practice for many decades; however, the effectiveness and safety of the drugs for this use have not been established, and FDA has not approved corticosteroids for such use. We started investigating this safety issue when we became aware of medical professionals' concerns about epidural corticosteroid injections and the risk of serious neurologic adverse events. This concern prompted us to review cases in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature.

To raise awareness of the risks of epidural corticosteroid injections in the medical community, FDA's Safe Use Initiative convened a panel of experts, including pain management experts to help define the techniques for such injections which would reduce preventable harm. The expert panel's recommendations will be released when they are finalized.

As part of FDA's ongoing effort to investigate this issue, we plan to convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

Injectable corticosteroids include methylprednisolone, hydrocortisone, triamcinolone, betamethasone, and dexamethasone. This safety issue is unrelated to the contamination of compounded corticosteroid injection products reported in 2012.

Current Drug Shortages Index (as of May 5, 2014):

The information provided in this section is provided voluntarily by manufacturers.

Amikacin Injection UPDATED 4/24/2013
Ammonium Chloride Injection (initial posting date 3/8/2013)
Amytal Sodium Injection (initial posting date 1/31/2013)
Atropine Sulfate Injection
Barium Sulfate for Suspension (initial posting date 10/12/2012)
Bumetanide Injection (initial posting date 6/21/2012) UPDATED 4/28/2014
Bupivacaine Hydrochloride (Marcaine, Sensorcaine) Injection UPDATED 4/28/2014
Caffeine and Ergotamine Tartrate (Cafergot) Tablets (initial posting date 3/8/2012) UPDATED 4/24/2014
Caffeine Anhydrous (125mg/mL); Sodium Benzoate (125mg/mL) Injection
Calcium Gluconate Injection (initial posting date 1/10/2013) UPDATED 4/24/2014
Cefazolin Injection (initial posting date 3/31/2014) UPDATED 4/28/2014
Chloramphenicol Sodium Succinate Injection (initial posting date 1/7/2014)
Chromic Chloride Injection UPDATED 4/28/2014
Cidofovir Injection (initial posting date 2/15/2013)
Clindamycin phosphate (Cleocin) Injection (initial posting date 10/2/2013) UPDATED 4/24/2014

Copper Injection (initial posting date 4/25/2013)
Cyanocobalamin Injection (initial posting date 1/25/2013) UPDATED 5/5/2014
Daunorubicin Hydrochloride Solution for Injection UPDATED 5/62014
Dexamethasone Sodium Phosphate Injection (initial posting date 1/15/2013) UPDATED 4/24/2014
Dexmethylphenidate Hydrochloride (Focalin) (initial posting date 2/13/2014) UPDATED 5/6/2014
Disopyramide Phosphate (Norpace) CR (initial posting date 4/18/2014)
Dobutamine Hydrochloride Injection (initial posting date 4/26/2013)
Doxorubicin (Adriamycin) Lyophilized Powder (initial posting date 12/2/2011)
Echothiophate Iodide (Phospholine Iodide) Ophthalmic Kit (initial posting date 3/20/2014)
Ephedrine Sulfate Injection (initial posting date 4/3/2014) UPDATED 5/1/2014
Epinephrine Injection (initial posting date 4/27/2012)
Epinephrine 1mg/mL (Preservative Free) (initial posting date 6/21/2012)
Erythrocin Lactobionate Lyophilized Powder for Injection (initial posting date 4/21/2014) UPDATED 4/28/2014
Ethiodol (Ethiodized Oil) Ampules
Fentanyl Citrate (Sublimaze) Injection
Heparin Sodium Injection (initial posting date 7/5/2012) UPDATED 5/5/2014
Intravenous Fat Emulsion
Ketorolac Tromethamine Injection
Leucovorin Calcium Lyophilized Powder for Injection UPDATED 5/6/2014
Leuprolide Acetate Injection
Lidocaine Hydrochloride (Xylocaine) Injection (initial posting date - 2/22/2012) UPDATED 4/28/2014
Liotrix (Thyrolar) Tablets
Lorazepam (Ativan) Injection UPDATED 4/28/2014
Magnesium Sulfate Injection UPDATED 4/28/2014
Mannitol (Osmitrol, Resectisol) Injection (initial posting date - 12/21/2011) UPDATED 4/24/2014
Mecasermin [rDNA origin] (Increlex) Injection (initial posting date - 4/26/2013)
Methazolamide (Glauctabs, Neptazane) Tablets (initial posting date - 6/29/2012) UPDATED 5/6/2014
Methyldopate Hydrochloride Injection
Methylin Chewable Tablets (initial posting date 2/19/2013)
Methylphenidate Hydrochloride ER Tablets (initial posting date 2/19/2013) UPDATED 4/24/2014
Methylphenidate Hydrochloride Tablets (initial posting date 2/19/2013) UPDATED 4/24/2014
Methylprednisolone Sodium Succinate Injection (initial posting date 2/14/2014) UPDATED 5/2/2014
Morphine Sulfate (Astramorph PF, Duramorph, Infumorph) Injection (Preservative Free) UPDATED 4/29/2014
Multi-Vitamin Infusion (Adult and Pediatric)
Nalbuphine Hydrochloride (Nubain) Injection (initial posting date 5/15/2012)
Neostigmine Methylsulfate Injection (initial posting date 1/14/2013)
Nitroglycerin in 5% Dextrose Injection (initial posting date 12/20/2013) UPDATED 4/29/2014
Nitroglycerin (Nitronal) Injection New!! (initial posting date 5/5/2014)
Ondansetron (Zofran) Injection
Pancuronium Bromide Injection
Papaverine Hydrochloride Injection (initial posting date 12/17/2012) UPDATED 5/5/2014
Phosphate (Glycophos) Injection (initial posting date 5/29/2013)
Piperacillin and Tazobactam (Zosyn) Injection (Initial Posting Date - 4/2/2014) UPDATED 5/5/2014
Potassium Acetate Injection, USP 2mEq/mL
Potassium Chloride Injection (initial posting date 5/15/2012)
Potassium Phosphate Injection
Procainamide HCL Injection
Prochlorperazine Injection (initial posting date 1/30/2012)

Reserpine Tablets (initial posting date 4/17/2013)
Rifampin for Injection (initial posting date 3/22/2013)
Secretin Synthetic Human (ChiRhoStim) Injection (ChiRhoStim) (initial posting date 6/15/2012)
Selenium Injection UPDATED 5/5/2014
Sincalide (Kinevac) Lyophilized Powder for Injection (initial posting date 6/21/2013) UPDATED 5/6/2014
Sodium Chloride 0.9% Injection Bags (initial posting date 1/15/2014) UPDATED 4/28/2014
Sodium Chloride 23.4%
Sodium Phosphate Injection
Succinylcholine (Anectine, Quelicin) Injection (initial posting date 8/17/2012)
Sufentanil Citrate (Sufenta) Injection
Telavancin (Vibativ) Injection
Tesamorelin (Egrifta) Injection Kit (initial posting date 3/26/2014)
Thiotepa (Thioplex) for Injection
Tiopronin (Thiola) (initial posting date 10/31/2013)
Tobramycin Solution for Injection
Trace Elements (initial posting date 1/24/2013) UPDATED 5/5/2014
Verapamil Hydrochloride Injection, USP (initial posting date 4/17/2013)
Vitamin A Palmitate (Aquasol A)
Zinc Injection (initial posting date 2/15/2012)