Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
December 14, 2016
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 – December 14, 2016

DATE: December 1, 2016

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 December meeting.
Material is arranged in order of the agenda.

Call to Order

Public Comment Forum

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

Update on Medication Coverage Authorization Unit/Chronic Medication Adherence Program Update– Appendix B

Action Item – Proposed Executive Session as recommended by the Office of Legal Services and Authorized by the Open Meetings Act, 25 O.S. § 307(B)(4) – Discussion of Pending and Potential Litigation/Claims

Action Item – Vote to Prior Authorize Acticlate® (Doxycycline Hyclate) – Appendix C

Action Item – Vote to Prior Authorize Jadenu™ (Deferasirox) and Ferriprox® (Deferiprone) – Appendix D

Action Item – Vote to Prior Authorize Pancreaze® (Pancrelipase), Pertzye® (Pancrelipase), and Viokace® (Pancrelipase) – Appendix E

Action Item – Vote to Prior Authorize BromSite™ (Bromfenac 0.075% Ophthalmic Solution) – Appendix F

Annual Review of Hepatitis C Medications and 30-Day Notice to Prior Authorize Viekira XR™ (Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir) and Epclusa® (Sofosbuvir/Velpatasvir) – Appendix G

30-Day Notice to Prior Authorize Exondys 51™ (Eteplirsen) – Appendix H

Annual Review of Otic Anti-Infective Medications and 30-Day Notice to Prior Authorize Otovel® (Ciprofloxacin/Fluocinolone Acetonide) – Appendix I

Annual Review of Maintenance Asthma & Chronic Obstructive Pulmonary Disease (COPD) Medications & 30-Day Notice to Prior Authorize Cinqair® (Reslizumab) and Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate) – Appendix J

Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Syndros™ (Dronabinol), Sustol® (Granisetron), and Bonjesta® (Doxylamine/Pyridoxine) – Appendix K

ORI-4403 • P.O. BOX 26901 • OKLAHOMA CITY, OKLAHOMA 73126-0901 • (405) 271-9039 • FAX: (405) 271-2615

Annual Review of Phosphate Binders and 30-Day Notice to Prior Authorize Fosrenol® (Lanthanum Carbonate), Velphoro® (Sucroferric Oxyhydroxide), and Auryxia™ (Ferric Citrate) – Appendix L

30-Day Notice to Prior Authorize Defitelio® (Defibrotide Sodium) – Appendix M

Annual Review of Testosterone Products – Appendix N

FDA and DEA Updates – Appendix O

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – December 14, 2016 @ 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. Acknowledgement of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. November 9, 2016 DUR Minutes – Vote
B. November 9, 2016 DUR Recommendations Memorandum
C. Correspondence

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

4. Update on Medication Coverage Authorization Unit/Chronic Medication Adherence Program Update – See Appendix B

A. Medication Coverage Activity for November 2016
B. Pharmacy Help Desk Activity for November 2016
C. Chronic Medication Adherence Program Update

Items to be presented by Joseph Young:

5. Action Item – Proposed Executive Session as Recommended by the Office of Legal Services and Authorized by the Open Meetings Act, 25 O.S. § 307(B)(4) – Discussion of Pending and Potential Litigation/Claims

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

6. Action Item – Vote to Prior Authorize Acticlate® (Doxycycline Hyclate) – See Appendix C

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Jadenu™ (Deferasirox) and Ferriprox® (Deferiprone) – See Appendix D

A. Introduction: Oral Iron Chelating Agents
B. Estimated Cost Savings: Oral Iron Chelating Agents
C. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Pancreaze® (Pancrelipase), Pertzye® (Pancrelipase), and Viokace® (Pancrelipase) – See Appendix E

A. Introduction
B. Pancreatic Enzyme Product Summaries
C. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize BromSite™ (Bromfenac 0.075% Ophthalmic Solution) – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

10. Annual Review of Hepatitis C Medications and 30-Day Notice to Prior Authorize Viekira XR™ (Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir) and Epclusa® (Sofosbuvir/Velpatasvir) – See Appendix G

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Hepatitis C Medications
D. Prior Authorization of Hepatitis C Medications
E. Market News and Updates
F. Regimen Comparison
G. Viekira XR™ (Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir) Product Summary
H. Epclusa® (Sofosbuvir/Velpatasvir) Product Summary
I. College of Pharmacy Recommendations
J. Utilization Details of Hepatitis C Medications

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

11. 30-Day Notice to Prior Authorize Exondys 51™ (Eteplirsen) – See Appendix H

A. Duchenne Muscular Dystrophy
B. Exondys 51™ (Eteplirsen) Product Summary
C. Market News and Updates
D. College of Pharmacy Recommendations

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

12. Annual Review of Otic Anti-Infective Medications and 30-Day Notice to Prior Authorize Otovel® (Ciprofloxacin/Fluocinolone Acetonide) – See Appendix I

A. Current Prior Authorization Criteria
B. Utilization of Otic Anti-Infective Medications
C. Prior Authorization of Otic Anti-Infective Medications
D. Market News and Updates
E. Otovel® (Ciprofloxacin/Fluocinolone Acetonide) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Otic Anti-Infective Medications

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

13. Annual Review of Maintenance Asthma & Chronic Obstructive Pulmonary Disease (COPD) Medications & 30-Day Notice to Prior Authorize Cinqair® (Reslizumab) and Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate) – See Appendix J

A. Current Prior Authorization Criteria
B. Utilization of Maintenance Asthma and COPD Medications
C. Prior Authorization of Maintenance Asthma and COPD Medications
D. Market News and Updates
E. Cinqair® (Reslizumab) Product Summary
F. Bevespi Aerosphere® Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Maintenance Asthma and COPD Medications

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

14. Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Syndros™ (Dronabinol), Sustol® (Granisetron), and Bonjesta® (Doxylamine/Pyridoxine) – See Appendix K

A. Current Prior Authorization Criteria
B. Utilization of Anti-Emetic Medications
C. Prior Authorization of Anti-Emetic Medications

D. Market News and Updates
E. Syndros™ (Dronabinol) Product Summary
F. Sustol® (Granisetron) Product Summary
G. Bonjesta® (Doxylamine/Pyridoxine) Product Summary
H. College of Pharmacy Recommendations
I. Utilization Details of Anti-Emetic Medications

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

15. Annual Review of Phosphate Binders and 30-Day Notice to Prior Authorize Fosrenol® (Lanthanum Carbonate), Velphoro® (Sucroferric Oxyhydroxide), and Auryxia™ (Ferric Citrate) – See Appendix L

A. Introduction
B. Utilization of Phosphate Binders
C. Market News and Updates
D. Phosphate Binders Product Comparison
E. Fosrenol® (Lanthanum Carbonate) Product Summary
F. Velphoro® (Sucroferric Oxyhydroxide) Product Summary
G. Auryxia™ (Ferric Citrate) Product Summary
H. College of Pharmacy Recommendations
I. Utilization Details of Phosphate Binders

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

16. 30-Day Notice to Prior Authorize Defitelio® (Defibrotide Sodium) – See Appendix M

A. Hepatic Veno-Occlusive Disease (VOD) Background Information
B. Defitelio® (Defibrotide Sodium) Product Summary
C. College of Pharmacy Recommendations

Non-presentation; questions only:

17. Annual Review of Testosterone Products – See Appendix N

A. Current Prior Authorization Criteria
B. Utilization of Testosterone Products
C. Prior Authorization of Testosterone Products
D. Market News and Updates
E. College of Pharmacy Recommendations
F. Utilization Details of Testosterone Products

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

18. FDA and DEA Updates – See Appendix O

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

19. Future Business* (Upcoming Product and Class Reviews)
No Meeting Scheduled for January 2017

A. Seizure Medications
B. Botulinum Toxins
C. Kanuma™ (Sebelipase Alfa)
D. Parkinson's Disease Medications
E. Xuriden™ (Uridine Triacetate)
F. Anti-Migraine Medications
G. Hyperkalemia Medications
H. Actinic Keratosis Medications

**Future business subject to change.*

20. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF NOVEMBER 9, 2016

BOARD MEMBERS:	PRESENT	ABSENT
Theresa Garton, M.D.	x	
Carla Hardzog-Britt, M.D.	x	
Anetta Harrell, Pharm.D.	x	
Ashley Huddleston, Pharm.D., BCOP	x	
John Muchmore, M.D., Ph.D.; Chairman	x	
James Osborne, Pharm.D.		x
Paul Louis Preslar, D.O., MBA; Vice Chairman	x	
James Rhymer, D.Ph.	x	
Bruna Varalli-Claypool, MHS, PA-C		x
Eric Winegardner, D.Ph.		x

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Melissa Abbott, Pharm.D.; Clinical Pharmacist	x	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Wendi Chandler, Pharm.D.; Clinical Pharmacist	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison		x
Erin Ford, Pharm.D.; Clinical Pharmacist		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	
Timothy Pham, Ph.D.; Postdoctoral Research Fellow	x	
Leslie Robinson, D.Ph.; PA Coordinator		x
Ashley Teel, Pharm.D.; Clinical Pharmacist		x
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist	x	
Graduate Students: Christina Bulkley, Pharm.D.		x
Corby Thompson, Pharm.D.		x
Visiting Pharmacy Student(s): N/A		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Marlene Asmussen, R.N.; Population Care Management Director	x	
Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm	x	
Kelli Brodersen, Marketing Coordinator		x
Michael Herndon, D.O.; Chief Medical Officer	x	
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO	x	
Jill Ratterman, D.Ph.; Clinical Pharmacist	x	
Garth Splinter, M.D.; M.B.A.; Deputy Chief Executive Officer	x	
Joseph Young, Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Eric Gardner, Vertex Pharma	Joseph Truong, Vertex Pharma	James Brock, US Pharm. Corp
Kristin Pareja, Otsuka	Doug Wood, Viiv Healthcare	Michele Puyear, Gilead
Brent Hildebrand, Gilead	Marc Parker, Sunovion	Jim Dunlap, PhRMA
Sean Seago, Merck	Maren Lehman, Merck	Brian Maves, Pfizer
Jimmy Boland, Sun Pharma	Mark DeClark, Lilly	Dr. Nighat Mehdi, CF Center

PRESENT FOR PUBLIC COMMENT:	
Joseph Truong	Vertex
Michele Puyear	Gilead
Dr. Nighat Mehdi	OU Cystic Fibrosis Center

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**

2A: AGENDA NO. 12 SPEAKER: JOSEPH TRUONG

2B: AGENDA NO. 12 SPEAKER: DR. NIGHAT MEHDI

2C: AGENDA NO. 13 SPEAKER: MICHELE PUYEAR

ACTION: NONE REQUIRED

AGENDA ITEM NO. 3: **ACKNOWLEDGEMENT OF DR. JIM RHYMER FOR SERVICE TO DUR BOARD**

Materials included in agenda packet; presented by Dr. Cothran

ACTION: NONE REQUIRED

AGENDA ITEM NO. 4: **APPROVAL OF DUR BOARD MEETING MINUTES**

4A: OCTOBER 12, 2016 DUR MINUTES

4B: OCTOBER 12, 2016 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Muchmore

Dr. Preslar moved to approve; seconded by Dr. Harrell

ACTION: MOTION CARRIED

AGENDA ITEM NO. 5: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/DRUG UTILIZATION REVIEW OF PRENATAL VITAMINS**

5A: MEDICATION COVERAGE ACTIVITY FOR OCTOBER 2016

5B: PHARMACY HELP DESK ACTIVITY FOR OCTOBER 2016

5C: DRUG UTILIZATION REVIEW OF PRENATAL VITAMINS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 6: **PROPOSED EXECUTIVE SESSION AS RECOMMENDED BY THE OFFICE OF LEGAL SERVICES AND AUTHORIZED BY THE OPEN MEETINGS ACT, 25 O.S. § 307(B)(4) – DISCUSSION OF PENDING AND POTENTIAL LITIGATION/CLAIMS**

Presented by Joseph Young

Dr. Harrell moved to approved; seconded by Dr. Preslar

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: **VOTE TO PRIOR AUTHORIZE ODOMZO® (SONIDEGIB), ERIVEDGE® (VISMODEGIB), KEYTRUDA® (PEMBROLIZUMAB), OPDIVO® (NIVOLUMAB), YERVOY® (IPILIMUMAB), TAFINLAR® (DABRAFENIB), ZELBORAF® (VEMURAFENIB), COTELLIC® (COBIMETINIB), MEKINIST® (TRAMETINIB), AND IMLYGIC® (TALIMOGENE LAHERPAREPVEC)**

7A: INTRODUCTION

7B: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Schmidt and Dr. Borders
Dr. Harrell moved to approve; seconded by Dr. Rhymer
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE RELISTOR® (METHYLNALTREXONE) TABLETS
8A: INTRODUCTION
8B: COST COMPARISON: MEDICATIONS FOR OPIOID INDUCED CONSTIPATION (CHRONIC NON-CANCER PAIN)
8C: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Adams
Dr. Rhymer moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE XELJANZ® XR (TOFACITINIB EXTENDED-RELEASE), TALTZ® (IXEKIZUMAB), INFLECTRA™ (INFLIXIMAB-DYYB), ERELZI™ (ETANERCEPT-SZZS), & AMJEVITA™ (ADALIMUMAB-ATTO)
9A: INTRODUCTION
9B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Hardzog-Britt moved to approve; seconded Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: VOTE TO PRIOR AUTHORIZE SYNERA® (LIDOCAINE/TETRACAINE TOPICAL PATCH)
10A: INTRODUCTION
10B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Harrell moved to approve; seconded Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: VOTE TO PRIOR AUTHORIZE ULTRAVATE® (HALOBETASOL PROPIONATE 0.05% LOTION), SERNIVO™ (BETAMETHASONE DIPROPIONATE 0.05% SPRAY), & FLURANDRENOLIDE 0.05% CREAM AND LOTION
11A: INTRODUCTION
11B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nawaz
Dr. Rhymer moved to approve; seconded Dr. Hardzog-Britt
ACTION: MOTION CARRIED

AGENDA ITEM NO. 12: ANNUAL REVIEW OF ORKAMBI® (LUMACAFTOR/IVACAFTOR) & KALYDECO® (IVACAFTOR)
12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF ORKAMBI® AND KALYDECO®
12C: PRIOR AUTHORIZATION OF ORKAMBI® AND KALYDECO®
12D: MARKET NEWS AND UPDATES
12E: COLLEGE OF PHARMACY RECOMMENDATIONS
12F: UTILIZATION DETAILS OF ORKAMBI® AND KALYDECO®
Materials included in agenda packet; presented by Dr. Nawaz
Dr. Hardzog-Britt moved to approve; seconded Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF HEPATITIS C MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE VIEKIRA XR™ (DASABUVIR/OMBITASVIR/PARITAPREVIR/RITONAVIR) AND EPCLUSA® (SOFOSBUVIR/VELPATASVIR)

13A: INTRODUCTION
13B: CURRENT PRIOR AUTHORIZATION CRITERIA
13C: UTILIZATION OF HEPATITIS C MEDICATIONS
13D: PRIOR AUTHORIZATION OF HEPATITIS C MEDICATIONS
13E: MARKET NEWS AND UPDATES
13F: REGIMEN COMPARISON
13G: VIEKIRA XR™ (DASABUVIR/OMBITASVIR/PARITAPREVIR/RITONAVIR) PRODUCT SUMMARY
13H: EPCLUSA® (SOFOSBUVIR/VELPATASVIR) PRODUCT SUMMARY
13I: COLLEGE OF PHARMACY RECOMMENDATIONS
13J: UTILIZATION DETAILS OF HEPATITIS C MEDICATIONS
Materials included in agenda packet
Agenda No. 13 tabled until December meeting
Dr. Harrell moved to table agenda item No. 13; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 14: 30-DAY NOTICE TO PRIOR AUTHORIZE JADENU™ (DEFERASIROX) AND FERRIPROX® (DEFERIPRONE)
14A: INTRODUCTION
14B: UTILIZATION OF ORAL IRON CHELATING AGENTS
14C: MARKET NEWS AND UPDATES
14D: ORAL IRON CHELATING AGENTS SUMMARY
14E: ESTIMATED COST SAVINGS
14F: COLLEGE OF PHARMACY RECOMMENDATIONS
14G: UTILIZATION DETAILS OF ORAL IRON CHELATING AGENTS
Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: ANNUAL REVIEW OF VARIOUS ANTIBIOTICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ACTICLATE® (DOXYCYCLINE HYCLATE)
15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF VARIOUS ANTIBIOTICS
15C: PRIOR AUTHORIZATION OF VARIOUS ANTIBIOTICS
15D: MARKET NEWS AND UPDATES
15E: COLLEGE OF PHARMACY RECOMMENDATIONS
15F: UTILIZATION DETAILS OF VARIOUS ANTIBIOTICS
Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: ANNUAL REVIEW OF PANCREATIC ENZYME PRODUCTS AND 30-DAY NOTICE TO PRIOR AUTHORIZE PANCREAZE® (PANCRELIPASE), PERTZYE® (PANCRELIPASE), AND VIOKACE® (PANCRELIPASE)
16A: INTRODUCTION
16B: UTILIZATION OF PANCREATIC ENZYME PRODUCTS
16C: MARKET NEWS AND UPDATES
16D: PANCREATIC ENZYME PRODUCT SUMMARIES
16E: ESTIMATED COST SAVINGS
16F: COLLEGE OF PHARMACY RECOMMENDATIONS
16G: UTILIZATION DETAILS OF PANCREATIC ENZYME PRODUCTS
Materials included in agenda packet; presented by Dr. Abbott
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: ANNUAL REVIEW OF OPHTHALMIC NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS) AND 30-DAY NOTICE TO PRIOR AUTHORIZE BROMSITE™ (BROMFENAC 0.075% OPHTHALMIC SOLUTION)

17A: CURRENT PRIOR AUTHORIZATION CRITERIA
17B: UTILIZATION OF OPHTHALMIC NSAIDS
17C: PRIOR AUTHORIZATION OF OPHTHALMIC NSAIDS
17D: MARKET NEWS AND UPDATES
17E: BROMSITE™ (BROMFENAC OPHTHALMIC SOLUTION) PRODUCT SUMMARY
17F: COLLEGE OF PHARMACY RECOMMENDATIONS
17G: UTILIZATION DETAILS OF OPHTHALMIC NSAIDS
Materials included in agenda packet; presented by Dr. Chandler
ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: ANNUAL REVIEW OF KEVEYIS™ (DICHLORPHENAMIDE)
18A: HYPERKALEMIC AND HYPOKALEMIC PERIODIC PARALYSIS BACKGROUND INFORMATION
18B: CURRENT PRIOR AUTHORIZATION CRITERIA
18C: UTILIZATION OF KEVEYIS™ (DICHLORPHENAMIDE)
18D: MARKET NEWS AND UPDATES
18E: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: FDA AND DEA UPDATES
Materials included in agenda packet; presented by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 20: FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)
20A: ASTHMA/COPD MEDICATIONS
20B: DEFITELIO® (DEFIBROTIDE)
20C: EXONDYS 51™ (ETEPLIRSEN)
20D: OTIC ANTI-INFECTIVES
20E: ANTI-EMETIC MEDICATIONS
20F: ELAPRASE® (IDURSULFASE)
20G: PHOSPHATE BINDERS
20H: TESTOSTERONE PRODUCTS
FUTURE BUSINESS SUBJECT TO CHANGE.
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 21: ADJOURNMENT
The meeting was adjourned at 5:22 p.m.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: November 10, 2016

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

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

Subject: DUR Board Recommendations from Meeting of November 9, 2016

Recommendation 1: Drug Utilization Review of Prenatal Vitamins

NO ACTION REQUIRED.

Based on the decline in the percentage of members utilizing prenatal vitamins (PV) compared to the number of deliveries, further educational efforts are warranted. Efforts in the prenatal class appear to have an initial increase with a waning effect over time. The College of Pharmacy recommends incorporating regular prenatal education, based on previous successful interventions, into its work-flow to maintain increased utilization of PV. Opportunities for new interventions will be sought wherever possible.

Recommendation 2: Proposed Executive Session as Recommended by the Office of Legal Services and Authorized by the Open Meetings Act, 25 O.S. § 307(B)(4) – Discussion of Pending and Potential Litigation/Claims

MOTION CARRIED by unanimous approval.

Recommendation 3: Vote to Prior Authorize Odomzo® (Sonidegib), Erivedge® (Vismodegib), Keytruda® (Pembrolizumab), Opdivo® (Nivolumab), Yervoy® (Ipilimumab), Tafinlar® (Dabrafenib), Zelboraf® (Vemurafenib), Cotellic® (Cobimetinib), Mekinist® (Trametinib), and Imlygic® (Talimogene Laherparepvec)

MOTION CARRIED by unanimous approval.

Odomzo® (Sonidegib) Approval Criteria [Basal Cell Carcinoma Diagnosis]:

1. Either of the following criteria must be met for approval:
    a. Diagnosis of locally advanced basal cell carcinoma (BCC) that has either:
        i. Recurred following surgery or radiation therapy; or
        ii. Surgery or radiation is contraindicated; or
    b. Diagnosis of metastatic basal cell carcinoma.

Erivedge® (Vismodegib) Approval Criteria [Basal Cell Carcinoma Diagnosis]:

1. Either of the following criteria must be met for approval:
    a. Diagnosis of locally advanced basal cell carcinoma (BCC) that has either:
        i. Recurred following surgery or radiation therapy; or
        ii. Surgery or radiation is contraindicated; or
    b. Diagnosis of metastatic basal cell carcinoma.

Keytruda® (Pembrolizumab) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. Pembrolizumab must be used as a single-agent; and
    c. Patient meets one of the following:
        i. Pembrolizumab is being used as first-line therapy; or
        ii. Pembrolizumab is being used as second-line therapy or subsequent therapy for disease progression if not previously used and patient has ECOG performance status 0 to 2; and
    d. The patient has not previously failed other PD-1 inhibitors [i.e. Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Hodgkin Lymphoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of relapsed or refractory classical Hodgkin lymphoma; and
        i. Exception: lymphocyte-predominant Hodgkin lymphoma
    b. Pembrolizumab must be used as a single-agent; and
    c. The patient has not previously failed other PD-1 inhibitors [i.e. Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of metastatic NSCLC; and
    b. The patient has not previously failed other PD-1 inhibitors [i.e. Opdivo® (nivolumab)]; and

c. Tumors express PD-L1 (FDA approved test); and
d. Patient meets one of the following:
    i. New diagnosis as first-line therapy (patient has not received chemotherapy to treat disease) if:
        1. Tumor does not express sensitizing EGFR mutations or ALK translocations
        2. ECOG performance status 0 to 1
    ii. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin); or
        1. Patients with EGFR-mutation-positive should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
            A. Examples of drugs for EGFR-mutation-positive tumors: osimertinib, eroltinib, afatinib, or gefitinib
        2. Patients with ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
            A. Examples of drugs for ALK-mutation-positive tumors: crizotinib, ceritinib, or alectinib
        3. ECOG performance status 0 to 2.

Keytruda® (Pembrolizumab) Approval Criteria [Head and Neck Cancer Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of recurrent or metastatic disease; and
    b. Squamous cell histology; and
    c. Patient has received prior platinum containing regimen (cisplatin or carboplatin); and
    d. ECOG performance status 0 to 1; and
    e. Dose does not exceed 200mg every three weeks.

Opdivo® (Nivolumab) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. Nivolumab must be used as a single-agent, or in combination with ipilimumab:
        i. As first-line therapy for untreated melanoma; or
        ii. As second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy:
            1. If the patient has not previously failed other PD-1 inhibitors [i.e. Keytruda® (pembrolizumab)]; and
            2. Patient has ECOG performance status 0 to 2
    c. Dose as follows:
        i. Single-agent: 240mg every two weeks
        ii. In combination with ipilimumab: 1mg/kg, followed by ipilimumab on the same day, every three weeks for four doses, then 240mg every two weeks.

Opdivo® (Nivolumab) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of metastatic NSCLC; and
    b. Tumor histology is one of the following:
        i. Adenocarcinoma; or
        ii. Squamous cell; or
        iii. Large Cell; and
    c. Nivolumab must be used as a single-agent; and
    d. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin); and
    e. ECOG performance status 0 to 2; and
    f. The patient has not previously failed other PD-1 inhibitors [i.e. Keytruda® (pembrolizumab)]; and
    g. Dose as follows:
        i. Single-agent: 240mg every two weeks.

Opdivo® (Nivolumab) Approval Criteria [Small Cell Lung Cancer Diagnosis]:

1. All of the following criteria must be met for approval:
    a. One of the following criteria is met:
        i. Disease relapsed within six months of initial chemotherapy; or
        ii. Disease is progressive on initial chemotherapy; and
    b. Nivolumab must be used as a single-agent or in combination with ipilimumab; and
    c. ECOG performance status 0 to 2
    d. The patient has not previously failed other PD-1 inhibitors [i.e. Keytruda® (pembrolizumab)].

Opdivo® (Nivolumab) Approval Criteria [Hodgkin Lymphoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of relapsed or refractory classical Hodgkin lymphoma; and
        i. Exception: lymphocyte-predominant Hodgkin lymphoma
    b. Nivolumab must be used as a single-agent; and
    c. The patient has not previously failed other PD-1 inhibitors [i.e. Keytruda® (pembrolizumab)].

Opdivo® (Nivolumab) Approval Criteria [Renal Cell Cancer Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of relapsed or surgically unresectable stage IV disease; and
    b. Tumor histology: predominantly clear cell; and
    c. Failed prior therapy with one of the following medications:
        i. Sunitinib; or
        ii. Sorafenib; or
        iii. Pazopanib; or
        iv. Axitinib; and
    d. Nivolumab must be used as a single-agent; and
    e. ECOG performance status 0 to 2; and
    f. The patient has not previously failed other PD-1 inhibitors [i.e. Keytruda® (pembrolizumab)]

g. Dose as follows:
    i. Single-agent: 240mg every two weeks.

Yervoy® (Ipilimumab) Approval Criteria [Unresectable or Metastatic Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. ECOG performance status 0 to 2; and
    b. Ipilimumab is used in combination with nivolumab as:
        i. First-line therapy; or
        ii. Second-line or subsequent therapy for disease progression if nivolumab was not previously used; and
    c. Ipilimumab is used as a single-agent for one of the following:
        i. First-line therapy as a single course of four treatments; or
        ii. Second-line or subsequent lines of therapy as a single course of four treatments; or
        iii. Retreatment, consisting of a 4-dose limit, for an individual who had no significant systemic toxicity during prior ipilimumab therapy, and whose disease progressed after being stable for greater than six months following completion of a prior course of ipilimumab, and for whom no intervening therapy has been administered; and
    d. Maximum dose of 3mg/kg will apply.

Yervoy® (Ipilimumab) Approval Criteria [Adjuvant Treatment of Melanoma]:

1. All of the following criteria must be met for approval:
    a. Patient has complete resection of melanoma with lymphadenectomy; and
    b. Patient has Stage III disease with regional nodes of greater than 1 mm and no in-transit metastasis; and
    c. Ipilimumab must be used as a single-agent; and
    d. Maximum doses of 10mg/kg will apply.

Yervoy® (Ipilimumab) Approval Criteria [Small Cell Lung Cancer Diagnosis]:

1. All of the following criteria must be met for approval:
    a. One of the following criteria is met:
        i. Disease relapsed within six months of initial chemotherapy; or
        ii. Disease is progressive on initial chemotherapy; and
    b. Used in combination with nivolumab; and
    c. ECOG performance status 0 to 2.

Tafinlar® (Dabrafenib) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Not indicated for wild-type BRAF melanoma
    c. Dabrafenib must be used as a single-agent or in combination with trametinib; and
    d. One of the following is met:
        i. Used as first-line therapy; or
        ii. Used as second-line therapy or subsequent therapy and patient has an ECOG performance status of 0 to 2.

Tafinlar® (Dabrafenib) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. All of the following criteria must be met for approval:
    a. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Not indicated for wild-type BRAF NSCLC
    b. Dabrafenib must be used as a single-agent or in combination with trametinib
    c. Diagnosis of refractory or metastatic disease.

Zelboraf® (Vemurafenib) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Not indicated for wild-type BRAF melanoma
    c. Vemurafenib must be used as a single-agent or in combination with cobimetinib; and
    d. One of the following is met:
        i. Used as first-line therapy; or
        ii. Used as second-line therapy or subsequent therapy and patient has an ECOG performance status of 0 to 2.

Zelboraf® (Vemurafenib) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. All of the following criteria must be met for approval:
    a. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Vemurafenib is not indicated for wild-type BRAF NSCLC
    b. Vemurafenib must be used as a single-agent
    c. Diagnosis of refractory or metastatic disease.

Zelboraf® (Vemurafenib) Approval Criteria [Hairy-Cell Leukemia Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Vemurafenib must be used as a single-agent; and
    b. Vemurafenib is being used to treat disease progression following failure of purine analog therapy (i.e. pentostatin, cladribine).

Cotellic® (Cobimetinib) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Cobimetinib is not indicated for wild-type BRAF melanoma
    c. One of the following is met:
        i. Used as first-line therapy in combination with vemurafenib; or
        ii. Used as second-line therapy or subsequent therapy with vemurafenib and patient has an ECOG performance status of 0 to 2.

Mekinist® (Trametinib) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Diagnosis of unresectable or metastatic melanoma; and
    b. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Trametinib is not indicated for wild-type BRAF melanoma.

c. One of the following is met:
    i. Used as first-line therapy in combination with dabrafenib; or
    ii. Used as second-line therapy or subsequent therapy with dabrafenib and patient has an ECOG performance status of 0 to 2; or
    iii. Used as second-line therapy or subsequent therapy as a single-agent if:
        1. Patient was intolerant to prior BRAF inhibitor therapy (dabrafenib, vemurafenib); and
        2. No evidence of disease progression on prior BRAF inhibitor therapy (dabrafenib, vemurafenib); and
        3. ECOG performance status is 0 to 2.

Mekinist® (Trametinib) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. All of the following criteria must be met for approval:
    a. BRAF V600E or V600K mutation detected by an FDA-approved test; and
        i. Trametinib is not indicated for wild-type BRAF NSCLC
    b. Trametinib must be used in combination with dabrafenib.
    c. Diagnosis of refractory or metastatic disease.

Imlygic® (Talimogene Laherparepvec) Approval Criteria [Melanoma Diagnosis]:

1. All of the following criteria must be met for approval:
    a. Patient has unresectable cutaneous, subcutaneous, or nodal lesions that are recurrent after initial surgery; and
        i. Talimogene laherparepvec is not indicated with visceral metastases.
    b. The patient is not immunocompromised or pregnant.

Recommendation 4: Vote to Prior Authorize Relistor® (Methylnaltrexone) Tablets

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Relistor® (methylnaltrexone) tablets with the following criteria:

Relistor® (Methylnaltrexone) Tablets Approval Criteria:

1. An FDA approved diagnosis of opioid-induced constipation (OIC) in members 18 years of age or older with chronic, non-cancer pain who are currently on chronic opioid therapy; and
2. Member must not have known or suspected gastrointestinal obstruction; and
3. Documentation of the underlying cause of chronic pain, or reason why member is on chronic opioid therapy; and
4. Documented and updated colon screening for members greater than 50 years of age; and
5. Documentation of hydration attempts and trials of at least three different types of products that failed to relieve constipation. Trials must be within the past 90 days. Products may be over-the-counter (OTC) or prescription (does not include fiber or stool softeners); and
    a. One of the three trials must be polyethylene glycol 3350 (PEG-3350); and

    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
6. A patient-specific, clinically significant reason why member cannot use Amitiza® (lubiprostone) or Movantik® (naloxegol) must be provided; and
7. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
8. Relistor® must be discontinued if treatment with the opioid pain medication is also discontinued.
9. A quantity limit of 90 tablets for a 30 day supply will apply.

Additionally the College of Pharmacy recommends updating the criteria for Relistor® injection with the changes noted in red:

Relistor® (Methylnaltrexone) Injection Approval Criteria (Chronic Non-Cancer Pain Diagnosis):

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of opioid-induced constipation (OIC) in patients with chronic pain unrelated to cancer; and
3. Documentation of the underlying cause of chronic pain, or reason why member is on chronic opioid therapy; and
4. Member must have current use of opioid medications; and
5. Documented and updated colon screening for members greater than 50 years of age; and
6. Documentation of hydration attempts and trials of at least three different types of products that failed to relieve constipation. Trials must be within the past 90 days. Products may be over-the-counter (OTC) or prescription (does not include fiber or stool softeners); and
    a. One of the three trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
7. Mechanical gastrointestinal obstruction has been ruled out; and
8. A patient-specific, clinically significant reason why member cannot use Amitiza® (lubiprostone) or Movantik® (naloxegol) must be provided; and
9. A patient-specific, clinically significant reason why member cannot use the tablet formulation of Relistor®; and
10. The 12mg single-use vials, syringes, or kits will be the preferred products. Criteria for consideration of 8mg single-use syringes:
    a. Weight range of 38kg to 62kg; and/or
    b. Caregiver unable to draw up dose from vial.
11. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
12. A quantity limit of 30 units per month will apply.

Recommendation 5: Vote to Prior Authorize Xeljanz® XR (Tofacitinib Extended-Release), Taltz® (Ixekizumab), Inflectra™ (Infliximab-dyyb), Erelzi™ (Etanercept-szzs), & Amjevita™ (Adalimumab-atto)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Orencia® ClickJect™ (abatacept autoinjector), Xeljanz® XR (tofacitinib extended-release), Taltz® (ixekizumab), Inflectra™ (infliximab-dyyb), Erelzi™ (etanercept-szzs), and Amjevita™ (adalimumab-atto) to Tier-3 of the Targeted Immunomodulator Agents Product Based Prior Authorization (PBPA) category. Current Tier-3 approval criteria for this category will apply.

- If the net cost of Inflectra™ (infliximab-dyyb), Erelzi™ (etanercept-szzs), and Amjevita™ (adalimumab-atto) is determined to be greater than the net cost of the reference product formulations of Inflectra™, Erelzi™, and Amjevita™ authorization would also require a patient-specific, clinically significant reason why the member could not use the reference product formulations of Inflectra™, Erelzi™, and Amjevita™.
- If the net cost of Xeljanz® XR (tofacitinib extended-release) and Orencia® ClickJect™ (abatacept autoinjector) is determined to be greater than the net cost of the immediate-release formulation or the prefilled syringe formulation authorization would also require a patient-specific, clinically significant reason why the member could not use the immediate-release formulation of Xeljanz® XR or the prefilled syringe formulation of Orencia® ClickJect™.

Additionally, the College of Pharmacy recommends the following criteria for Humira® (adalimumab) for a diagnosis of noninfectious intermediate and posterior uveitis or panuveitis:

Humira® (Adalimumab) for Noninfectious Intermediate and Posterior Uveitis or Panuveitis Approval Criteria:

1. A diagnosis of noninfectious intermediate uveitis, posterior uveitis, or panuveitis in adults; and
2. A failed trial with a corticosteroid injection or systemic corticosteroid in which member has had an inadequate response; or
3. A patient-specific, clinically significant reason a trial of corticosteroid treatment is inappropriate for the member.

Lastly, the College of Pharmacy recommends the following criteria for Ilaris® (canakinumab) for a diagnosis of tumor necrosis factor receptor associated periodic syndrome (TRAPS), hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD), or familial Mediterranean fever (FMF):

Ilaris® (Canakinumab) for Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), or Familial Mediterranean Fever (FMF) Approval Criteria:

1. A diagnosis of tumor necrosis factor receptor associated periodic syndrome (TRAPS) with chronic or recurrent disease activity defined as six flares per year; or
2. A diagnosis of hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); or
3. A diagnosis of familial Mediterranean fever (FMF) with documented active disease despite colchicine therapy or documented intolerance to effective doses of colchicine; and
4. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Targeted Immunomodulator Agents*		
Tier-1 (DMARDs appropriate to disease state)	**Tier-2***	**Tier-3**
6-mercaptopurine	adalimumab (Humira®)	abatacept (Orencia®)
azathioprine	etanercept (Enbrel®)	**adalimumab-atto (Amjevita™)**
hydroxychloroquine		alefacept (Amevive®)
leflunomide		anakinra (Kineret®)
mesalamine		apremilast (Otezla®)
methotrexate		canakinumab (Ilaris®)¥
minocycline		certolizumab pegol (Cimzia®)
NSAIDs		**etanercept-szzs (Erelzi™)**
oral corticosteroids		golimumab (Simponi® & Simponi® Aria™)
		infliximab (Remicade®)
		infliximab-dyyb (Inflectra™)
		ixekizumab (Taltz®)
		rituximab (Rituxan®)
		secukinumab (Cosentyx®)
		tocilizumab (Actemra®)
		tofacitinib (Xeljanz® & **Xeljanz® XR**)
		ustekinumab (Stelara®)
		vedolizumab (Entyvio™)

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. Tier-2 drugs subject to move to Tier-3. Appropriate laboratory monitoring must be verified by the prescriber prior to approval.
DMARDs = Disease modifying antirheumatic drugs; NSAIDs = Nonsteroidal anti-inflammatory drugs
¥Unique criteria applies for a diagnosis of Cryopyrin-Associated Periodic Syndromes (CAPS), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), or Familial Mediterranean Fever (FMF).

Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and
2. A trial of at least one Tier-1 medication in the last 90 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. For a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) authorization of a Tier-2 product requires history of failure of a mesalamine product (does not have to be within the last 90 days) and a trial of one Tier-1 in the last 90 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
4. Prior stabilization on the Tier-2 medication documented within the last 100 days.

Tier-3 Approval Criteria:

1. An FDA approved diagnosis; and
2. Recent trials of one Tier-1 medication and all available Tier-2 medications that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. Prior stabilization on the Tier-3 medication documented within the last 100 days; or
4. A unique FDA-approved indication not covered by Tier-2 products.

Humira® (Adalimumab) for Hidradenitis Suppurativa Approval Criteria:

1. A diagnosis of moderate-to-severe hidradenitis suppurativa (HS); and

2. Hurley Stage II or III disease; and
3. The member must have at least 3 abscesses or inflammatory nodules; and
4. Previous failure of at least two of the following: topical or systemic antibiotics, oral or intralesional corticosteroids, dapsone, cyclosporine, antiandrogens (spironolactone or oral contraceptives), finasteride, or surgery.

Ilaris® (Canakinumab) Approval Criteria [Cryopyrin-Associated Periodic Syndromes (CAPS) Diagnosis]:

1. An FDA approved indication of Cryopyrin-Associated Periodic Syndromes (CAPS) verified by genetic testing. This includes Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 4 years of age and older; and
2. The member must not be using a tumor necrosis factor blocking agent (e.g. adalimumab, etanercept, and infliximab) or anakinra; and
3. Ilaris® should not be initiated in patients with active or chronic infection including hepatitis B, hepatitis C, human immunodeficiency virus, or tuberculosis; and
4. The following dosing requirements must be met:
    a. Dosing should not be more often than once every 8 weeks; and
    b. Dosing (requires recent weight in kilograms):
        i. Body weight greater than 40kg: 150mg
        ii. Body weight 15kg to 40kg: 2mg/kg. If inadequate response, may be increased to 3mg/kg.
5. Approvals will be for the duration of one year.

Recommendation 6: Vote to Prior Authorize Synera® (Lidocaine/Tetracaine Topical Patch)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Synera® (lidocaine/tetracaine topical patch) with the following criteria:

Synera® (Lidocaine/Tetracaine Topical Patch) Approval Criteria:

1. Member must be 3 years of age or older; and
2. Member must have an FDA approved need for local dermal analgesia for superficial venous access or superficial dermatological procedures; and
3. A patient-specific, clinically significant reason why the member cannot use EMLA® (lidocaine/prilocaine) cream, which is available without a prior authorization, must be provided; and
4. The total number of procedures must be provided on the prior authorization request; and
5. A quantity limit of two patches per day will apply.

Recommendation 7: Vote to Prior Authorize Prior Authorize Ultravate® (Halobetasol Propionate 0.05% Lotion), Sernivo™ (Betamethasone Dipropionate 0.05% Spray), & Flurandrenolide 0.05% Cream and Lotion

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes to the Topical Corticosteroid Product Based Prior Authorization (PBPA) category:

1. The placement of Ultravate® (halobetasol 0.05% lotion) into Tier-2 of the ultra-high to high potency category; and
2. The placement of Sernivo™ (betamethasone dipropionate 0.05% topical spray), flurandrenolide 0.05% cream, and flurandrenolide 0.05% lotion into Tier-2 of the medium-high to medium potency category; and
3. Move Beta-Val® (betamethasone valerate 0.1% ointment and lotion) to Tier-1 of the medium-high to medium potency category; and
4. Move hydrocortisone butyrate 0.1% solution and Lidex E® (fluocinonide emollient) cream to Tier-2 of the medium-high to medium potency category; and
5. Move Temovate® (clobetasol propionate 0.05% gel and solution) to Tier-2 of the ultra-high to high potency category; and
6. Move Diprolene® (augmented betamethasone dipropionate gel) to Tier-1 of the ultra-high to high potency category.

Topical Corticosteroids	
Tier-1	**Tier-2**
Ultra-High to High Potency	
augmented betamethasone dipropionate (**Diprolene AF®**) **C**	amcinonide **C, O, L**
augmented betamethasone dipropionate (Diprolene®) G	augmented betamethasone dipropionate (**Diprolene®**) **O, L**
betamethasone dipropionate (**Diprosone®**) **O**	betamethasone dipropionate (**Diprosone®**) **C**
fluocinonide 0.05% **C, O, So**	clobetasol propionate 0.05% (**Clobex®**) **L, Sh, Spr**; (**Olux®**) **F**, (**Olux-E®**) **F**
halobetasol propionate (**Ultravate®**) **C**	clobetasol propionate 0.05% (**Temovate®**) **C, O**
	clobetasol propionate 0.05% (Temovate®) G, So
	desoximetasone 0.25% (**Topicort®**) **C, O, Spr**
	desoximetasone 0.05% (**Topicort®**) **G**
	diflorasone diacetate 0.05% (**Apexicon®**) **C** (**Apexicon E®**) **C, O**
	fluocinonide 0.05% **G**
	fluocinonide 0.1% (**Vanos®**) **C**
	halcinonide (**Halog®**) **C, O**
	halobetasol propionate 0.05% (**Ultravate®**) **O**
	halobetasol propionate 0.05% (Ultravate®) L
	halobetasol propionate/lactic acid (**Ultravate® X**) **C**
Medium-High to Medium Potency	
betamethasone dipropionate (**Betanate®**) **L**	**betamethasone dipropionate 0.05% (Sernivo™) Spr**
betamethasone valerate 0.1% (**Beta-Val®**) **C**	betamethasone dipropionate/calcipotriene (**Taclonex®**) **O, Sus, Spr**
fluticasone propionate (**Cutivate®**) **C, O**	betamethasone valerate 0.12% (**Luxiq®**) **F**
mometasone furoate (**Elocon®**) **C, L**	calcipotriene/betamethasone dipropionate (**Enstilar®**) **F**

Topical Corticosteroids	
Tier-1	**Tier-2**
betamethasone valerate 0.1% (Beta-Val®) O, L	desoximetasone 0.05% (**Topicort LP®**) **C**
	fluocinolone acetonide 0.025% (**Synalar®**) **C, O**
	fluocinonide emollient (Lidex E®) C
	flurandrenolide tape (**Cordran®**)
	flurandrenolide 0.05% C, L
	fluticasone propionate (**Cutivate®**) **L**
	hydrocortisone butyrate 0.1% So
	hydrocortisone butyrate 0.1% **C, O**
	hydrocortisone probutate (**Pandel®**) **C**
	hydrocortisone valerate 0.2% **C, O**
	hydrocortisone valerate (**Westcort®**) **C, O**
	mometasone furoate 0.1% **O**
	prednicarbate (**Dermatop®**) **O, C**
	triamcinolone acetonide (**Kenalog®**) **Spr**
Low potency	
alclometasone dipropionate (**Aclovate®**) **C, O**	clocortolone pivalate (**Cloderm®**) **C**
fluocinolone acetonide 0.01% (**Synalar®**) **C**	desonide 0.05% **C,O**
hydrocortisone acetate 2.5% **C, O, L**	desonide 0.05% (**Desonate®**) **G**
hydrocortisone/urea (**U-Cort®**) **C**	desonide 0.05% (**Verdeso®**) **F, L**
	desonide/emollient (**Desowyn®** kit) **C, O**
	fluocinolone acetonide 0.01% (**Capex®**) **Sh**
	fluocinolone acetonide 0.01% (**Synalar®**) **So,** (**Derma-Smooth®; Derma-Smooth FS®**) **Oil**
	hydrocortisone 2.5% (**Texacort®**) **So**
	hydrocortisone/pramoxine (**Pramosone®**) **C, L**

C= Cream; O = Ointment; L = Lotion; G = Gel; Sh = Shampoo; So = Solution; Spr = Spray;
Sus = Suspension; F = Foam

Recommendation 8: Annual Review of Orkambi® (Lumacaftor/Ivacaftor) & Kalydeco® (Ivacaftor)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends updating the Orkambi® (lumacaftor/ivacaftor) and Kalydeco® (ivacaftor) approval criteria to reflect the new FDA approved age expansions:

Orkambi® (Lumacaftor/Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in patients who are homozygous for the *F508del* mutation in the CFTR gene detected by genetic testing; and
2. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the CFTR gene; and
3. Orkambi® will not be approved for patients with CF other than those homozygous for the *F508del* mutation; and
4. Member must be **6 years of age or older**; and
5. Members using Orkambi® must be supervised by a pulmonary specialist; and

6. The prescriber must verify that ALT, AST, and bilirubin will be assessed prior to initiating Orkambi®, every three months during the first year of treatment, and annually thereafter; and
7. Members must not be taking any of the following medications concomitantly with Orkambi®: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort; and
8. A quantity limit of four tablets per day or 112 tablets per 28 days will apply.
9. Initial approval will be for the duration of three months, after which time compliance will be required for continued approval. After six months of utilization, compliance and information regarding efficacy, such as improvement in FEV_1, will be required for continued approval.

Kalydeco® (Ivacaftor) Approval Criteria:

1. An FDA approved indication of cystic fibrosis (CF) with a *G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N,* or *S549R* mutation in the CFTR gene detected by genetic testing; and
2. Member must be age **2 years of age or older**; and
3. A quantity limit of two tablets per day, or 56 tablets per 28 days will apply.
4. Initial approval will be for six months, after which time compliance and information regarding efficacy, such as improvement in FEV_1, will be required for continued approval.

Recommendation 9: Annual Review of Hepatitis C Medications and 30-Day Notice to Prior Authorize Viekira XR™ (Dasabuvir/Ombitasvir/Paritaprevir/ Ritonavir) and Epclusa® (Sofosbuvir/Velpatasvir)

MOTION TO TABLE CARRIED by unanimous approval.

Recommendation 10: 30-Day Notice to Prior Authorize Jadenu™ (Deferasirox) and Ferriprox® (Deferiprone)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Various Antibiotics and 30-Day Notice to Prior Authorize Acticlate® (Doxycycline Hyclate)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Pancreatic Enzyme Products and 30-Day Notice to Prior Authorize Pancreaze® (Pancrelipase), Pertzye® (Pancrelipase), and Viokace® (Pancrelipase)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Ophthalmic Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and 30-Day Notice to Prior Authorize BromSite™ (Bromfenac 0.075% Ophthalmic Solution)

NO ACTION REQUIRED.

Recommendation 14: Annual Review of Keveyis™ (Dichlorphenamide)

NO ACTION REQUIRED.

November 7, 2016

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

Dear Dr. Holderread and Members of the Drug Utilization Review Board,

On behalf of patients and families with cystic fibrosis (CF), we write to share information following the Food and Drug Administration's (FDA) approval of lumacaftor/ivacaftor (Orkambi®) for all CF patients age 6 years and older who have two copies of the *F508del* mutation in the CF gene. The FDA's label expansion to children age 6 years and older presents an opportunity to preserve health and lung function in these individuals and significantly slow the progression of the disease. Therefore, we are encouraged by the board's recommendation to add Orkambi to the preferred drug list (PDL) per the FDA's approved label expansion.

About Cystic Fibrosis
Cystic fibrosis is caused by a genetic mutation resulting in the malfunction of a protein known as the cystic fibrosis transmembrane conductance regulator (*CFTR*). Decreased *CFTR* function causes irreversible damage and the associated symptoms of cystic fibrosis leading to early death, usually by respiratory failure. As the world's leader in the search for a cure for CF and an organization dedicated to ensuring access to high quality, specialized CF care, the Cystic Fibrosis Foundation accredits 120 care centers, including 2 in Oklahoma, and 55 affiliate programs nationally that provide multidisciplinary, patient-centered care in accordance with systematically reviewed, data-driven clinical practice guidelines. Treatment options for this rare, life-threatening disease are extremely limited.

About Orkambi (lumcaftor/ivacaftor)
Orkambi is the only FDA-approved medication that improves the function of *CFTR* for individuals with the *F508del* mutation. Restricted access to this life-saving therapy could result in severe and avoidable health consequences for CF patients. People with cystic fibrosis have a fundamental medical need for increased *CFTR* protein function. Symptomatic therapies such as inhaled antibiotics and mucolytics are intended to combat bacterial infections and aid in clearing mucus, but they do not increase *CFTR* protein function and therefore do not address the underlying cause of cystic fibrosis. Even when these other therapies are partially successful in clearing mucus from the airways, CF patients still require timely access to an appropriate *CFTR* modulator.

CYSTIC FIBROSIS FOUNDATION NATIONAL OFFICE | 6931 ARLINGTON ROAD BETHESDA, MD 20814 | TEL. 800 FIGHT CF FAX 301.951.6378 | WEB WWW.CFF.ORG

The fixed dose combination therapy of lumacaftor and ivacaftor has been shown to improve airway surface liquid properties, reduce airway obstruction, and improve deficiencies in non-respiratory organ systems. Evidence show significant improvements in lung function (FEV_1) as well as trends indicating a reduced rate of pulmonary exacerbations, increased body mass index (BMI), and improvement in patient-reported respiratory outcomes (CFQ-R). Furthermore, a post-approval study of cystic fibrosis patients treated with Orkambi showed a reduced rate of decline in lung function compared to controls.[1]

The FDA approved expanded label extends these benefits to people with CF ages 6 and older with two copies of the *F508del* mutation. Initiation of Orkambi at an early age provides the greatest potential for an enduring health benefit and extended quality of life because evidence of the beginnings of CF-related damage to the lungs have been observed in CF children studied within the first year of their lives, including air trapping, bronchial wall thickening, obstruction, and bronchiectasis.[2-5] By preserving lung function in children with FDA-indicated CFTR mutations, this modulating therapy can mitigate disease progression and may keep young people from experiencing costly hospitalizations, declining health status, and deteriorating quality of life and premature death. It is not medically reasonable or responsible to withhold an effective treatment until the patient suffers a permanent and irreversible decline in health and loss of lung function.

The totality of efficacy evidence is indicative of overall lumacaftor/ivacaftor-associated benefits. We support the recommendation to make lumacaftor/ivacaftor available to all patients age 6 and older with two copies of the *F508del* mutation when the patient's treating physician determines it is medically necessary and appropriate to begin the therapy.

Sincerely,

Bruce C. Marshall, MD
Senior Vice President of Clinical Affairs

Lisa Feng, MPH
Senior Director, Access Policy & Innovation

CYSTIC FIBROSIS FOUNDATION NATIONAL OFFICE
6931 ARLINGTON ROAD BETHESDA, MD 20814
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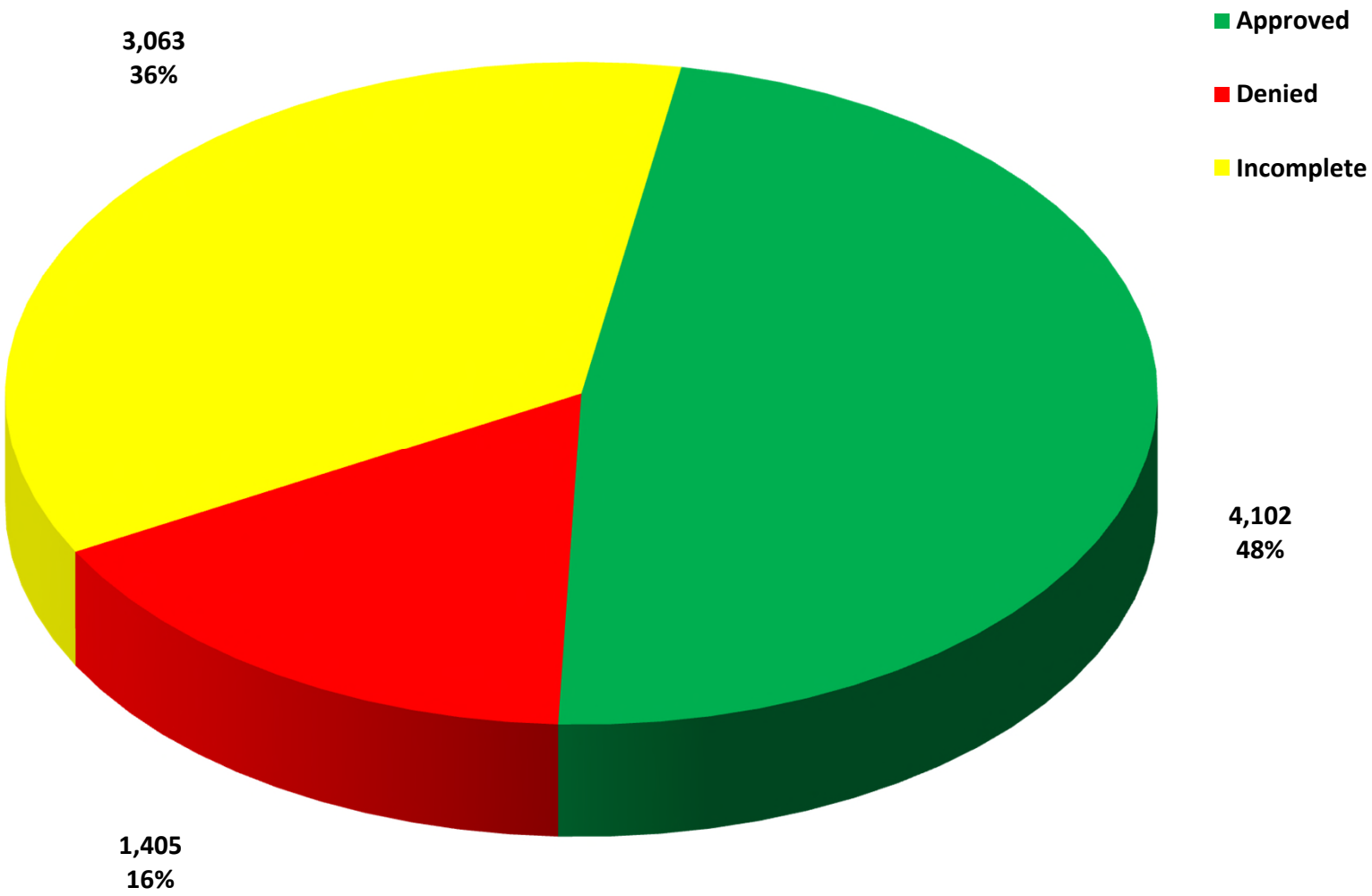
WEB WWW.CFF.ORG

References:

1. Konstan, et al. Evidence for reduced rate of lung function decline and sustained benefit with combination lumacaftor and ivacaftor therapy in patients ≥ 12 years of age with cystic fibrosis homozygous for the F508del-CFTR mutation. Poster session presented at: 8th European Conference on Rare Diseases and Orphan Products; 2016 May 26-28; Edinburgh, Scotland.
2. Kraemer, Richard, Peter Birrer, and Sabina Liechti-Gallati. "Genotype-phenotype association in infants with cystic fibrosis at the time of diagnosis." *Pediatric research* 44.6 (1998): 920-926.
3. Kraemer R, Aebi C, Casaulta Aebischer C, Gallati S, Early Detection of Lung Disease and Its Association with the Nutritional Status, Genetic Background and Life Events in Patients with Cystic Fibrosis. Respiration 2000;67:477-490.
4. Sly PD, Brennan S, Gangell C, de Klerk N, Murray C, Mott L, et al. Lung disease at diagnosis in infants with cystic fibrosis detected by newborn screening. *Am J Respir Crit Care Med.* 2009;180(2):146-52.
5. Hall GL, Logie KM, Parsons F, Schulzke SM, Nolan G, Murray C, et al. (2011) Air Trapping on Chest CT Is Associated with Worse Ventilation Distribution in Infants with Cystic Fibrosis Diagnosed following Newborn Screening. PLoS ONE 6(8): e23932. doi:10.1371/journal.pone.0023932.

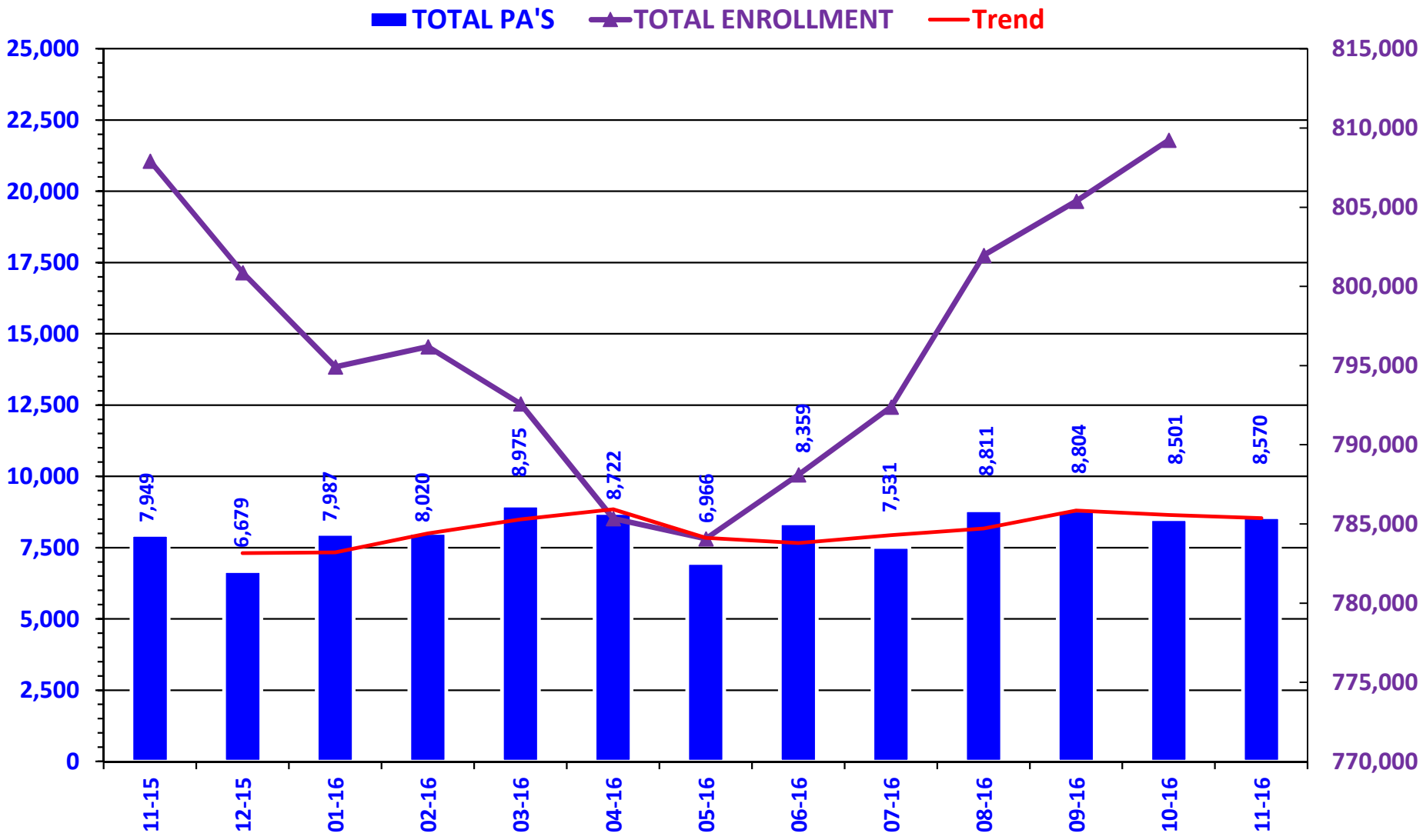
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: NOVEMBER 2016



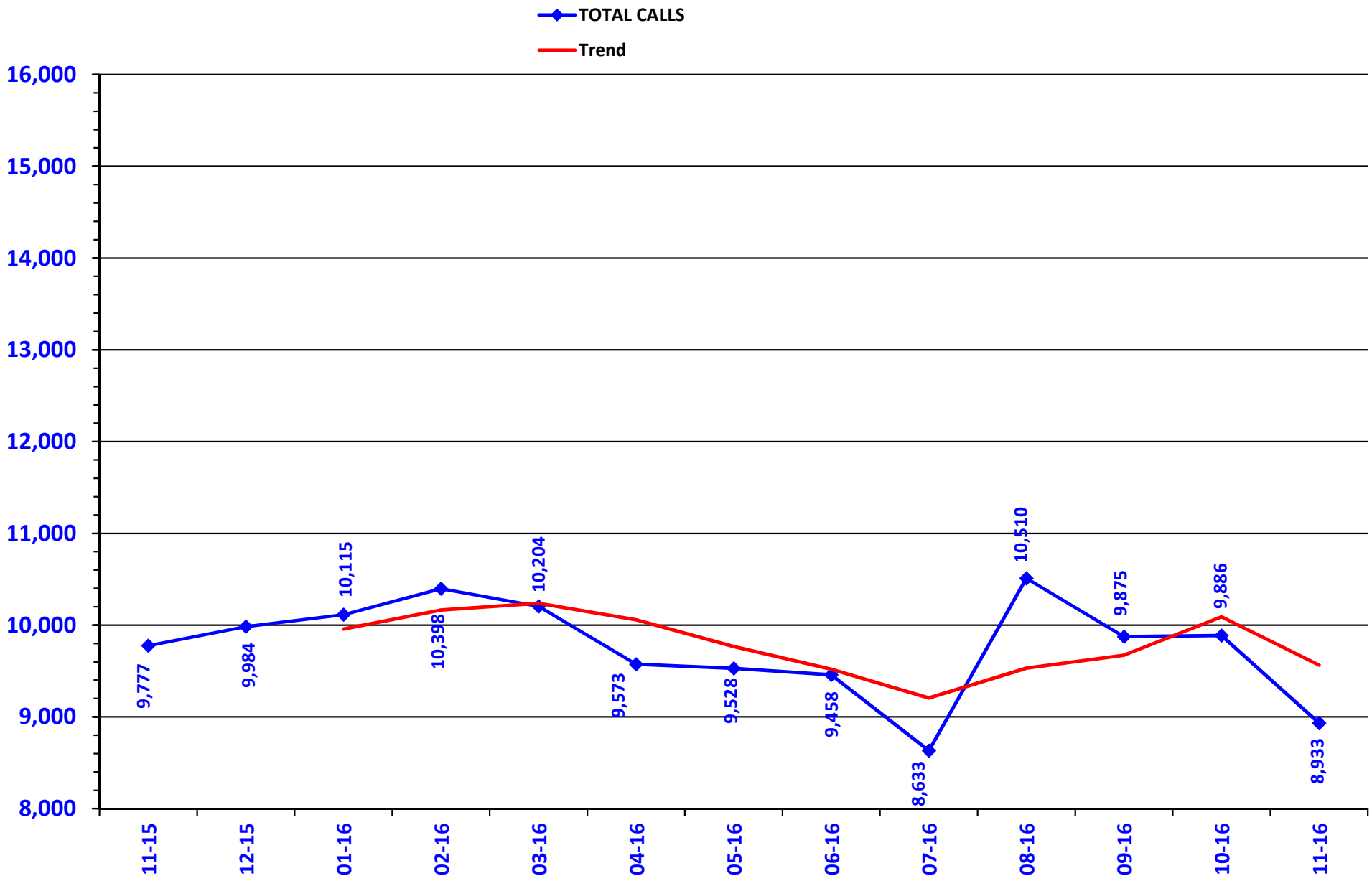
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: NOVEMBER 2015 – NOVEMBER 2016



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
NOVEMBER 2015 – NOVEMBER 2016



Prior Authorization Activity

11/1/2016 Through 11/30/2016

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	430	146	90	194	352
Analgesic - NonNarcotic	20	0	5	15	0
Analgesic, Narcotic	522	298	54	170	160
Angiotensin Receptor Antagonist	10	3	2	5	355
Antiasthma	97	19	25	53	351
Antibiotic	13	2	1	10	185
Anticonvulsant	109	46	13	50	344
Antidepressant	83	20	11	52	328
Antidiabetic	230	83	38	109	345
Antifungal	10	1	1	8	3
Antihistamine	163	124	7	32	343
Antimigraine	32	7	8	17	210
Antineoplastic	19	12	0	7	152
Antiulcers	142	24	49	69	222
Antiviral	68	38	19	11	9
Anxiolytic	61	46	7	8	244
Atypical Antipsychotics	370	219	27	124	334
Biologics	94	47	10	37	305
Bladder Control	63	17	15	31	338
Blood Thinners	228	129	23	76	304
Botox	45	36	8	1	341
Buprenorphine Medications	254	200	14	40	72
Cardiovascular	88	37	13	38	339
Chronic Obstructive Pulmonary Disease	94	10	28	56	352
Constipation/Diarrhea Medications	112	22	37	53	195
Contraceptive	24	17	2	5	317
Dermatological	82	16	44	22	104
Diabetic Supplies	510	294	28	188	211
Endocrine & Metabolic Drugs	81	59	0	22	130
Erythropoietin Stimulating Agents	26	17	2	7	100
Fibromyalgia	208	32	103	73	325
Fish Oils	11	3	3	5	359
Gastrointestinal Agents	132	25	33	74	88
Genitourinary Agents	15	3	8	4	244
Glaucoma	12	0	4	8	0
Growth Hormones	83	61	11	11	146
Hepatitis C	79	41	21	17	9
HFA Rescue Inhalers	103	19	21	63	322
Insomnia	25	3	7	15	145
Insulin	81	19	18	44	341
Miscellaneous Antibiotics	18	1	3	14	23
Multiple Sclerosis	54	20	14	20	202
Muscle Relaxant	53	3	20	30	21
Nasal Allergy	75	11	15	49	208
Neurological Agents	73	54	4	15	339
NSAIDs	215	32	65	118	301
Ocular Allergy	30	0	11	19	0
Ophthalmic Anti-infectives	14	1	5	8	23
Osteoporosis	16	6	5	5	358
Other*	261	46	70	145	212
Otic Antibiotic	22	7	2	13	8
Pediculicide	36	16	4	16	10
Respiratory Agents	31	20	0	11	139

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Statins	43	9	14	20	327
Stimulant	854	427	101	326	340
Synagis	280	121	90	69	137
Testosterone	56	12	27	17	341
Topical Antifungal	44	4	10	30	12
Topical Corticosteroids	111	4	37	70	273
Vitamin	64	18	23	23	341
Pharmacotherapy	43	40	0	3	280
Emergency PAs	0	0	0	0	
Total	**7,222**	**3,047**	**1,330**	**2,845**	

Overrides					
Brand	45	26	12	7	301
Dosage Change	366	341	1	24	10
High Dose	5	4	0	1	274
Ingredient Duplication	34	26	0	8	10
Lost/Broken Rx	102	96	1	5	13
NDC vs Age	95	71	3	21	230
Nursing Home Issue	55	40	3	12	10
Opioid Quantity	15	13	0	2	145
Other*	31	28	1	2	14
Quantity vs. Days Supply	553	377	49	127	260
STBS/STBSM	15	14	0	1	50
Stolen	15	13	1	1	8
Temporary Unlock	1	1	0	0	2
Third Brand Request	30	17	4	9	20
Wrong D.S. on Previous Rx	1	1	0	0	11
Overrides Total	**1,348**	**1,055**	**75**	**218**	
Total Regular PAs + Overrides	**8,570**	**4,102**	**1,405**	**3,063**	

Denial Reasons	
Unable to verify required trials.	2,401
Does not meet established criteria.	1,429
Lack required information to process request.	622

Other PA Activity	
Duplicate Requests	600
Letters	8,650
No Process	6
Changes to existing PAs	594
Helpdesk Initiated Prior Authorizations	693
PAs Missing Information	32

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

Chronic Medication Adherence Program Update

Oklahoma Health Care Authority
December 2016

Prescriber Mailing: Maintenance Diabetes and Cardiovascular Medications

The Chronic Medication Adherence (CMA) educational mailing is processed quarterly and sent to prescribers with members on chronic maintenance medications for diabetes, blood pressure, or cholesterol. The purpose of these mailings is to encourage medication adherence and improve the quality of care for SoonerCare members on these medications.

Previously, prescribers were selected randomly to receive letters if they met the inclusion criteria for the mailing module. In February 2016, the CMA mailing changed to sending the educational letters to the same consistent prescribers. Included prescribers will receive four letters per year that alternate between diabetes and cardiovascular medications, to better inform them of their SoonerCare patients using maintenance medications and to make their patients' adherence more convenient to track over time including any improvements or changes. Inclusion criteria requires the prescriber to have two or more SoonerCare patients taking diabetes, blood pressure, and cholesterol medications. A total of 231 prescribers were selected for inclusion in the consistent mailings. The review period for each mailing is one year and patients are assigned to prescribers if they are the last prescriber of record for a maintenance medication on paid pharmacy claims.

Each mailing includes a prescriber summary report with a "star rating" based on their overall percentage of patients considered adherent to chronic maintenance medications. Adherence is estimated by measuring the Proportion of Days Covered (PDC), or percent of days in the past year covered by prescription claims. A patient is considered adherent if their PDC is greater than or equal to 80%. A patient is considered non-adherent if their PDC is less than 80%. A higher percentage (and corresponding star rating) is better and indicates that more of their patients are adherent to their maintenance medications. Each mailing also includes a list of medication adherence patient resources intended to offer prescribers methods to improve their patients' adherence.

Cardiovascular Mailing Summary

- Addresses adherence to maintenance renin angiotensin system (RAS) antagonists [e.g., angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors] and HMG-CoA reductase inhibitors (i.e., statins).

Date Letter Processed	Total Letters Mailed	Total Members Included
February 2015	345	6,672
August 2015	259	4,497
February 2016	231	3,835
August 2016	221	4,588

Adherence is shown in the Provider Summary Report as a percentage for RAS antagonists and as a percentage for statins, with a corresponding star rating for each category. The star ratings for the percentage of patients that are adherent to RAS antagonists or statins are based on the 2016 Medicare Star Ratings. However, a rating of zero stars is exclusive to SoonerCare. A key is shown below to illustrate the star ratings and adherence percentages for each star rating.

RAS antagonists:

5 Stars: Excellent (≥ 85%)

4 Stars: Above Average (≥ 82% to < 85%)

3 Stars: Average (≥ 78% to < 82%)

2 Stars: Below Average (≥ 76% to < 78%)

1 Star: Poor (≥ 60% to < 76%)

0 Stars: Very Poor (< 60%)

Statins:

5 Stars: Excellent (≥ 83%)

4 Stars: Above Average (≥ 78% to < 83%)

3 Stars: Average (≥ 73% to < 78%)

2 Stars: Below Average (≥ 68% to < 73%)

1 Star: Poor (≥ 60% to < 68%)

0 Stars: Very Poor (< 60%)

Diabetes Mailing Summary

- Addresses adherence to maintenance medications for diabetes excluding insulin and Symlin® (pramlintide).

Date Letter Processed	Total Letters Mailed	Total Members Included
November 2014	457	2,894
May 2015	177	975
November 2015	378	2,288
May 2016	224	2,127

Adherence is shown in the Provider Summary Report as a percentage and corresponding star rating for all diabetes medications (excluding insulin and Symlin®). The star ratings for the percentage of patients that are adherent to diabetes medications are based on the 2016 Medicare Star Ratings. However, a rating of zero stars is exclusive to SoonerCare. A key is shown below to illustrate the star ratings and adherence percentages for each star rating.

5 Stars: Excellent (≥ 95%)

4 Stars: Above Average (≥ 83% to < 95%)

3 Stars: Average (≥ 80% to < 83%)

2 Stars: Below Average (≥ 75% to < 80%)

1 Star: Poor (≥ 60% to < 75%)

0 Stars: Very Poor (< 60%)

Example Star Rating[1]

Report date: <Report Date>
NPI: <Prescriber NPI>

Provider: <Provider Name>
SoonerCare Provider ID: <Provider ID>

Percentage of patients adherent to RAS antagonists: 66.67%

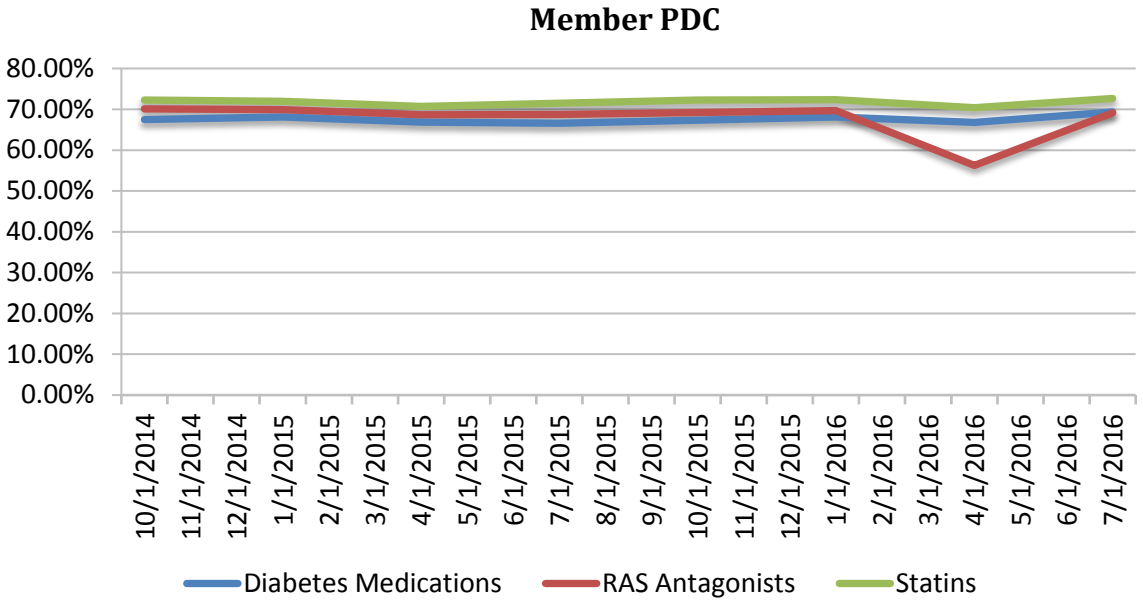
1 out of 5 stars

Percentage of patients adherent to statins: 60.00%

1 out of 5 stars

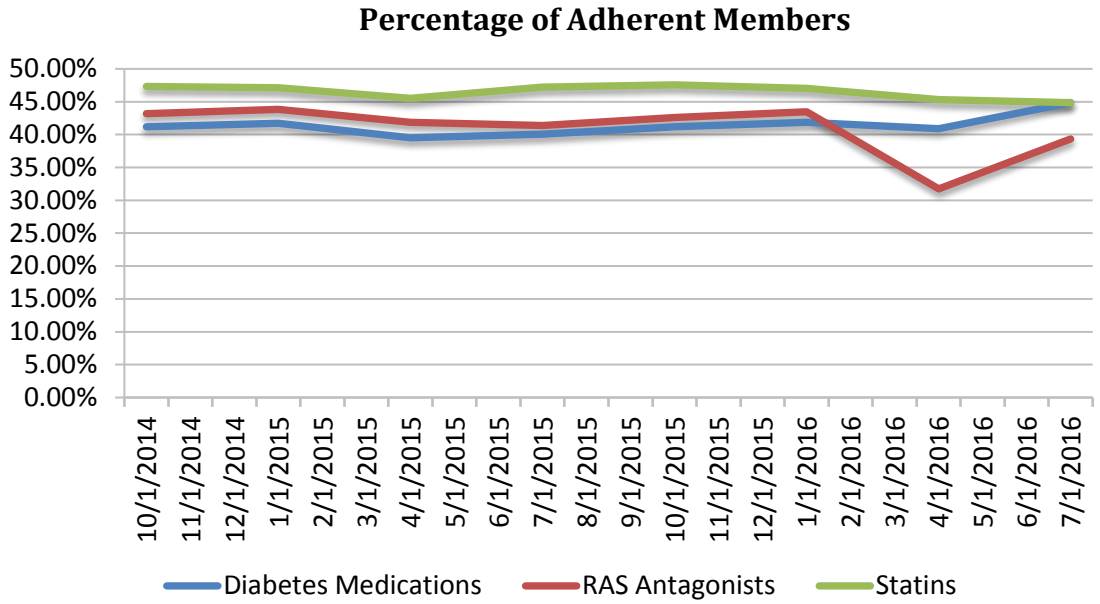
Chronic Medication Adherence Trends by Drug Category

The average member PDC and the percent of adherent members is tracked for all drug categories each time a mailing is processed. The average member PDC based on drug category is tracked in the following line graph. The line graph below depicts the PDC for all SoonerCare members utilizing the targeted maintenance medications and does not differentiate those members who were included in a mailing.



The following line graph shows trends in the percentage of adherent members for each drug category since the CMA initiative commenced. The line graph depicts the percentage of adherent members for all SoonerCare members utilizing the targeted maintenance medications and does not differentiate those members who were included in a mailing. Once several mailings have been processed under the new format with consistent prescribers, the College of

Pharmacy will reevaluate prescriber percentages of adherent members by just those included in the mailings.



Both graphs show similar trends with a recent decline in adherence in April followed by an increase towards baseline. While the decline in April 2016 is significant, a similar, less pronounced decline can be noted in April 2015; these trends may be a result of yearly fluctuation. The College of Pharmacy will continue to monitor member adherence with the goal of achieving a member PDC of 80% or greater and a five star rating of prescriber percentage of adherent members. Once several mailings have been processed under the new format with consistent prescribers, the College of Pharmacy will reevaluate prescriber percentages of adherent members by just those included in the mailings. Results of the new format will be reported to the Drug Utilization Review (DUR) Board.

[1] Centers for Medicare & Medicaid Services: Medicare 2016 Part C & D Star Rating Technical Notes. Available online at: https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovgenin/performancedata.html. Last updated 04/05/2016. Last accessed 11/15/2016.

Appendix C

Vote to Prior Authorize Acticlate® (Doxycycline Hyclate)

Oklahoma Health Care Authority
December 2016

Introduction[1,2]

- **Acticlate® (doxycycline hyclate) 75mg capsules** were approved by the U.S. Food and Drug Administration (FDA) in April 2016 for various indications, including for the treatment of Rickettsial infections; sexually transmitted infections; respiratory tract infections; specific bacterial infections; ophthalmic infections; anthrax, including inhalational anthrax (post-exposure); as an alternative treatment for select infections when penicillin is contraindicated; as an adjunctive treatment for acute intestinal amebiasis and severe acne; and for the prophylaxis of malaria. Acticlate® 75mg and 150mg tablets were FDA approved in 2014.
- Acticlate® capsules are not currently available on the market; therefore, cost information is not yet available. Generic doxycycline hyclate 20mg, 50mg, and 100mg capsules and tablets are available without prior authorization.

Recommendations

The College of Pharmacy recommends the prior authorization of Acticlate® (doxycycline hyclate) 75mg capsules with the following criteria:

Oral Antibiotic Special Formulation Approval Criteria:

1. Member must have a patient-specific, clinically significant reason why the immediate release formulation and/or other cost effective therapeutic equivalent medication(s) cannot be used.

[1] FDA NDA Approval: Acticlate® (Doxycycline Hyclate) Capsules. Available online at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails. Issued 04/26/2016. Last accessed 11/22/2016.
[2] Acticlate® Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/acticlate/. Last revised 05/19/2016. Last accessed 11/22/2016.

Appendix D

Vote to Prior Authorize Jadenu™ (Deferasirox) and Ferriprox® (Deferiprone)

Oklahoma Health Care Authority
December 2016

Introduction: Oral Iron Chelating Agents[1,2,3,4,5]

- **Exjade® (deferasirox) tablets for oral suspension** are indicated for the treatment of transfusion-induced iron overload in ages 2 years and older, and for the treatment of non-transfusion-dependent thalassemia (NTDT) syndromes in ages 10 years and older. Exjade® has a boxed warning for renal failure, hepatic failure, and gastrointestinal hemorrhage. Exjade® tablets must be dispersed in water, orange juice, or apple juice to obtain a suspension prior to taking.
- **Ferriprox® (deferiprone) oral tablets and oral solution** are indicated for the treatment of transfusion-induced iron overload due to thalassemia syndromes when current chelation therapy is inadequate in adult patients. Ferriprox® has a boxed warning for agranulocytosis and neutropenia.
- **Jadenu™ (deferasirox) oral tablets** are indicated for the treatment of transfusion-induced iron overload in ages 2 years and older, and for the treatment of non-transfusion-dependent thalassemia (NTDT) syndromes in ages 10 years and older. Jadenu™ has a boxed warning for renal failure, hepatic failure, and gastrointestinal hemorrhage. There are no clinical data in patients taking Jadenu™; U.S. Food and Drug Administration (FDA) approval of Jadenu™ was based on Exjade® clinical trials, as they contain the same active ingredient.

Estimated Cost Savings: Oral Iron Chelating Agents

Exjade® was FDA approved in 2005 and has significant federal rebates, making it much more cost efficient than Jadenu™ or Ferriprox®. The estimated annual cost savings, based on SoonerCare fiscal year 2016 utilization data and the average net cost per claim for Exjade® after taking into account federal rebates, if members using Jadenu™ or Ferriprox® switched to Exjade®, would be approximately $712,922.49.

Recommendations

Based on the low net cost of Exjade® (deferasirox) and significant cost savings if members using Jadenu™ (deferasirox) or Ferriprox® (deferiprone) switched to Exjade® (deferasirox), the College of Pharmacy recommends the prior authorization of Jadenu™ (deferasirox) and Ferriprox® (deferiprone) with the following criteria:

Jadenu™ (Deferasirox) and Ferriprox® (Deferiprone) Approval Criteria:

1. An FDA approved diagnosis; and
2. A patient-specific, clinically significant reason other than convenience why the member cannot use Exjade® (deferasirox) must be provided; and
3. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

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[1] Exjade® Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/exjade-1/. Last revised 08/12/2016. Last accessed 11/22/2016.
[2] Ferriprox® Tablets Prescribing Information. ApoPharma USA, Inc. Available online at: http://www.ferriprox.com/us/pdf/ferriprox_full_pi.pdf. Last revised 02/2015. Last accessed 11/22/2016.
[3] Ferriprox® Solution Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/ferriprox/. Last revised 09/30/2015. Last accessed 11/22/2016.
[4] Jadenu™ Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/jadenu/. Last revised 08/12/2016. Last accessed 11/22/2016.
[5] Micromedex 2.0: Drug Comparison (Deferiprone and Deferasirox). Available online at: http://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.ShowDrugCompareResults. Last revised 11/17/2016. Last accessed 11/22/2016.

Appendix E

Vote to Prior Authorize Pancreaze® (Pancrelipase), Pertzye® (Pancrelipase), and Viokace® (Pancrelipase)

Oklahoma Health Care Authority
December 2016

Introduction[1,2,3]

Exocrine pancreatic insufficiency (EPI) is a condition associated with diseases affecting the pancreas, such as chronic pancreatitis and cystic fibrosis (CF). The leading cause of EPI is chronic pancreatitis. The most common cause of EPI in children is CF. Malnutrition, steatorrhea, and weight loss may develop in patients with EPI. The main treatment for EPI is pancreatic enzyme replacement therapy (PERT). Pancreatic enzyme products (PEPs) are extracts of porcine pancreas and contain a combination of lipase, protease, and amylase. There are currently five U.S. Food and Drug Administration (FDA)-approved PEPs available. These products are not interchangeable.

Creon® and Zenpep® were FDA approved in 2009 and have significant federal and supplemental rebates, making them more cost efficient than Pancreaze®, Pertzye®, or Viokace®. The estimated annual cost savings would be approximately $160,000 if members using Pancreaze®, Pertzye®, or Viokace® switched to Creon® or Zenpep®, based on SoonerCare fiscal year 2016 utilization data and the average cost per unit for Creon® and Zenpep® after taking into account federal and supplemental rebates.

Pancreatic Enzyme Product Summaries[3,4,5,6,7,8]

Comparison of Pancreatic Enzyme Products

Brand Name	Initial FDA Approval	FDA Approved Indications	Available Strengths (units of lipase/protease/amylase)
Creon®	2009	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis, pancreatectomy, or other conditions	Delayed-release capsules: 3,000/9,500/15,000 6,000/19,000/30,000 12,000/38,000/60,000 24,000/76,000/120,000 36,000/114,000/180,000
Zenpep®	2009	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsules: 3,000/10,000/16,000 5,000/17,000/27,000 10,000/34,000/55,000 15,000/51,000/82,000 20,000/68,000/109,000 25,000/85,000/136,000 40,000/136,000/218,000

Brand Name	Initial FDA Approval	FDA Approved Indications	Available Strengths (units of lipase/protease/amylase)
Pancreaze®	2010	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsules: 2,600/6,200/10,850 4,200/14,200/24,600 10,500/35,500/61,500 16,800/56,800/98,400 21,000/54,700/83,900
Pertzye®	2012	Treatment of exocrine pancreatic insufficiency due to cystic fibrosis or other conditions	Delayed-release capsules: 4,000/14,375/15,125 8,000/28,750/30,250 16,000/57,500/60,500
Viokace®	2012	Treatment of exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatectomy, in combination with a proton pump inhibitor	Immediate-release tablets: 10,440/39,150/39,150 20,880/78,300/78,300

Recommendations

The College of Pharmacy recommends the prior authorization of Pancreaze®, Pertzye®, and Viokace® with the following criteria:

Pancreaze®, Pertzye®, and Viokace® Approval Criteria:

1. An FDA approved diagnosis of pancreatic insufficiency; and
2. Documented trials of inadequate response to Creon® and Zenpep® or a patient-specific, clinically significant reason why the member cannot use Creon® or Zenpep®.

Based on the lower net cost of Creon® and Zenpep®, the College of Pharmacy does not recommend the prior authorization of Creon® or Zenpep® at this time.

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[1] Nakajima K, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. *Core Evidence*. 2012;7:77-91. doi:10.2147/CE.S26705.

[2] Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clinical and Experimental Gastroenterology*. 2011;4:55-73. doi:10.2147/CEG.S17634.

[3] PL Detail-Document, Comparison of Pancreatic Enzyme Products. *Pharmacist's Letter/Prescriber's Letter*. January 2013.

[4] Creon® Package Insert. AbbVie, Inc. Available online at: http://www.rxabbvie.com/pdf/creon_PI.pdf. Last revised 03/2015. Last accessed 09/28/2016.

[5] Zenpep® Package Insert. Aptalis Pharma US, Inc. Available online at: http://www.allergan.com/assets/pdf/zenpep_pi. Last revised 03/2014. Last accessed 09/28/2016.

[6] Pancreaze® Package Insert. Janssen Pharmaceuticals, Inc. Available online at: http://www.pancreaze.net/PDF/PANCREAZE.pdf. Last revised 06/2016. Last accessed 12/02/2016.

[7] Pertzye® Package Insert. Digestive Care, Inc. Available online at: http://chiesiusa.com/wp-content/uploads/PERTZYE_PI.pdf. Last revised 10/2016. Last accessed 10/18/2016.

[8] Viokace® Package Insert. Aptalis Pharma US, Inc. Available online at: http://www.allergan.com/assets/pdf/viokace_pi. Last revised 03/2012. Last accessed 09/28/2016.

Appendix F

Vote to Prior Authorize BromSite™ (Bromfenac 0.075% Ophthalmic Solution)

Oklahoma Health Care Authority
December 2016

Introduction[1]

BromSite™ (bromfenac 0.075% ophthalmic solution) is indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery. Bromfenac is a nonsteroidal anti-inflammatory drug (NSAID) that has anti-inflammatory activity. The mechanism of action is thought to be due to its ability to block prostaglandin synthesis by inhibiting cyclooxygenase 1 and 2. Prostaglandins have been shown in many animal models to be mediators of certain kinds of intraocular inflammation. BromSite™ is available as a 0.075% ophthalmic solution. It is formulated in DuraSite®, a delivery vehicle that stabilizes small molecules in a polymeric mucoadhesive matrix, creating a gel forming drop. This extends the residence time of the drug relative to conventional eye drops. The recommended dosing is one drop into the affected eye twice daily (morning and evening) one day prior to surgery, the day of surgery, and 14 days post-surgery. The national average drug acquisition costs (NADAC) for the current Tier-2 bromfenac ophthalmic NSAID solutions, Bromday™ (bromfenac 0.09%) and Prolensa™ (bromfenac 0.07%), are $87.53 and $204.69 per bottle respectively. The wholesale acquisition cost (WAC) for BromSite™ per bottle is $240.00, making it consistent with current Tier-2 ophthalmic NSAID drug pricing.

Recommendations

The College of Pharmacy recommends the placement of BromSite™ (bromfenac 0.075% ophthalmic solution) into Tier-2 of the Ophthalmic Nonsteroidal Anti-Inflammatory Drugs Product Based Prior Authorization Category (PBPA). Current Tier-2 criteria for this category will apply.

Ophthalmic Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)	
Tier-1	**Tier-2**
diclofenac (Voltaren®) 0.1% solution	bromfenac (Bromday™) 0.09% solution
flurbiprofen (Ocufen®) 0.03% solution*	**bromfenac (BromSite™) 0.075% solution**
ketorolac (Acular®) 0.5% solution	bromfenac (Prolensa™) 0.07% solution
	ketorolac (Acular LS®) 0.4% solution
	ketorolac (Acuvail®) 0.45% solution
	nepafenac (Nevanac™) 0.1% suspension
	nepafenac (Ilevro™) 0.3% suspension

*Not a required Tier-1 trial. Does not have to be attempted for approval of a Tier-2 medication.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Ophthalmic Nonsteroidal Anti-Inflammatory Drug (NSAID) Tier-2 Approval Criteria:

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

[1] U.S. Food and Drug Administration (FDA). BromSite™ Prescribing Information. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206911s000lbl.pdf. Last revised 04/2016. Last accessed 11/2016.

Appendix G

Fiscal Year 2016 Annual Review of Hepatitis C Medications and 30-Day Notice to Prior Authorize Viekira XR™ (Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir) and Epclusa® (Sofosbuvir/Velpatasvir)

Oklahoma Health Care Authority
December 2016

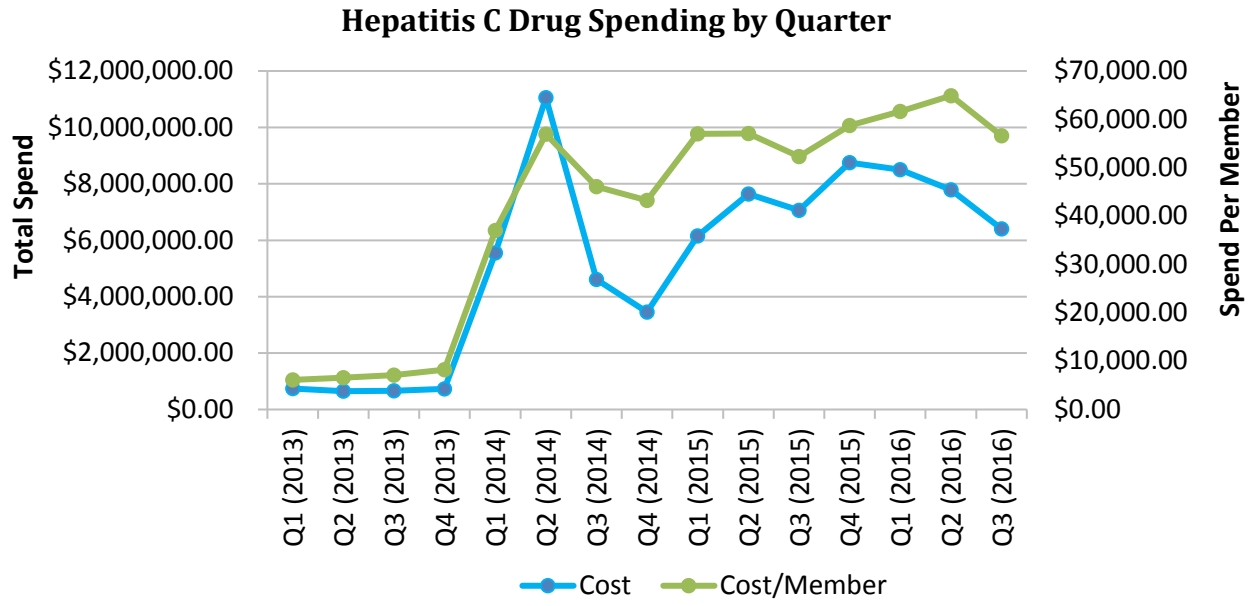
Introduction

Sovaldi® (sofosbuvir) and Olysio® (simeprevir), both approved by the U.S. Food and Drug Administration (FDA) in the fourth quarter of 2013, were previously restricted under Oklahoma law, preventing prior authorization management by the Oklahoma Health Care Authority. The state law was changed in May of 2014 allowing for prior authorization implementation of the hepatitis C medications effective July 1, 2014.

As new direct-acting antivirals (DAAs) were FDA approved, they were subsequently reviewed and recommended to be prior authorized by the DUR board. Harvoni® (ledipasvir/sofosbuvir) was reviewed in November 2014, Viekira Pak™ (dasabuvir/ombitasvir/paritaprevir/ritonavir) was reviewed in January 2015, Daklinza™ (daclatasvir) and Technivie™ (ombitasvir/paritaprevir/ritonavir) were reviewed in December 2015, and Zepatier™ (elbasvir/grazoprevir) was reviewed in April 2016. The newer treatment regimens correlated with an increase in cost ranging from $54,600.00 to $297,356.64 per regimen.

	Fiscal Year 2013	Fiscal Year 2014	Fiscal Year 2015	Fiscal Year 2016
Total Hepatitis C Drug Spending	$2,990,929.48	$17,993,807.47	$21,863,385.60	$32,105,818.63

Costs do not reflect rebated prices or net costs.



Current Prior Authorization Criteria

Viekira Pak™ (ombitasvir/paritaprevir/ritonavir/dasabuvir), Harvoni® (sofosbuvir/ledipasvir), Sovaldi® (sofosbuvir), and Zepatier™ (elbasvir/grazoprevir) are the preferred direct-acting antivirals for treatment of chronic hepatitis C genotype-1. Use of Sovaldi® (sofosbuvir) and Olysio® (simeprevir) in combination, Olysio® (simeprevir) alone, or Sovaldi® (sofosbuvir) and Daklinza™ (daclatasvir) in combination for treatment of HCV genotype-1 requires patient-specific, clinically significant reasoning why Viekira Pak™, Harvoni®, Sovaldi® with peginterferon and ribavirin, or Zepatier™ are not appropriate for the member. Detailed prior authorization criteria similar to the currently prior authorized medications can be found at the end of this report in the recommendations section.

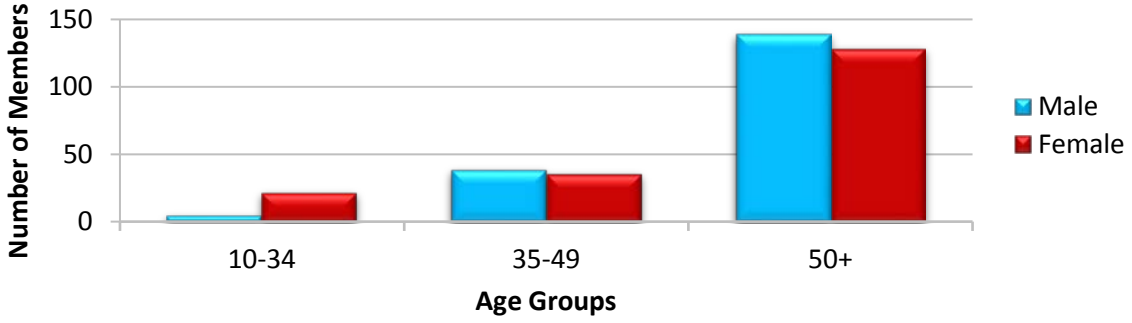
Utilization of Hepatitis C Medications: Fiscal Year 2016

Comparison of Fiscal Years

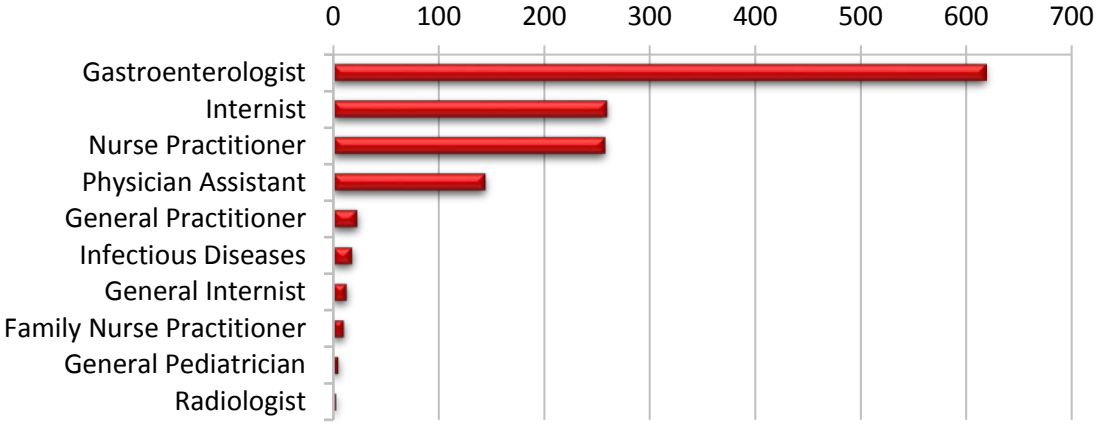
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	291	1,272	$21,863,385.60	$17,188.20	$615.61	90,199	35,515
2016	371	1,355	$32,105,818.63	$23,694.33	$847.57	75,856	37,880
% Change	**27.50%**	**6.50%**	**46.80%**	**37.90%**	**37.70%**	**-15.90%**	**6.70%**
Change	**80**	**83**	**$10,242,433.03**	**$6,506.13**	**$231.96**	**-14,343**	**2,365**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Demographics of Members Utilizing Hepatitis C Medications



Top Prescriber Specialties of Hepatitis C Medications by Number of Claims



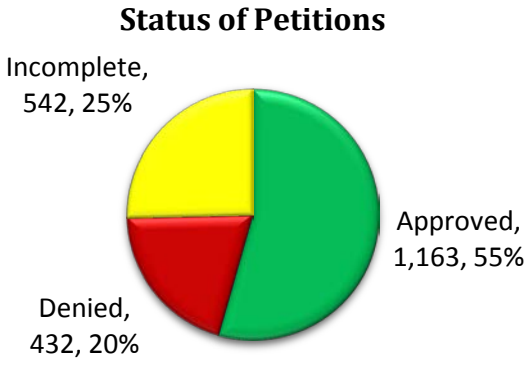
Hepatitis C Summary Statistics for Treated Members*

Parameter	Details
Number of Unduplicated Treated Members*	824 Unduplicated Members
Genotype	**Genotype-1:** 69.0% **Genotype-2:** 15.6% **Genotype-3:** 14.8% **Genotype-4:** 0.6%
Fibrosis Score	**Average:** 3.06 **F2:** 33.8% **F3:** 21.4% **F4:** 42.8% **Decompensated:** 0.3% **Other:** 1.8%
Pre-Treatment Viral Load (HCV RNA)	**Average:** 4,533,205 IU/mL
Prior Treatment Experience	**Treatment-Experienced Members:** 18.3% **Treatment-Naïve Members:** 81.7%
Treatment Length	**Average:** 12.8 weeks **8 weeks:** 21.7% **12 weeks:** 63.8% **16 weeks:** 1.4% **24 weeks:** 13.0%
Compliance[¥]	**Before PA:** 18.8% of members noncompliant **After PA:** 2.4% of members noncompliant
SVR Cure Rate/Cost Per Cure	92.2% Cure Rate[+] Based on cure rate and drug spending during allotted time frame (12/01/2013-03/31/2016), the estimated cost per cure in the SoonerCare population is $99,685.88-$205,887.18. Range due to partial SVR response rate.

*Table includes data collected from 07/01/2014 to 10/14/2016; total number of unduplicated members treated includes data from 12/01/2013 to 10/05/2016 (treated members are those with at least one paid claim).
HCV RNA = Hepatitis C Virus Ribonucleic Acid; PA = Prior Authorization; SVR = Sustained Virologic Response at least 12 weeks after therapy completion
[¥]Compliance before prior authorization was defined as an appropriate regimen length of 12 or 24 weeks.
[+]SVR Cure rate includes data from members who started therapy from 12/01/2013-03/31/2016. The cure rate is based only on members for whom SoonerCare was able to obtain SVR responses (SVR response rate: 55.6%).

Prior Authorization of Hepatitis C Medications

There were 2,137 prior authorization requests submitted for 592 unique members for hepatitis C medications during fiscal year 2016. Approvals are granted for 28 days of therapy each time, so members will have a prior authorization request for each refill of therapy. The following chart shows the status of the submitted petitions.



Market News and Updates[1,2,3,4,5,6,7,8,9,10]

Anticipated Patent Expiration(s):

- Olysio® (simeprevir): September 2029
- Sovaldi® (sofosbuvir): December 2030
- Zepatier™ (elbasvir/grazoprevir): May 2031
- Daklinza™ (daclatasvir): June 2031
- Technivie™ (ombitasvir/paritaprevir/ritonavir): April 2032
- Harvoni® (ledipasvir/sofosbuvir): September 2032
- Viekira Pak™ (ombitasvir/paritaprevir/ritonavir/dasabuvir): September 2032

New FDA Approval(s):

- **June 2016:** The FDA approved Epclusa® (sofosbuvir/velpatasvir), an oral combination of a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor and an HCV NS5A inhibitor, for the treatment of all six major genotypes of chronic hepatitis C. Epclusa® is indicated in patients with and without cirrhosis, and in combination with ribavirin for patients with decompensated cirrhosis.
- **July 2016:** The FDA approved Viekira XR™ (ombitasvir/paritaprevir/ritonavir/dasabuvir), a once-daily version of Viekira Pak™, for the treatment of patients with genotype-1 chronic hepatitis C. Viekira XR™ is dosed as three tablets once daily with a meal. Previously approved Viekira Pak™ is dosed as two tablets containing ombitasvir, paritaprevir, and ritonavir in the morning, along with one dasabuvir tablet in the morning and one in the evening, each time with a meal.

New Indication(s):

- **April 2016:** AbbVie announced the FDA approval of their supplemental New Drug Application (sNDA) for use of Viekira Pak™ without ribavirin in patients with genotype-1b chronic hepatitis C and compensated cirrhosis. The approval was based on results from the TURQUOISE-III study in which Viekira Pak™ demonstrated a 100% Sustained Virologic Response (SVR) rate in genotype-1b patients with compensated cirrhosis.

Safety Update(s):

- **October 2016:** The FDA released a drug safety communication regarding the risk of hepatitis B virus (HBV) reactivation in patients treated with DAAs for hepatitis C who have a current or had a previous HBV infection. Some cases of HBV reactivation resulted

in serious liver problems or death. The FDA is requiring the addition of a boxed warning to the DAA drug labels. It is recommended that prescribers screen and monitor for HBV in all patients receiving DAA treatment. The SoonerCare prior authorization criteria for DAAs requires documentation of initiation of immunization with HBV vaccines or screening for HBV prior to approval.

Pipeline News:

- **April 2016:** AbbVie announced positive results for its investigational, pan-genotypic regimen of ABT-493 and ABT-530 used in the treatment of genotype-1 patients who have failed previous treatment with DAAs. The regimen in combination with ribavirin achieved a 91% SVR12 rate after 12 weeks of treatment.
- **April 2016:** A pilot study presented at the 2016 International Liver Congress revealed a 100% SVR12 rate after treatment with only six weeks of Harvoni® (ledipasvir/ sofosbuvir). The study was conducted in 20 patients with acute HCV genotype-1. The authors concluded that a shorter treatment duration did not appear to hinder efficacy.
- **July 2016:** A phase 2a study of three weeks of treatment with an NS3 protease inhibitor and dual NS5A inhibitor-NS5B nucleotide analogue in non-cirrhotic patients with chronic HCV genotype-1b demonstrated a 100% SVR12 rate. Patients were only included in the three week treatment group if they achieved an ultrarapid virologic response defined as plasma HCV RNA <500 IU/mL by day two. The authors concluded that shortening the duration of therapy was effective and could reduce costs and adverse events.
- **September 2016:** Achillion Pharmaceuticals announced positive interim results from a phase 2a study of odalasvir and AL-335 with or without simeprevir for six or eight weeks in treatment-naïve patients with genotype-1 chronic HCV infection. The combination with simeprevir demonstrated a 100% SVR24 rate after 8 weeks of treatment.

Regimen Comparison[11,12,13,14,15,16,17,18,19]

The following table shows the current FDA approved or American Association for the Study of Liver Disease (AASLD)/Infectious Diseases Society of America (IDSA) guidance recommended regimens of DAA medications for the treatment of chronic HCV infection in treatment-naïve patients with or without compensated cirrhosis. The table is not all-inclusive and may exclude regimens where a shorter treatment duration is recommended in the guidance or FDA approved labeling. Specific regimens are used in particular patient populations depending on comorbidities, pre-treatment viral load, prior hepatitis C treatment experience, fibrosis stage, cirrhosis status, and baseline viral polymorphisms. Regimens marked with a star are not currently FDA approved, but are recommended by the AASLD/IDSA treatment guidance. Many non-FDA approved regimens were only studied in very small treatment populations with limited SVR data. SVR rates found in clinical studies should not be compared across studies, but can be used as a measure of clinical efficacy for each regimen. SVR rates were obtained from studies cited in the AASLD/IDSA treatment guidance or from an individual product's package labeling. SVR rates may vary across studies even when used in similar patient populations. Some SVR percentages in the following table may contain treatment-experienced patients or combined cirrhotic and non-cirrhotic patients if the study did not differentiate. Overall SVR percentages for genotypic subtypes may be reported together if the study did not differentiate.

Genotype	Host Factors	Treatment Regimen	Total Cost	SVR**
Genotype-1a◊	Treatment-naïve, Non-cirrhotic	**DAC** + **SOF** 12 wks	$142,710.12	98% (1a & 1b)
		EBR/GZR +/- RBV 12 or 16 wks	$54,600.00-$73,324.16	92%-100%⁺
		LED/SOF 8 or 12 wks	$60,804.80-$91,207.20	93% or 96%
		PAR/RIT/OMB/DAS + RBV 12 wks	$83,711.88	96%-97%
		SIM + **SOF** 12 wks	$148,285.20	97% (1a & 1b)
		SOF + RBV + PEG IFN 12 wks	$93,652.44	92%¥
		VEL/SOF 12 wks	$74,760.00	98%¥
	Treatment-naïve, Cirrhotic	**DAC** + **SOF** 12 weeks	$142,710.12	91% (1a & 1b)
		EBR/GZR +/- RBV 12 or 16 wks	$54,600.00-$73,324.16	92%-100%⁺
		LED/SOF 12 wks	$91,207.20	94% (1a & 1b)
		PAR/RIT/OMB/DAS + RBV 24 wks	$167,423.76	95%
		SIM + **SOF** +/- RBV 24 wks	$296,570.40-$297,356.64	100%
		SOF + RBV + PEG IFN 12 wks	$93,652.44	79%-92%¥ (1a & 1b)
		VEL/SOF 12 wks	$74,760.00	98%¥
Genotype-1b◊	Treatment-naïve, Non-cirrhotic	**DAC** + **SOF** 12 wks	$142,710.12	98% (1a & 1b)
		EBR/GZR 12 wks	$54,600.00	98%
		LED/SOF 8 or 12 wks	$60,804.80-$91,207.20	98%
		PAR/RIT/OMB/DAS 12 wks	$83,318.76	100%
		SIM + **SOF** 12 wks	$148,285.20	957 (1a & 1b)
		SOF + RBV + PEG IFN 12 wks	$93,652.44	83%¥
		VEL/SOF 12 wks	$74,760.00	99%¥
	Treatment-naïve, Cirrhotic	**DAC** + **SOF** 12 wks	$142,710.12	91% (1a & 1b)
		EBR/GZR 12 wks	$54,600.00	98%
		LED/SOF 12 wks	$91,207.20	94% (1a & 1b)
		PAR/RIT/OMB/DAS 12 wks	$83,318.76	100%
		SIM + **SOF** +/- RBV 24 wks	$296,570.40-$297,356.64	100%
		SOF + RBV + PEG IFN 12 wks	$93,652.44	79%-83%¥ (1a & 1b)
		VEL/SOF 12 wks	$74,760.00	98%¥
Genotype-2	Treatment-naïve, Non-cirrhotic	***DAC** + **SOF** 12 wks	$142,710.12	100%
		SOF + RBV 12 wks	$82,318.32	97%
		VEL/SOF 12 wks	$74,760.00	99%-100%¥
	Treatment-naïve, Cirrhotic	***DAC** + **SOF** 16 or 24 wks	$190,280.16-$285,420.24	Not Available
		SOF + RBV 12 wks	$82,318.32	83%
		VEL/SOF 12 wks	$74,760.00	99%-100%¥
Genotype-3	Treatment-naïve, Non-cirrhotic	**DAC** + **SOF** 12 wks	$142,710.12	97%
		SOF + RBV 24 wks	$164,636.64	93%
		VEL/SOF 12 wks	$74,760.00	98%
	Treatment-naïve, Cirrhotic	**DAC** + **SOF** + RBV 12 wks	$143,103.24	83%
		SOF + RBV 24 wks	$164,636.64	92%
		VEL/SOF 12 wks	$74,760.00	93%
Genotype-4◊	Treatment-naïve, Non-cirrhotic	**EBR/GZR** 12 wks	$54,600.00	97%
		LED/SOF 12 wks	$91,207.20	93%
		PAR/RIT/OMB + RBV 12 wks	$77,046.48	100%
		SOF + RBV + PEG IFN 12 wks	$93,652.44	96%¥
		VEL/SOF 12 wks	$74,760.00	100%¥
	Treatment-naïve, Cirrhotic	**EBR/GZR** 12 wks	$54,600.00	97%
		LED/SOF 12 wks	$91,207.20	93%
		***PAR/RIT/OMB** + RBV 12 wks	$77,046.48	96%-97%
		SOF + RBV + PEG IFN 12 wks	$93,652.44	79%-96%¥
		VEL/SOF 12 wks	$74,760.00	100%¥
Genotype-5 or 6	Treatment-naïve, Cirrhotic & Non	**LED/SOF** 12 wks	$91,207.20	GT5: 93%, GT6: 96%
		VEL/SOF 12 wks	$74,760.00	GT5: 97%, GT6: 100%

*Not an FDA approved regimen, **SVR = Sustained virologic response 12 weeks after therapy completion in clinical studies
¥Percentage includes cirrhotic & non-cirrhotic patients. For SOF regimen lower % may include genotype-4 and both -1a and -1b subtypes.
⁺Lower % accounts for those with baseline resistance associated variants (RAVs) & some cirrhotic patients; lower % shown is for 12 weeks without RBV.
◊Simeprevir + PEG IFN + RBV for 12 weeks followed by 12 or 36 additional weeks PEG IFN + RBV excluded for genotypes 1 and 4.
Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
SIM = simeprevir SOF = sofosbuvir LED = ledipasvir PAR = paritaprevir RIT = ritonavir OMB = ombitasvir GT = Genotype
DAS = dasabuvir DAC = daclatasvir EBR = elbasvir GZR = grazoprevir VEL = velpatasvir RBV = ribavirin PEG IFN = peginterferon alfa
RBV dosing based on >75kg patient (1200mg).

Viekira XR™ (Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir) Product Summary[12]

FDA Approval: July 2016

Indications: Viekira XR™ [ombitasvir (OMB)/paritaprevir (PAR)/ritonavir (RIT)/dasabuvir (DAS)] is a fixed-dose combination of DAS, a HCV non-nucleoside NS5B palm polymerase inhibitor, OMB, a HCV NS5A inhibitor, PAR, a HCV NS3/4A protease inhibitor, and RIT, a CYP3A inhibitor. OMB/PAR/RIT/DAS is indicated for patients with genotype-1b infection without cirrhosis or with compensated cirrhosis and genotype-1a infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.

Dosing:

- Viekira XR™ is available as 200mg DAS/8.33mg OMB/50mg PAR/33.3mg RIT extended-release oral tablets. It is dispensed in a carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons, and each weekly carton contains seven daily dose packs. Each daily dose pack contains three Viekira XR™ tablets.
- The recommended dosage of OMB/PAR/RIT/DAS is three tablets by mouth once daily. OMB/PAR/RIT/DAS must be taken with a meal because administration under fasting conditions may result in reduced virologic response and possible development of resistance. Patients should swallow tablets whole. The recommended treatment regimens and duration can be found in the following table:

Patient Population	Treatment	Duration
Genotype-1a, w/o cirrhosis	**OMB/PAR/RIT/DAS** + RBV	12 weeks
Genotype-1a, w/ compensated cirrhosis	**OMB/PAR/RIT/DAS** + RBV	24 weeks
Genotype-1b, with or w/o compensated cirrhosis	**OMB/PAR/RIT/DAS**	12 weeks

w/o = without; w/ = with; PAR = paritaprevir; RIT = ritonavir; OMB = ombitasvir; DAS = dasabuvir; RBV = ribavirin

- OMB/PAR/RIT/DAS may be used in combination with ribavirin. The recommended dose of ribavirin when administered with OMB/PAR/RIT/DAS is based on weight (1,000mg per day for patients less than 75kg and 1,200mg per day for those weighing at least 75kg).

Mechanism of Action: OMB/PAR/RIT/DAS combines three direct-acting HCV antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

- DAS is an inhibitor of HCV RNA-dependent RNA polymerase encoded by the NS5B gene, which is essential for replication of the viral genome.
- OMB is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly.
- PAR is an inhibitor of HCV NS3/4A protease, which is necessary for the proteolytic cleavage of the HCV encoded polyprotein and is essential for viral replication.
- RIT is not active against HCV. RIT is a potent CYP3A inhibitor that increases peak and trough plasma concentrations of PAR and overall drug exposure.

Contraindications:

- When OMB/PAR/RIT/DAS is administered with ribavirin the contraindications to ribavirin also apply to the combination regimen.

- OMB/PAR/RIT/DAS is contraindicated in moderate-to-severe hepatic impairment (Child-Pugh B and C) due to risk of potential toxicity.
- OMB/PAR/RIT/DAS is contraindicated in patients with known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome).
- OMB/PAR/RIT/DAS is contraindicated when taken with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events *(see table below)*.
- OMB/PAR/RIT/DAS is contraindicated when taken with drugs that are moderate or strong inducers of CYP3A and strong inducers of CYP2C8 and may lead to reduced efficacy of OMB/PAR/RIT/DAS *(see table below)*.
- OMB/PAR/RIT/DAS is contraindicated when taken with drugs that are strong inhibitors of CYP2C8 and may increase DAS plasma concentrations and the risk of QT prolongation *(see table below)*.

Drugs that are Contraindicated with Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir		
Concomitant Drug Class	**Drug(s) within Class that are Contraindicated**	**Clinical Comment(s)**
Alpha 1-Adrenoreceptor Antagonist	alfuzosin HCl	Potential for hypotension.
Anti-Anginal	ranolazine	Potential for serious reactions.
Antiarrhythmic	dronedarone	Potential for serious reactions such as cardiac arrhythmias.
Anticonvulsants	carbamazepine, phenytoin, phenobarbital	OMB/PAR/RIT/DAS exposures may decrease leading to a potential loss of therapeutic activity.
Anti-Gout	colchicine	Potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment.
Antihyperlipidemic	gemfibrozil	Increase in DAS concentrations by 10-fold which may increase the risk of QT prolongation.
Antimycobacterial	rifampin	OMB/PAR/RIT/DAS exposures may decrease leading to a potential loss of therapeutic activity.
Antipsychotic	lurasidone, pimozide	Lurasidone: potential for serious reactions. Pimozide: potential for serious reactions such as cardiac arrhythmias.
Ergot Derivatives	ergotamine, dihydorergotamine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of RIT and ergot derivatives.
Ethinyl Estradiol-Containing Products	ethinyl estradiol containing-medications such as combined oral contraceptives	Potential for ALT elevations.
GI Motility Agent	cisapride	Potential for serious reactions such as cardiac arrhythmias.
Herbal Products	St. John's wort	OMB/PAR/RIT/DAS exposures may decrease leading to a potential loss of therapeutic activity.
HMG-CoA Reductase Inhibitors	lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Non-Nucleoside Reverse Transcriptase Inhibitors	efavirenz	Co-administration of efavirenz with PAR, RIT was poorly tolerated and resulted in liver enzyme elevations.
PDE5 inhibitor	sildenafil when dosed for the treatment of pulmonary arterial hypertension	Increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.

Drugs that are Contraindicated with Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir		
Concomitant Drug Class	**Drug(s) within Class that are Contraindicated**	**Clinical Comment(s)**
Sedatives/Hypnotics	triazolam, orally administered midazolam	May cause increases in concentration of these benzodiazepines; the potential exists for prolonged or increased sedation or respiratory depression.

Table modified from: Viekira XR™ Product Information. AbbVie Inc.
PAR = paritaprevir; RIT = ritonavir; OMB = ombitasvir; DAS = dasabuvir; GI = gastrointestinal; ALT = alanine transaminase; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; PDE5 = phosphodiesterase-5

Warnings and Precautions:

- Risk of Hepatic Decompensation and Hepatic Failure in Patients with Cirrhosis: Hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported in patients treated with OMB/PAR/RIT/DAS. Most patients with these severe outcomes had evidence of advanced cirrhosis prior to initiating therapy. Reported cases typically occurred within one to four weeks of initiating therapy and were characterized by the acute onset of rising direct serum bilirubin levels without ALT elevations in association with clinical signs and symptoms of hepatic decompensation.
- Increased Risk of Alanine Transaminase (ALT) Elevations: During clinical trials with OMB/PAR/RIT/DAS, elevations of ALT to greater than five times the upper limit of normal (ULN) occurred in approximately 1% of subjects. ALT elevations were typically asymptomatic, occurred in the first four weeks of treatment, and declined within two to eight weeks of onset with continued dosing.
    - These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications. Ethinyl estradiol-containing medications should be discontinued prior to starting treatment with OMB/PAR/RIT/DAS. Alternative methods of contraception are recommended.
    - Hepatic laboratory testing should be performed during the first four weeks of starting treatment and as clinically indicated thereafter.
- Risks Associated with Ribavirin Combination Treatment: The warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen.
- Risks of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions: The concomitant use of OMB/PAR/RIT/DAS and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of OMB/PAR/RIT/DAS and possible development of resistance, or possible clinically significant adverse reactions from greater exposures of concomitant drugs or components of OMB/PAR/RIT/DAS *(see drug interactions section)*.
- Risk of HIV-1 Protease Inhibitor Drug Resistance in HCV/HIV-1 Co-Infected Patients: The ritonavir component of OMB/PAR/RIT/DAS is also an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance-associated substitutions. Any HCV/HIV-1 co-infected patients treated with OMB/PAR/RIT/DAS should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV-1 protease inhibitor drug resistance.

Adverse Reactions: The most common adverse reactions (≥5%) reported during OMB/PAR/RIT/DAS clinical trials include the following:

- Asthenia
- Fatigue
- Nausea
- Insomnia
- Pruritus
- Skin Reactions

Use in Special Populations:

- Pregnancy: There are no adequate and well-conducted studies in pregnant women. When OMB/PAR/RIT/DAS is administered with ribavirin, the combination is contraindicated in pregnant women and in men whose female partners are pregnant.
- Nursing Mothers: It is not known whether any of the components of OMB/PAR/RIT/DAS are present in human milk. Unchanged OMB, PAR and its hydrolysis product, and DAS were the predominant components observed in the milk of lactating rats.
- Females and Males of Reproductive Potential: If OMB/PAR/RIT/DAS is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen.
- Pediatric Use: The safety and effectiveness of OMB/PAR/RIT/DAS in pediatric patients have not been established.
- Geriatric Use: No dosage adjustment of OMB/PAR/RIT/DAS is warranted in geriatric patients. Of the total number of subjects in clinical studies of OMB/PAR/RIT/DAS, 8.5% were 65 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.
- Renal Impairment: No dosage adjustment of OMB/PAR/RIT/DAS is required for patients with mild, moderate, or severe renal impairment including those on dialysis.

Drug Interactions:

Established and Other Potentially Significant Drug Interactions		
Concomitant Drug Class	**Effect on Concentration**	**Clinical Comment and Labeling Recommendations**
ARBs valsartan, losartan, candesartan	Increased ARBs	Decrease ARB dose and monitor for hypotension and/or worsening renal function.
Antiarrhythmics amiodarone, bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine	Increased antiarrhythmics	Concentration monitoring is recommended for antiarrhythmics.
Antidiabetic Medications metformin	No metformin change	Monitor for lactic acidosis and worsening renal function. Concomitant use in patients with renal insufficiency or hepatic impairment is not recommended.
Antifungals ketoconazole, voriconazole	Increased ketoconazole Decreased voriconazole	The maximum daily dose of ketoconazole limited to 200mg. Co-administration with voriconazole is not recommended.

Established and Other Potentially Significant Drug Interactions		
Concomitant Drug Class	**Effect on Concentration**	**Clinical Comment and Labeling Recommendations**
Antipsychotics quetiapine	Increased quetiapine	Consider alternative anti-HCV therapy to avoid increases in quetiapine exposures. If co-administration is necessary, reduce quetiapine dose to 1/6th of current dose & monitor.
CCBs amlodipine, nifedipine, diltiazem, verapamil	Increased CCBs	Decrease dose of CCB (amlopidine should be decreased by ≥50%). Monitoring for edema and hypotension is recommended.
Corticosteroids (Inhaled/Nasal) fluticasone	Increased fluticasone	Alternative corticosteroids should be considered.
Diuretics furosemide	Increased furosemide	Monitoring is recommended.
HIV-Antiviral Agents atazanavir/RIT, darunavir/RIT, lopinavir/RIT, rilpivirine	Increased PAR with atazanavir & lopinavir Decreased darunavir Increased rilpivirine	Atazanavir 300mg should only be given in morning. Co-administration with darunavir/RIT, lopinavir/RIT, or rilpivirine is not recommended.
HMG CoA Reductase Inhibitors pravastatin, rosuvastatin	Increased pravastatin Increased rosuvastatin	Pravastatin dose should not exceed 40mg per day. Rosuvastatin dose should not exceed 10mg per day.
Immunosuppressants cyclosporine, tacrolimus	Increased cyclosporine Increased tacrolimus	The dose of cyclosporine should be reduced to 1/5th of the current dose. The dose of tacrolimus should be reduced.
LABA salmeterol	Increased salmeterol	Co-administration is not recommended.
Narcotic Analgesics hydrocodone/acetaminophen, buprenorphine/naloxone	Increased hydrocodone Increased buprenorphine	Decrease dose of hydrocodone by 50% and monitor for respiratory depression and sedation. Buprenorphine patients should be monitored for sedation and cognitive effects.
Sedatives/Hypnotics alprazolam	Increased alprazolam	Clinical monitoring and a potential need for a decrease in alprazolam dose is recommended.

Table modified from: Viekira XR™ Product Information. AbbVie Inc.

Not all drug interactions from prescribing information are included in above table. Consult the prescribing information for a detailed list of clinically significant drug interactions.

ARBs = angiotensin receptor blockers; CCBs = calcium channel blockers; PAR = paritaprevir; RIT = ritonavir; HIV = human immunodeficiency virus; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A; LABA = Long-Acting Beta-Adrenoceptor Agonist

Epclusa® (Sofosbuvir/Velpatasvir) Product Summary[19]

FDA Approval: June 2016

Indications: Epclusa® (sofosbuvir [SOF]/velpatasvir [VEL]) is a fixed-dose combination of SOF, a HCV nucleotide analog NS5B polymerase inhibitor, and VEL, a HCV NS5A inhibitor, indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection with or without compensated cirrhosis and in decompensated cirrhosis in combination with ribavirin.

Dosing:

- Epclusa® is available as a fixed-dose oral tablet containing 400mg of SOF and 100mg of VEL. It is dispensed in a monthly bottle for a total of 28 days of therapy.
- The recommended dosage of SOF/VEL is one tablet by mouth once daily with or without food. The recommended treatment regimens and duration can be found in the following table.

Patient Population	Treatment Regimen and Duration
Patients w/o cirrhosis and patients w/ compensated cirrhosis	**SOF/VEL** for 12 weeks
Patients w/ decompensated cirrhosis	**SOF/VEL** + ribavirin for 12 weeks

w/o = without; w/ = with; SOF = sofosbuvir; VEL = velpatasvir

- When SOF/VEL is used in combination with ribavirin, the recommended dose of ribavirin is based on weight (1,000mg per day for patients less than 75kg and 1,200mg per day for those weighing at least 75kg).
- No dosage regimen of SOF/VEL can be given for patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] less than 30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) due to higher exposures (up to 20-fold) of the SOF metabolite.

Mechanism of Action:

- SOF is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase, which is required for viral replication. SOF is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate (GS-461203), which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator.
- VEL is an inhibitor of the HCV NS5A protein, which is required for viral replication.

Contraindications:

- When SOF/VEL is taken in combination with ribavirin, the contraindications to ribavirin also apply to the combination regimen.

Warnings and Precautions:

- <u>Serious Symptomatic Bradycardia When SOF Is Co-administered with Amiodarone and Another HCV DAA:</u> Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is co-administered with SOF in combination with daclatasvir (DAC) or simeprevir (SIM). Bradycardia has generally occurred within hours to days, but cases have been observed up to two weeks

after initiating HCV treatment. Bradycardia generally resolved after discontinuation of HCV treatment. Co-administration of amiodarone with SOF/VEL is not recommended.

- Risk of Reduced Therapeutic Effect Due to Concomitant Use of SOF/VEL with Inducers of P-glycoprotein (P-gp) and/or Moderate-to-Potent Inducers of Cytochrome (CYP) P450: Drugs that are inducers of P-gp and/or moderate-to-potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of SOF and/or VEL, leading to potentially reduced therapeutic effect of SOF/VEL. The use of these agents with SOF/VEL is not recommended.
- Risks Associated with Ribavirin Combination Treatment: If SOF/VEL is administered with ribavirin, the warnings and precautions for ribavirin, in particular the pregnancy avoidance warning, apply to this combination regimen.

Adverse Reactions: The most common adverse reactions (≥5%) reported during SOF/VEL clinical trials include the following:

- Headache
- Fatigue
- Nausea
- Asthenia
- Insomnia

Use in Special Populations:

- Pregnancy: No adequate human data are available to establish whether or not SOF/VEL poses a risk to pregnancy outcomes. In animal reproduction studies, no evidence of adverse developmental outcomes was observed with SOF/VEL at exposures greater than those in humans. When SOF/VEL is administered with ribavirin, the combination is contraindicated in pregnant women and in men whose female partners are pregnant.
- Nursing Mothers: It is not known whether SOF/VEL and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed infant. The predominant circulating metabolite of SOF (GS-331007) was the primary component observed in the milk of lactating rats, without effect on nursing pups.
- Females and Males of Reproductive Potential: If SOF/VEL is administered with ribavirin, the information for ribavirin with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen.
- Pediatric Use: The safety and effectiveness of SOF/VEL in pediatric patients have not been established.
- Geriatric Use: No overall differences in safety or effectiveness have been observed between geriatric subjects and younger subjects in SOF/VEL clinical trials.
- Renal Impairment: No dosage adjustment of SOF/VEL is required for patients with mild or moderate renal impairment. The safety and efficacy of SOF/VEL have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or ESRD requiring hemodialysis.
- Hepatic Impairment: No dosage adjustment of SOF/VEL is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with SOF/VEL and ribavirin.

Drug Interactions:

Established and Other Potentially Significant Drug Interactions		
Concomitant Drug Class	**Effect on Concentration**	**Clinical Comment**
Acid Reducing Agents antacids, H_2-receptor antagonists, proton pump inhibitors	Decreased VEL	Drugs that increase gastric pH are expected to decrease concentration of VEL. Antacids should be separated by 4 hours. H_2-receptor antagonists may be administered simultaneously with or 12 hours apart at a dose that does not exceed equivalent to famotidine 40mg twice daily. Co-administration of omeprazole or other proton-pump inhibitors is not recommended.
Antiarrhythmics digoxin, amiodarone	Increased digoxin Effect on amiodarone, SOF, and VEL unknown	Monitor serum digoxin levels. Co-administration with amiodarone is not recommended.
Anticancers topotecan	Increased topotecan	Co-administration is not recommended.
Anticonvulsants carbamazepine, phenytoin, phenobarbital, oxcarbazepine	Decreased SOF Decreased VEL	Co-administration is not recommended.
Antimycobacterials rifabutin, rifampin, rifapentine	Decreased SOF Decreased VEL	Co-administration is not recommended.
HIV-Antiviral Agents efavirenz, tipranavir/ritonavir, tenofovir DF	Decreased VEL with efavirenz or tipranavir/ritonavir Increased tenofovir DF	Co-administration with efavirenz or tipranavir/ritonavir is not recommended. Monitor for tenofovir-associated adverse reactions.
Herbal Supplements: St. John's wort	Decreased SOF Decreased VEL	Co-administration is not recommended.
HMG CoA Reductase Inhibitors rosuvastatin, atorvastatin	Increased rosuvastatin Increased atorvastatin	Co-administration with rosuvastatin or atorvastatin may significantly increase the concentration of rosuvastatin or atorvastatin, which is associated with increased risk of myopathy, including rhabdomyolysis. Rosuvastatin may be administered at a dose that does not exceed 10mg. Atorvastatin patients should be monitored closely for myopathy and rhabdomyolysis.

Table modified from: Epclusa® Product Information. Gilead Sciences Inc.
Not all drug interactions from prescribing information are included in above table. Consult the prescribing information for a detailed list of clinically significant drug interactions.
SOF = sofosbuvir; VEL = velpatasvir; H_2 = histamine-2; HIV = human immunodeficiency virus; DF = disproxil fumarate; HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A

Recommendations

The College of Pharmacy recommends the following:

1. The prior authorization of Viekira XR™ (ombitasvir/paritaprevir/ritonavir/dasabuvir) and Epclusa® (sofosbuvir/velpatasvir) with criteria similar to the other prior authorized hepatitis C medications.
2. The removal of the minimum METAVIR fibrosis score of F2. The removal of the fibrosis score requirement will be phased in as follows: Members with a fibrosis score of F1 will be eligible for approval July 1, 2017 and members with a fibrosis score of F0 will be eligible for approval January 1, 2018.
3. Updating the criteria regarding alcohol and illicit IV drug use for all DAA's to the following: Prescriber must agree to counsel members on potential harms of illicit IV drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy.

The following table highlights the preferred regimens for each genotype in treatment-naïve and PEG-IFN and RBV-experienced members (listed in alphabetical order). Additional regimens other than those listed may be considered based on patient-specific clinical situations.

Genotype	Patient Factors	Preferred Regimen(s)
Genotype-1		
1	Treatment-naïve, non-cirrhotic	Harvoni® for 8 or 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks 1a: Viekira Pak™ or Viekira XR™ + RBV for 12 weeks 1b: Viekira Pak™ or Viekira XR™ for 12 weeks 1a: Zepatier™ for 12 weeks (without baseline RAVs) 1a: Zepatier™ + RBV for 16 weeks (with baseline RAVs) 1b: Zepatier™ for 12 weeks
1	Treatment-naïve, cirrhotic	Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks 1a: Viekira Pak™ or Viekira XR™ + RBV for 24 weeks 1b: Viekira Pak™ or Viekira XR™ for 12 weeks 1a: Zepatier™ for 12 weeks (without baseline RAVs) 1a: Zepatier™ + RBV for 16 weeks (with baseline RAVs) 1b: Zepatier™ for 12 weeks
1	Treatment-experienced, non-cirrhotic	Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks 1a: Viekira Pak™ or Viekira XR™ + RBV for 12 weeks 1b: Viekira Pak™ or Viekira XR™ for 12 weeks 1a: Zepatier™ for 12 weeks (without baseline RAVs) 1a: Zepatier™ + RBV for 16 weeks (with baseline RAVs) 1b: Zepatier™ for 12 weeks

Genotype	Patient Factors	Preferred Regimen(s)
1	Treatment-experienced, cirrhotic	1a: Harvoni® + RBV for 12 weeks 1b: Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks 1a: Viekira Pak™ or Viekira XR™ + RBV for 24 weeks 1b: Viekira Pak™ or Viekira XR™ for 12 weeks 1a: Zepatier™ for 12 weeks (without baseline RAVs) 1a: Zepatier™ + RBV for 16 weeks (with baseline RAVs) 1b: Zepatier™ for 12 weeks
Genotype-2		
2	Treatment-naïve, non-cirrhotic	Epclusa® for 12 weeks Sovaldi® + RBV for 12 weeks
2	Treatment-naïve, cirrhotic	Epclusa® for 12 weeks (with RBV if decompensated) Sovaldi® + RBV for 12 weeks
2	Treatment-experienced, non-cirrhotic	Epclusa® for 12 weeks Sovaldi® + RBV for 12 weeks
2	Treatment-experienced, cirrhotic	Epclusa® for 12 weeks (with RBV if decompensated) Sovaldi® + RBV for 12 weeks
Genotype-3		
3	Treatment-naïve, non-cirrhotic	Epclusa® for 12 weeks Sovaldi® + RBV for 24 weeks (only if can't use Epclusa®)
3	Treatment-naïve, cirrhotic	Epclusa® for 12 weeks (with RBV if decompensated) Sovaldi® + RBV for 24 weeks (only if can't use Epclusa®)
3	Treatment-experienced, non-cirrhotic	Epclusa® for 12 weeks Sovaldi® + RBV for 24 weeks (only if can't use Epclusa®)
3	Treatment-experienced, cirrhotic	Epclusa® + RBV for 12 weeks Sovaldi® + RBV for 24 weeks (only if can't use Epclusa®)
Genotype-4		
4	Treatment-naïve, non-cirrhotic	Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks Technivie™ + RBV for 12 weeks Zepatier™ for 12 weeks
4	Treatment-naïve, cirrhotic	Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks Technivie™ + RBV for 12 weeks Zepatier™ for 12 weeks
4	Treatment-experienced, non-cirrhotic	Harvoni® for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks Technivie™ + RBV for 12 weeks Zepatier™ + RBV for 16 weeks

Genotype	Patient Factors	Preferred Regimen(s)
4	Treatment-experienced, cirrhotic	Harvoni® + RBV for 12 weeks Sovaldi® + RBV + PEG IFN for 12 weeks Technivie™ + RBV for 12 weeks Zepatier™ + RBV for 16 weeks
Genotype-5 or 6		
5 or 6	Treatment-naïve or experienced, non-cirrhotic or cirrhotic	Harvoni® for 12 weeks

Not all regimens included are FDA approved.
All regimens are either FDA approved, recommended in AASLD/IDSA treatment guidance, or have study data indicating efficacy.
If not specified, regimen applies to all genotypic subtypes.
RBV = Ribavirin; PEG IFN = peginterferon alfa; RAV= resistance-associated polymorphisms
Preferred regimens based on clinical efficacy data, guideline recommendations, supplemental rebate participation, and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Viekira Pak™ **and Viekira XR™** (ombitasvir/paritaprevir/ritonavir/dasabuvir), Harvoni® (sofosbuvir/ledipasvir), Sovaldi® (sofosbuvir), and Zepatier™ (elbasvir/grazoprevir) are the preferred direct-acting antivirals for the treatment of chronic hepatitis C genotype-1. Use of Sovaldi® (sofosbuvir) and Olysio® (simeprevir) in combination, Olysio® (simeprevir) alone, or Sovaldi® (sofosbuvir) and Daklinza™ (daclatasvir) in combination for the treatment of HCV genotype-1 requires patient-specific, clinically significant reasoning why Viekira Pak™, Viekira XR™, Harvoni®, Sovaldi® with peginterferon and ribavirin, or Zepatier™ (elbasvir/grazoprevir) are not appropriate for the member. Detailed criteria for medications with no changes to the coverage criteria are not included in the criteria on the following pages. The criteria for each medication may include FDA approved regimens or AASLD guideline recommended regimens that are not included in the SoonerCare preferred regimens table. Preferred regimens for each genotype can be found in the preferred regimens table. Additional regimens other than those listed in the preferred regimens table may be considered based on patient-specific clinical situations.

Viekira Pak™ and Viekira XR™ (Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir)
Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of Chronic Hepatitis C (CHC) genotype-1; and
3. Member must have a METAVIR fibrosis score of F2 or greater or equivalent scoring with an alternative test. Fibrosis testing type and scoring must be indicated on prior authorization request (Members with a fibrosis score of F1 will be eligible for approval July 1, 2017 and members with a fibrosis score of F0 will be eligible for approval January 1, 2018); and
4. Viekira Pak™ or Viekira XR™ must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated by a gastroenterologist, infectious disease specialist, or transplant specialist for hepatitis C therapy within the last three months; and
5. Hepatitis C Virus (HCV) genotype/subtype testing must be confirmed and indicated on prior authorization request; and

6. Pre-treatment viral load (HCV-RNA) must be confirmed and indicated on the petition. Viral load should have been taken within the last three months; and
7. The following regimens and requirements based on prior treatment experience, genotypic subtype, and cirrhosis will apply:
   a. **Genotype 1a, without cirrhosis:**
      i. Viekira Pak™ or Viekira XR™ with weight-based ribavirin for 12 weeks
   b. **Genotype 1a, with compensated cirrhosis:**
      i. Viekira Pak™ or Viekira XR™ with weight-based ribavirin for 24 weeks
      ii. Viekira Pak™ or Viekira XR™ with weight-based ribavirin for 12 weeks may be considered for some patients based on prior treatment history
   c. **Genotype 1b, without cirrhosis or with compensated cirrhosis:**
      i. Viekira Pak™ or Viekira XR™ for 12 weeks
   d. New regimens will apply as approved by the FDA
8. Member must not have previously failed treatment with a hepatitis C protease inhibitor (non-responder or relapsed); and
9. Member must sign and submit the Hepatitis C Intent to Treat contract; and
10. Member's pharmacy must submit the Hepatitis C Therapy Pharmacy Agreement for each member on therapy; and
11. The prescriber must verify that they will provide SoonerCare with all necessary labs to evaluate hepatitis C therapy efficacy including Sustained Viral Response (SVR-12); and
12. Prescriber must agree to counsel members on potential harms of illicit IV drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
13. Must have documentation of initiation of immunization with the hepatitis A and B vaccines; and
14. Member must not have decompensated cirrhosis or moderate-to-severe hepatic impairment (Child-Pugh B and C); and
15. Female members must not be pregnant and must have a pregnancy test immediately prior to therapy initiation. Male and female members must be willing to use two forms of non-hormonal birth control while on therapy (and for six months after therapy completion for those on ribavirin); and
16. The prescriber must verify that the member's ALT levels will be monitored during the first four weeks of starting treatment and as clinically indicated thereafter; and
17. Member must not be taking the following medications: alfuzosin, ranolazine, carbamazepine, phenytoin, phenobarbital, colchicine, gemfibrozil, rifampin, lurasidone, pimozide, ergotamine, dihydroergotamine, methylergonovine, ethinyl estradiol, cisapride, St. John's wort, lovastatin, simvastatin, efavirenz, sildenafil, triazolam, oral midazolam, darunavir/ritonavir, lopinavir/ritonavir, riilpivirine, and salmeterol; and
18. 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; and
19. Prescribing physician must verify that they will work with the member to ensure the member remains adherent to hepatitis C therapies; and

20. Members must be adherent for continued approval. Treatment gaps of therapy longer than 3 days/month will result in denial of subsequent requests for continued therapy.
21. Approvals for treatment regimen initiation for 12 weeks of therapy will not be granted prior to the 10th of a month, and for 24 weeks of therapy prior to the 15th of a month in order to prevent prescription limit issues from affecting the member's compliance.

Epclusa® (Sofosbuvir/Velpatasvir) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of Chronic Hepatitis C (CHC) genotype-1, genotype-2, genotype-3, genotype-4, genotype-5, or genotype-6; and
3. Member must have a METAVIR fibrosis score of F2 or greater or equivalent scoring with an alternative test. Fibrosis testing type and scoring must be indicated on prior authorization request (Members with a fibrosis score of F1 will be eligible for approval July 1, 2017 and members with a fibrosis score of F0 will be eligible for approval January 1, 2018); and
4. Epclusa® must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated for hepatitis C treatment by a gastroenterologist, infectious disease specialist, or transplant specialist within the last three months; and
5. Hepatitis C Virus (HCV) genotype testing must be confirmed and indicated on prior authorization request; and
6. Pre-treatment viral load (HCV-RNA) must be confirmed and indicated on the petition. Viral load should have been taken within the last three months; and
7. The following regimens and requirements based on cirrhosis status will apply:
   a. **Genotype-1, -2, -3, -4, -5, -6:**
      i. **Treatment-naïve or treatment-experienced without cirrhosis or with compensated cirrhosis (Child-Pugh A):**
         1. Epclusa® for 12 weeks
      ii. **Treatment-naïve or treatment-experienced with decompensated cirrhosis (Child-Pugh B and C):**
         1. Epclusa® + weight-based ribavirin for 12 weeks
   b. New regimens will apply as approved by the FDA
8. Member must sign and submit the Hepatitis C Intent to Treat contract; and
9. Member's pharmacy must submit the Hepatitis C Therapy Pharmacy Agreement for each member on therapy; and
10. The prescriber must verify that they will provide SoonerCare with all necessary labs to evaluate hepatitis C therapy efficacy including Sustained Virologic Response (SVR-12); and
11. Prescriber must agree to counsel members on potential harms of illicit IV drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
12. Must have documentation of initiation of immunization with the hepatitis A and B vaccines; and
13. Member must not have severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30mL/min/1.73m^2); and

14. Female members must not be pregnant and must have a pregnancy test immediately prior to therapy initiation. Male and female members must be willing to use two forms of non-hormonal birth control while on therapy (and for six months after therapy completion for ribavirin users); and
15. Member must not be taking the following medications: H_2-receptor antagonists at doses greater than 40mg famotidine equivalent, amiodarone, omeprazole or other proton pump inhibitors, topotecan, rifampin, rifabutin, rifapentine, carbamazepine, eslicarbazepine, phenytoin, phenobarbital, oxcarbazepine, efavirenz, tenofovir disoproxil fumarate, tipranavir/ritonavir, St. John's wort, and rosuvastatin doses exceeding 10mg; and
16. If member is using antacids they must agree to separate antacid and Epclusa® administration by four hours; and
17. 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; and
18. Prescribing physician must verify that they will work with the member to ensure the member remains adherent to hepatitis C therapies; and
19. Members must be adherent for continued approval. Treatment gaps of therapy longer than 3 days/month will result in denial of subsequent requests for continued therapy.
20. Approvals for treatment regimen initiation for 12 weeks of therapy will not be granted prior to the 10th of a month in order to prevent prescription limit issues from affecting the member's compliance.

Utilization Details of Hepatitis C Medications: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	% COST	COST/ CLAIM
SOFOSBUVIR PRODUCTS						
SOVALDI 400MG TAB	320	105	$9,461,859.18	3.05	29.47%	$29,568.31
Subtotal	**320**	**105**	**$9,461,859.18**	**3.05**	**29.47%**	**$29,568.31**
SOFOSBUVIR/LEDIPASVIR PRODUCTS						
HARVONI 400/90MG TAB	585	246	$19,459,629.97	2.38	60.61%	$33,264.32
Subtotal	**585**	**246**	**$19,459,629.97**	**2.38**	**60.61%**	**$33,264.32**
DACLATASVIR PRODUCTS						
DAKLINZA 60MG TAB	107	36	$2,372,858.81	2.97	7.39%	$22,176.25
Subtotal	**107**	**36**	**$2,372,858.81**	**2.97**	**7.39%**	**$22,176.25**
OMBITASVIR/PARITAPREVIR/RITONAVIR/DASABUVIR PRODUCTS						
VIEKIRA PAK 12.5/75/50/250MG	24	11	$703,879.62	2.18	2.19%	$29,328.32
Subtotal	**24**	**11**	**$703,879.62**	**2.18**	**2.19%**	**$29,328.32**
ELBASVIR/GRAZOPREVIR PRODUCTS						
ZEPATIER 50/100MG	3	1	$48,356.36	3	0.15%	$16,118.79
Subtotal	**3**	**1**	**$48,356.36**	**3**	**0.15%**	**$16,118.79**
RIBAVIRIN PRODUCTS						
RIBAVIRIN TAB 200MG	186	69	$18,041.04	2.7	0.06%	$96.99
RIBASPHERE TAB 200MG	65	25	$7,455.82	2.6	0.02%	$114.70
RIBAVIRIN CAP 200MG	33	10	$5,445.91	3.3	0.02%	$165.03

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	% COST	COST/ CLAIM
MODERIBA TAB 200MG	24	10	$2,515.70	2.4	0.01%	$104.82
RIBASPHERE CAP 200MG	1	1	$96.01	1	0.00%	$96.01
Subtotal	**309**	**107**	**$33,554.48**	**2.89**	**0.11%**	**$108.59**
PEGINTERFERON PRODUCTS						
PEGASYS INJ	4	1	$14,639.56	4	0.05%	$3,659.89
PEG-INTRON KIT 150 RP	2	1	$7,363.10	2	0.02%	$3,681.55
PEGINTRON KIT 150MCG	1	1	$3,677.55	1	0.01%	$3,677.55
Subtotal	**7**	**3**	**$25,680.21**	**2.33**	**0.08%**	**$3,668.60**
TOTAL	**1,355**	**371***	**$32,105,818.63**	**3.65**	**100%**	**$23,694.33**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 09/2016. Last accessed 10/19/2016.
[2] U.S. Food and Drug Administration (FDA). FDA approved Epclusa for treatment of chronic Hepatitis C virus infection. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm508915.htm. Issued 06/28/2016. Last accessed 10/19/2016.
[3] Epclusa® Product Information. Gilead Sciences, Inc. Available online at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf. Last revised 06/2016. Last accessed 10/19/2016.
[4] Lowes, R. FDA Approves Once-Daily Viekira XR for Hepatitis C. *Medscape*. Available online at: http://www.medscape.com/viewarticle/866680. Issued 07/2016. Last accessed 10/19/2016.
[5] AbbVie. AbbVie Receives U.S. FDA Approval of Supplemental New Drug Application for Viekira Pak™ (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets) without Ribavirin in Genotype 1b Chronic Hepatitis C Patients with Compensated Cirrhosis. Available online at: https://news.abbvie.com/news/abbvie-receives-us-fda-approval-supplemental-new-drug-application-for-viekira-pak-ombitasvir-paritaprevir-and-ritonavir-tablets-dasabuvir-tablets-without-ribavirin-in-genotype-1b-chronic-hepatitis-c-patients-with-compensated-cirrhosis.htm. Issued 04/25/2016. Last accessed 10/19/2016.
[6] U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. Available online at: http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm. Issued 10/04/2016. Last accessed 10/19/2016.
[7] AbbVie. AbbVie's Investigational, Pan-Genotypic Regimen of ABT-493 and ABT-530 Shows High SVR Rates in Genotype 1 Hepatitis C Patients Who Failed Previous Therapy with Direct-Acting Antivirals. Available online at: https://news.abbvie.com/news/abbvies-investigational-pan-genotypic-regimen-abt-493-and-abt-530-shows-high-svr-rates-in-genotype-1-hepatitis-c-patients-who-failed-previous-therapy-with-direct-acting-antivirals.htm. Issued 04/15/2016. Last accessed 10/19/2016.
[8] Cara, E. 6 Weeks of Antiviral Treatment May Be Enough Time To Cure Hepatitis C Patients: Study. *Medical Daily*. Available online at: http://www.medicaldaily.com/antiviral-treatment-hepatitis-c-cure-382313. Issued 04/17/2016. Last accessed 10/19/2016.
[9] Lau G, Benhamou Y, Chen G, et al. Efficacy and safety of 3-week response-guided triple direct-acting antiviral therapy for chronic hepatitis C infection: a phase 2, open-label, proof-of-concept study. *Lancet* 2016; 1(2): 97-104.
[10] Achillion Pharmaceuticals Inc. Achillion Announces 100% SVR Reported in Janssen's Phase 2a Trial Evaluating Triple Combination of Odalasvir, AL-335, and Simeprevir for Genotype 1 Treatment-Naive HCV. *GlobeNewswire*. Available online at: https://globenewswire.com/news-release/2016/09/09/870753/0/en/Achillion-Announces-100-SVR-Reported-in-Janssen-s-Phase-2a-Trial-Evaluating-Triple-Combination-of-Odalasvir-AL-335-and-Simeprevir-for-Genotype-1-Treatment-Naive-HCV.html. Issued 09/09/2016. Last accessed 10/19/2016.
[11] American Association For The Study of Liver Diseases (AASLD)/Infectious Diseases Society of America (IDSA). Recommendations for testing, managing, and treating hepatitis C. Available online at: http://www.hcvguidelines.org. Last revised 09/27/2016. Last accessed 10/19/2016.
[12] Viekira XR™ Product Information. AbbVie Inc. Available online at: http://www.rxabbvie.com/pdf/viekiraxr_pi.pdf. Last revised 07/2016. Last accessed 10/20/2016.
[13] Harvoni® Product Information. Gilead Sciences, Inc. Available online at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/harvoni/harvoni_pi.pdf. Last revised 06/2016. Last accessed 10/20/2016.
[14] Olysio™ Product Information. Janssen Therapeutics, LP. Available online at: www.olysio.com/shared/product/olysio/prescribing-information.pdf. Last revised 05/2016. Last accessed 10/20/2016.
[15] Sovaldi® Product Information. Gilead Sciences, Inc. Available online at: www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/sovaldi/sovaldi_pi.pdf. Last revised 08/2015. Last accessed 10/20/2016.
[16] Daklinza™ Product Information. Bristol-Myers Squibb Company. Available online at: http://packageinserts.bms.com/pi/pi_daklinza.pdf. Last revised 04/2016. Last accessed 10/20/2015.
[17] Technivie™ Product Information. AbbVie Inc. Available online at http://www.rxabbvie.com/pdf/technivie_pi.pdf. Last revised 06/2016. Last accessed 10/20/2016.
[18] Zepatier™ Product Information. Merck and Co. Inc. Available online at: http://www.merck.com/product/usa/pi_circulars/z/zepatier/zepatier_pi.pdf. Last revised 01/2016. Last accessed 10/20/2016.
[19] Epclusa® Product Information. Gilead Sciences, Inc. Available online at: http://www.gilead.com/~/media/Files/pdfs/medicines/liver-disease/epclusa/epclusa_pi.pdf. Last revised 06/2016. Last accessed 10/20/2016.

Appendix H

30-Day Notice to Prior Authorize Exondys 51™ (Eteplirsen)

Oklahoma Health Care Authority
December 2016

Duchenne Muscular Dystrophy[1,2,3]

Duchenne muscular dystrophy (DMD) is the most common muscular dystrophy affecting 1 in 3,500 boys born worldwide. DMD clinically manifests in patients age 3 to 7 years, with development of lordosis, a waddling gait, and the Gower's sign. Most patients are wheelchair bound by age 12. DMD remains an incurable illness with a mortality rate of 100%. Death often occurs by age 25, typically from lung disorders.

Most cases of DMD are due to the inheritance of an X-linked recessive mutation characterized by a defective gene for dystrophin (a protein in the muscles). Genetic mutations that disturb the reading frame produce a severely truncated, completely dysfunctional dystrophin protein product or no protein at all. Dystrophin protein is essential to the structural stability of the muscle fibers. Without dystrophin, muscles are susceptible to mechanical injury and undergo repeated cycles of necrosis and regeneration. As the disease progresses, dead muscle fibers are cleared away by macrophages and replaced by fatty and connective tissue elements. This gives a deceptively healthy appearance to the muscle called pseudohypertrophy, especially in the calves and forearms. DMD affects more than the skeletal muscles. Dystrophin is also found in the heart, brain, and smooth muscle. Late-stage cardiac fibrosis can lead to output failure and pulmonary congestion, a common cause of death. Additionally, cardiac fibrosis can include cardiomyopathy and conduction abnormalities, which can cause fatal arrhythmias. Affected children frequently have varying degrees of mild cognitive impairment. However, an occasional child with DMD may have average or above-average intelligence.

Glucocorticoids are the mainstay of treatment for DMD, and are offered for patients 4 years of age and older whose motor skills have plateaued or are declining. The current treatment guidelines from the American Academy of Neurology recommend the use of prednisone or deflazacort. Deflazacort is not available in the United States as it has not been approved by the U.S. Food and Drug Administration (FDA). The current guidelines suggest prednisone should be offered for improving strength and pulmonary function, and may be offered for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age. The current guidelines indicate that deflazacort and prednisone may be equivalent in improving motor function. Other treatments are based on the individual needs of the patient. It is recommended that cardiac and lung function be regularly monitored. Treatments may include angiotensin converting enzyme (ACE) inhibitors and/or beta blockers for patients with ventricular dysfunction. A step-wise sequence of respiratory interventions for patients with DMD is recommended, starting with volume recruitment/deep lung inflation methods and progressing as needed. Calcium and vitamin D supplements are recommended due to risk factors for bone health in these patients. Orthopedic interventions to maintain

function, nutritional consultation, and gentle exercise or physical therapy are also recommended for these patients.

Several investigative treatments for DMD exist and include: gene therapy, exon skipping, ataluren, creatine, deacetylase inhibitors, myostatin inactivation, and cell therapy. In September 2016, the FDA granted an accelerated approval of Exondys 51™ (eteplirsen) for the treatment of patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping. This mutation is present in approximately 13% of patients with DMD. Eteplirsen is the first FDA approved medication for DMD.

Exondys 51™ (Eteplirsen) Product Summary[4]

FDA Approved: September 2016

Indications: Eteplirsen is an antisense oligonucleotide indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication was approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with eteplirsen. A clinical benefit of eteplirsen has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

Dosing:

- Eteplirsen is available as a 50mg/mL injection for intravenous use.
- It is supplied as 100mg/2mL and 500mg/10mL single-dose vials. Dilution is required prior to administration.
- The recommended dosing is 30mg per kilogram of body weight given once weekly. The weekly dose is administered as an intravenous infusion over 35 to 60 minutes.

Mechanism of Action: Eteplirsen is designed to bind to exon 51 of dystrophin pre-messenger ribonucleic acid (mRNA), resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 51 skipping. Exon skipping is intended to allow for production of an internally truncated dystrophin protein.

Contraindications:

- None

Adverse Reactions: The most common adverse reactions during Study 1 of clinical trials with an incidence at least 25% more than placebo include the following:

- Balance Disorder
- Contact Dermatitis
- Vomiting

Because of the small numbers of patients included in the study, these represent crude frequencies that may not reflect the frequencies observed in practice.

In 88 patients who received eteplirsen for up to 208 weeks in clinical studies, the following events were reported in ≥10% of patients:

- Vomiting
- Contusion
- Excoriation
- Arthralgia
- Rash
- Catheter Site Pain
- Upper Respiratory Tract Infection

There have been reports of transient erythema, facial flushing, and elevated temperature occurring on days of eteplirsen infusion.

Use in Special Populations:

- Pregnancy: There are no human or animal data available to assess the use of eteplirsen during pregnancy.
- Lactation: There are no human or animal data to assess the effect of eteplirsen on milk production, the presence of eteplirsen in milk, or the effects of eteplirsen on the breastfed infant.
- Pediatric Use: Eteplirsen is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, including pediatric patients. Intravenous administration of eteplirsen to juvenile male rats once weekly for 10 weeks beginning on postnatal day 14 resulted in renal tubular necrosis at the highest dose tested (900mg/kg) and decreased bone densitometry parameters at all doses. The kidney findings were associated with clinical pathology changes. No effects were observed on the male reproductive system, neurobehavioral development, or immune function. An overall no-effect dose was not identified. Plasma eteplirsen exposure at the lowest dose tested (100mg/kg) was similar to that in humans at the recommended human dose (30mg/kg).
- Geriatric Use: DMD is largely a disease of children and young adults; therefore, there is no geriatric experience with eteplirsen.
- Renal or Hepatic Impairment: Eteplirsen has not been studied in patients with renal or hepatic impairment.

Efficacy: Eteplirsen was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.

- Study 1: Patients were randomized to receive weekly infusions of eteplirsen (30mg/kg, n=4 or 50mg/kg, n=4) or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least six months. There was no significant difference in change in 6MWD between patients treated with eteplirsen and those treated with placebo.
- Study 2: All twelve patients who participated in Study 1 continued treatment with open-label eteplirsen weekly for an additional four years in Study 2. The four patients who had been randomized to placebo were re-randomized 1:1 to eteplirsen 30mg/kg/week or 50mg/kg/week such that there were six patients on each dose.

Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with eteplirsen, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of eteplirsen compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with eteplirsen was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with eteplirsen in Study 1, it is not possible to estimate dystrophin production in response to eteplirsen in Study 1. No data was provided in the prescribing information on the 6MWT for Study 2.

- Study 3: There were thirteen patients treated with open-label eteplirsen (30mg/kg) weekly for 48 weeks. Each patient had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least six months. Dystrophin levels in muscle tissue were assessed by Western blot. In the twelve patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with eteplirsen ($p<0.05$). The median increase after 48 weeks was 0.1%.

Cost:

Medication	Cost Per mL	Cost Per 30 Days of Therapy*
Exondys 51™ (eteplirsen)	**$800.00**	**$32,000.00 - $160,000.00**

Cost does not reflect rebated price or net cost. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
*Cost per 30 days of therapy given as a range from approximate weight at age of onset to young adulthood based on recommended dosing.

Market News and Updates[3,5,6,7,8,9,10,11,12,13,14,15]

Guideline Update(s):

- **February 2016:** A practice guideline update summary: Corticosteroid Treatment of Duchenne Muscular Dystrophy reported by the Guideline Development Subcommittee of the American Academy of Neurology (AAN) was published in the journal of *Neurology*. This update to the 2005 AAN guideline recommends that in children with DMD, prednisone should be used to improve strength and pulmonary function. Prednisone may be used for improving timed motor function, reducing the need for scoliosis surgery, and delaying cardiomyopathy onset by 18 years of age. Deflazacort may be used for improving strength and timed motor function, as well as delaying age at loss of ambulation by 1.4 to 2.5 years. Additionally, deflazacort may be used for improving pulmonary function, reducing the need for scoliosis surgery, delaying cardiomyopathy onset, and increasing survival at 5 to 15 years of follow-up. The AAN found insufficient evidence to establish a difference in effect on cardiac function with use of prednisone or deflazacort. The AAN found that prednisone may be associated with increased weight gain in the first years of treatment compared with deflazacort.

Deflazacort may be associated with increased risk of cataracts compared with prednisone. As previously noted, deflazacort is not available in the United States.

Other News:

- **January 2016:** The FDA declined approval of BioMarin Pharmaceutical, Inc.'s new drug application (NDA) for drisapersen (Kyndrisa™). Drisapersen is an antisense oligonucleotide that induces exon skipping to provide a molecular patch for dystrophin transcripts produced by certain mutated dystrophin genes. Specifically, it is for the treatment of DMD patients amenable to exon 51 skipping. The FDA concluded, after its Peripheral and Central Nervous System (PCNS) Drugs Advisory Committee meeting in November 2015, that the research doesn't clearly provide substantial evidence of the drug's effectiveness or that the drug has an acceptable risk-benefit profile. In biomarker studies using Western blot, post-treatment dystrophin levels remained very similar to pretreatment levels. BioMarin reports ongoing drisapersen extension studies will continue, as will the ongoing clinical trials for other exon-skipping oligonucleotides, while it explores next steps for this application.
- **April 2016:** The FDA PCNS Drugs Advisory Committee met to discuss the NDA for eteplirsen, submitted by Sarepta Therapeutics, Inc., for the treatment of patients with DMD amenable to exon 51 skipping. The meeting attendees included more than a thousand public attendees and more than four hours of comments from patients, families, advocates, scientists, and legislators. The FDA review found little support for efficacy. The FDA also pointed out several possible issues with the use of historical controls for comparison to eteplirsen-treated patients. For example, the mean age of steroid start was over one year later in the control group than in eteplirsen-treated patients (age 6.4 years vs. 5.2 years). There were differences in the steroid regimens used as well. The FDA noted several other issues in the clinical trials that may affect the reliability of the results. Overall, the statistical conclusion was that the data did not provide statistical evidence to support the efficacy in subjects who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. The committee vote was split, seven members found no evidence that eteplirsen was clinically effective in treating DMD (vs. three in favor and three abstentions), and seven members found that the drug did not produce dystrophin at a level likely to result in clinical benefit (vs. six in favor). After the meeting, the FDA delayed its decision and requested additional data.
- **September 2016:** The additional data requested by the FDA for eteplirsen showed a mean increase in dystrophin to just 0.2% to 0.3% of normal. The main FDA scientific reviewers all opposed approval of eteplirsen, but Janet Woodcock, MD, director of the FDA's Center for Drug Evaluation and Research, overruled them. Dr. Woodcock suggested that the extremely small increase in dystrophin might conceivably translate to clinical benefit. She further indicated that considering the life-threatening nature of the disease and the lack of reasonable alternative treatments, the FDA should exercise "the greatest flexibility possible" under its statutory authority in considering eteplirsen's efficacy. The internal FDA review staff appealed to Commissioner Robert Califf, MD, who upheld Dr. Woodcock's decision to approve eteplirsen. However, Dr. Califf called for a retraction of the eteplirsen study stating, "In view of the scientific deficiencies identified

in this analysis, I believe it would be appropriate to initiate a dialogue that would lead to a formal correction or retraction (as appropriate) of the published report." With the approval, the manufacturer was told to conduct a randomized trial to verify the clinical benefit of eteplirsen. Sarepta was given a deadline of May 2021 for submission of its results. The FDA could withdraw approval of the drug if the trial fails to show clinical benefit. Controversy continues as there are concerns that demonstrating only slight differences in laboratory testing, but utilizing the patient community to gain FDA approval may be setting a precedent for future approvals of this type. Due to the high cost and efficacy concerns associated with eteplirsen, insurance companies are divided. Cigna and Blue Shield have agreed to cover it; however, Anthem is calling the drug investigational and will not be covering it.

Pipeline:

- **Ataluren:** On December 23, 2014, PTC Therapeutics announced the beginning of a rolling NDA submission for ataluren (Translarna®), a new therapy for DMD. The rolling submission allows manufacturers to submit completed portions of the NDA for review by the FDA on an ongoing basis, potentially avoiding delays in the approval process. Ataluren is a protein restoration therapy for patients with genetic diseases caused by a nonsense mutation. It is estimated that 13% of boys with DMD have a nonsense mutation in the dystrophin gene. Ataluren enables a read-through of the premature stop codon in the mRNA of DMD patients, leading to production of full-length functional dystrophin protein. In February 2016, the FDA issued PTC a Refuse to File (RTF) letter. The FDA stated that the NDA for ataluren was not sufficiently complete to allow a substantial review. By July 2016, PTC announced they submitted an appeal to the FDA via the formal dispute process. This would allow continuing discussions about the RTF decision with the next level of FDA management. Within the dispute resolution process, PTC indicated willingness to consider multiple paths to advance a potential FDA approval, including the possibility of conducting an additional clinical trial under accelerated approval. In October 2016, PTC announced the FDA denied the company's first appeal of the RTF. The company intends to escalate its appeal to the next supervisory level of the FDA. Additionally, the company anticipates that multiple cycles of appeals to progressively higher levels of the FDA may be required. PTC states that a full and fair review of the data by the FDA is needed to properly assess ataluren, including an advisory committee meeting that allows clinical experts and representatives of the patient community to express their views on ataluren for the treatment of DMD. Ataluren initially received marketing authorization in Europe in August 2014. The authorization is subject to annual renewal and certain conditions. Ataluren is currently available to patients in more than 20 countries outside of the United States.
- **Deflazacort:** On January 19, 2015, Marathon Pharmaceuticals announced that the FDA had given deflazacort, an oxazoline derivative of prednisolone, a fast track designation for the treatment of patients with DMD. The FDA ruling also makes the drug eligible for the accelerated approval and priority review process. The drug was previously granted orphan drug status for the treatment of patients with DMD. Marathon filed two NDA's

(one for immediate-release tablets and one for oral suspension) in August 2016. A decision by the FDA is anticipated in February 2017. If approved, deflazacort would be the first FDA approved oral medication for DMD. The NDA filing included data from studies showing that deflazacort improved muscle strength and other functional outcomes in patients with DMD regardless of genetic etiology. During the FDA review process, Marathon is making deflazacort available to patients in the United States, at no cost, through Access DMD™, an expanded access program (EAP) operating under FDA authorization. Although it has never been approved in the United States, deflazacort is widely prescribed in Canada and a number of European countries.

- **SRP-4053:** Sarepta Therapeutics reports there are current Phase 1 and 2 clinical trials in Europe for SRP-4053, for DMD patients amenable to exon 53 skipping. They also report a candidate for exon 45 skipping, SRP-4045, has entered early clinical development in the United States. According to Sarepta, 8% of DMD patients may be amenable to exon 53 skipping and another 8% may be amenable to exon 45 skipping. They report having other drug candidates in discovery and preclinical development that are designed to skip exons 44, 52, 50, 43, 55, 8, and 35.

Recommendations

The College of Pharmacy recommends the prior authorization of Exondys 51™ (eteplirsen) with the following criteria:

Exondys 51™ (Eteplirsen) Approval Criteria:

1. An FDA approved diagnosis of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amendable to exon 51 skipping; and
2. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

[1] Nair DG. Dystrophinopathies. *Medscape*. Available online at: http://emedicine.medscape.com/article/1173204-overview. Last revised 10/05/2016. Last accessed 11/14/2016.
[2] Darras BT. Treatment of Duchenne and Becker Muscular Dystrophy. *Up-To-Date*. Available online at: http://www.uptodate.com/contents/treatment-of-duchenne-and-becker-muscular-dystrophy?source=search_result&search=duchenne&selectedTitle=2%7E69#H4016787759. Last revised 10/27/2016. Last accessed 11/14/2016.
[3] Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy. *Neurology* 2016; 86(5): 465-472.
[4] U.S. Food and Drug Administration (FDA). Exondys 51™ Prescribing Information. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206488lbl.pdf. Last revised 09/2016. Last accessed 11/11/2016.
[5] Anderson P. FDA Declines Approval for Drisapersen in DMD. *Medscape*. Available online at: http://www.medscape.com/viewarticle/857406. Last revised 01/18/2016. Last accessed 11/16/2016.
[6] U.S. Food and Drug Administration (FDA). FDA Briefing Document: Peripheral and Central Nervous System Drugs Advisory Committee Meeting. Available online at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm497063.pdf. Issued 04/25/2016. Last accessed 11/14/2016.
[7] Kesselheim AS, Avorn J. Approving a Problematic Muscular Dystrophy Drug: Implications for FDA Policy. *JAMA*. Published online October 24, 2016. doi:10.1001/jama.2016.16437.
[8] Ault A. Duchenne Drug Approval Still Leaves Bad Taste for Many. *Medscape*. Available online at: http://www.medscape.com/viewarticle/871383#vp_1. Issued 11/03/2016. Last accessed 11/14/2016.
[9] FDA commissioner calls for retraction of eteplirsen study. *Pharmacy Practice News*. Available online at: https://pharmacist.com/fda-commissioner-calls-retraction-eteplirsen-study. Issued 09/23/2016. Last accessed 11/14/2016.
[10] Buck M. New Drugs for Children in the Food and Drug Administration Pipeline. *Medscape*. Available online at: http://www.medscape.com/viewarticle/842142_3. Last revised 02/2015. Last accessed 11/11/2016.
[11] PTC Therapeutics, Inc. News Release. PTC Receives Refuse to File Letter from FDA for Translarna™ (ataluren). Available online at: http://ir.ptcbio.com/releasedetail.cfm?ReleaseID=956451. Issued 02/23/2016. Last accessed 11/22/2016.
[12] PTC Therapeutics, Inc. News Release. PTC Therapeutics Provides Regulatory Update on Translarna™ (ataluren). Available online at: http://ir.ptcbio.com/releasedetail.cfm?ReleaseID=980974. Issued 07/25/2016. Last accessed 11/22/2016.
[13] PTC Therapeutics, Inc. News Release. PTC Therapeutics Provides Regulatory Update on Translarna™ (ataluren) for Nonsense Mutation Duchenne Muscular Dystrophy. Available online at: http://ir.ptcbio.com/releasedetail.cfm?releaseid=993823. Issued 10/17/2016. Last accessed 11/22/2016.
[14] Marathon Pharmaceuticals, LLC. FDA Accepts Marathon Pharmaceuticals' New Drug Applications for Deflazacort for the Treatment of Duchenne Muscular Dystrophy and Grants Priority Review. Available online at: http://marathonpharma.com/news/2016/08/fda-accepts-marathon-pharmaceuticals-new-drug-applications-for-deflazacort-for-the-treatment-of-duchenne-muscular-dystrophy-and-grants-priority-review/. Issued 08/10/2016. Last accessed 11/16/2016.
[15] Sarepta Therapeutics. Our Pipeline: Exon-Skipping For Duchenne. Available online at: https://www.sarepta.com/pipeline/exon-skipping-duchenne. Last accessed 11/11/2016.

Appendix I

Fiscal Year 2016 Annual Review of Otic Anti-Infective Medications and 30-Day Notice to Prior Authorize Otovel® (Ciprofloxacin/Fluocinolone Acetonide)

Oklahoma Health Care Authority
December 2016

Current Prior Authorization Criteria

Otic Anti-Infective Medication Tier-2 Approval Criteria:

1. Member must have an adequate 14-day trial of at least two Tier-1 medications; or
2. Approval may be granted if there is a unique FDA approved indication not covered by Tier-1 medications or infection by an organism not known to be covered by any of the Tier-1 medications.

Otic Anti-Infective Medication Special Prior Authorization (PA) Approval Criteria:

1. Diagnosis of acute otitis externa; and
2. Recent trials (within the last six months) with all other commonly used topical otic anti-infectives that have failed to resolve infection; or
3. Allergy to all available products and failure of acetic acid alone.

Otic Anti-Infective Medications		
Tier-1	**Tier-2**	**Special PA**
acetic acid (VoSol®, Acetasol®)	chloroxylenol/benzocaine/HC (Trioxin®)	acetic acid/HC (Acetasol® HC, VoSol® HC)
ciprofloxacin/dexamethasone (Ciprodex®)	ciprofloxacin (Cetraxal®)	
ciprofloxacin/HC (Cipro® HC)	finafloxacin (Xtoro™)	
neomycin/colistin/HC/ thonzonium (Coly-Mycin® S)	neomycin/polymyxin B/HC (Cortisporin®, Pediotic®)	
	ofloxacin (Floxin® Otic)	

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. HC = hydrocortisone

Utilization of Otic Anti-Infective Medications: Fiscal Year 2016

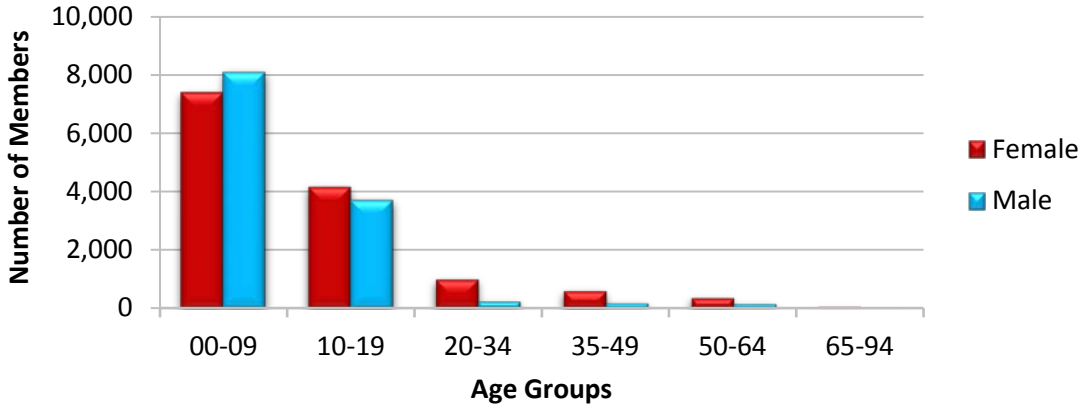
Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	25,630	32,859	$1,373,302.34	$41.79	$4.00	270,936	343,496
2016	25,936	31,905	$4,568,068.51	$143.18	$12.80	266,115	356,759
% Change	**1.20%**	**-2.90%**	**232.60%**	**242.60%**	**220.00%**	**-1.80%**	**3.90%**
Change	**306**	**-954**	**$3,194,766.17**	**$101.39**	**$8.80**	**-4,821**	**13,263**

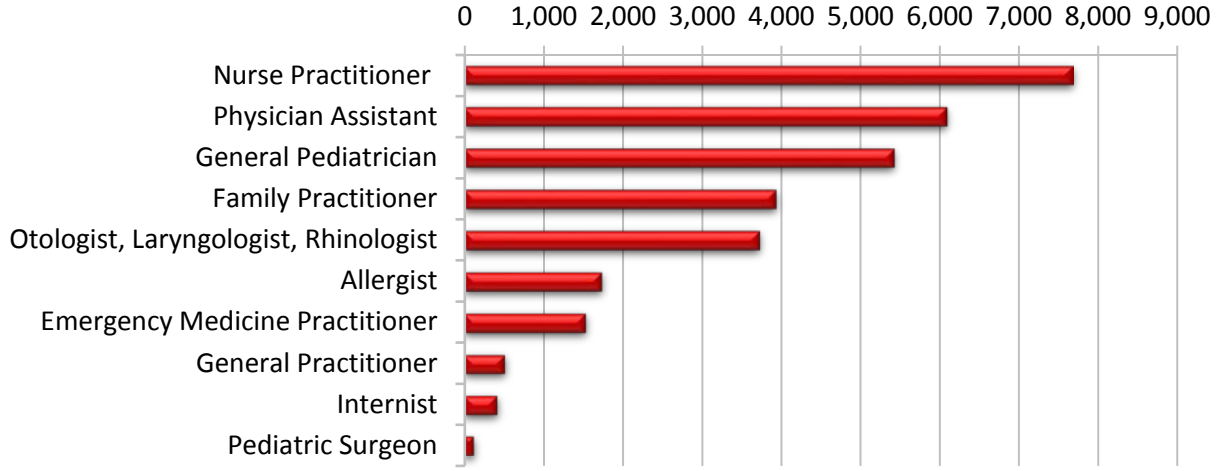
*Total number of unduplicated members. Costs do not reflect rebated prices or net costs.

- Some Tier-1 products are supplementally rebated products; therefore, the cost increase shown in the previous table does not reflect the net cost increase.

Demographics of Members Utilizing Otic Anti-Infective Medications



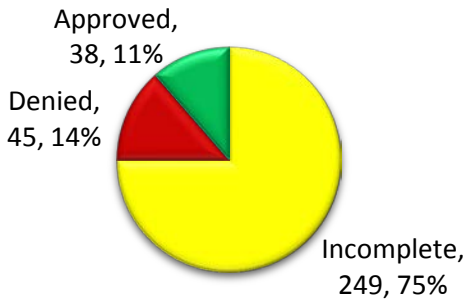
Top Prescriber Specialties of Otic Anti-Infective Medications by Number of Claims



Prior Authorization of Otic Anti-Infective Medications

There were 332 prior authorization requests submitted for otic anti-infective medications during fiscal year 2016. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3]

Anticipated Patent Expiration(s):

- Ciprodex® (ciprofloxacin/dexamethasone): June 2025
- Xtoro™ (finafloxacin): August 2031

Guideline Update(s):

- **February 2016:** The Clinical Practice Guideline: Otitis Media with Effusion (Update) was published in the supplemental issue of *Otolaryngology-Head and Neck Surgery*. The changes from the previous guidelines include enhanced emphasis on patient education and shared decision making, a new algorithm to clarify action statement relationships, and new, expanded recommendations for the diagnosis and management of otitis media with effusion (OME). This publication included thirteen key action statements with seven of them being rated as strong recommendations. A strong recommendation is defined as one in which the benefits of the recommended approach clearly exceed the harms (or, in the case of a strong negative recommendation, that the harms clearly exceed the benefits) and that the quality of the supporting evidence is high (grade A or B). In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms. Grade A includes a systematic review of randomized trials and grade B includes randomized trials or observational studies with dramatic effects or highly consistent evidence. The key action statements that are strongly recommended include the following:
    - The clinician should document the presence of middle ear effusion with pneumatic otoscopy when diagnosing OME in a child.
    - The clinician should perform pneumatic otoscopy to assess for OME in a child with otalgia, hearing loss, or both.
    - Clinicians should obtain tympanometry in children with suspected OME for whom the diagnosis is uncertain after performing (or attempting) pneumatic otoscopy.
    - Clinicians should manage the child with OME who is not at risk with watchful waiting for three months from the date of effusion onset (if known) or three months from the date of diagnosis (if onset is unknown).

  The key action statements that are strongly recommended against include the following:
    - Clinicians should recommend against using intranasal steroids or systemic steroids for treating OME.
    - Clinicians should recommend against using systemic antibiotics for treating OME.
    - Clinicians should recommend against using antihistamines, decongestants, or both for treating OME.

  The publication indicates that these recommendations should provide primary care physicians and other health care providers with assistance in managing children with OME.

News:

- **July 2015:** The U.S. Food and Drug Administration (FDA) announced its intention to take enforcement action against companies that manufacture and/or distribute certain unapproved prescription ear drop products (known as otic products) labeled to relieve

ear pain, infection, and inflammation. The unapproved prescription ear drops contain active ingredients such as benzocaine and hydrocortisone, and have not been evaluated by the FDA for safety, effectiveness, and quality. The FDA reports that the labels on these products do not disclose that they lack FDA approval, and health care professionals may not be aware of their unapproved status. The FDA's action stems from concerns that patients taking unapproved drugs may be at greater risk because there is no proven safety or effectiveness information. Further, these products may be contaminated or manufactured incorrectly, which could result in patients receiving the wrong dose, even when administered according to the labeled directions for use. The FDA informed the companies that they must stop manufacturing these unapproved prescription otic products or be subject to enforcement actions, including seizure, injunction, and/or criminal proceedings. The unapproved products have been removed from the SoonerCare tier chart in the recommendations section of this report and will no longer be covered by SoonerCare. Unapproved prescription otic drug products containing the following ingredients are covered by this action:

- benzocaine
- benzocaine and antipyrine
- benzocaine, antipyrine, and zinc acetate
- benzocaine, chloroxylenol, and hydrocortisone
- chloroxylenol and pramoxine
- chloroxylenol, pramoxine, and hydrocortisone

Otovel® (Ciprofloxacin/Fluocinolone Acetonide) Product Summary[4]

FDA Approved: April 2016

Indications: Otovel® (ciprofloxacin/fluocinolone acetonide) is a combination of ciprofloxacin, a fluoroquinolone antibacterial, and fluocinolone acetonide, a corticosteroid, indicated for the treatment of acute otitis media with tympanostomy tubes (AOMT) in pediatric patients (age 6 months of age and older) due to *Staphylococcus aureus, Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.

Dosing:

- Otovel® is available as an otic solution containing ciprofloxacin 0.3% and fluocinolone acetonide 0.025%.
- It is supplied in single-dose, preservative-free vials containing 0.25mL of solution. Fourteen single-dose vials are packaged in a protective foil pouch contained in a carton.
- The contents of one single-dose vial (0.25mL) are to be instilled into the affected ear canal twice daily for seven days.
- It is recommended that the patient or caregiver warm the otic solution by holding the vial in the hand for 1 to 2 minutes before instilling it in the ear, to avoid dizziness.

Mechanism of Action:

- Ciprofloxacin, a fluoroquinolone antibiotic, interferes with enzyme deoxyribonucleic acid (DNA) gyrase, which is needed for the synthesis of bacterial DNA.

- Fluocinolone acetonide, a corticosteroid, inhibits the local biosynthesis of prostaglandins, which explains part of its anti-inflammatory efficacy. At the cellular level, corticosteroids induce peptides called lipocortins. Lipocortins antagonize phospholipase A2, an enzyme which causes the breakdown of leukocyte lysosomal membranes to release arachidonic acid. This action decreases the subsequent formation and release of endogenous inflammatory mediators including prostaglandins, kinins, histamine, liposomal enzymes, and the complement system.

Contraindications:

- Known hypersensitivity to fluocinolone acetonide or other corticosteroids, ciprofloxacin or other quinolones, or to any other components of Otovel®.
- Viral infections of the external ear canal, including varicella and herpes simplex infections and fungal otic infections.

Warnings and Precautions:

- Hypersensitivity Reactions: Ciprofloxacin/fluocinolone acetonide should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, angioedema (including laryngeal, pharyngeal, or facial edema), airway obstruction, dyspnea, urticaria, and itching.
- Potential for Microbial Overgrowth with Prolonged Use: Prolonged use of ciprofloxacin/fluocinolone acetonide may result in overgrowth of non-susceptible bacteria and fungi. If the infection is not improved after one week of treatment, it is recommended that cultures should be obtained to guide further treatment. If such infections occur, it is recommended to discontinue use of ciprofloxacin/fluocinolone acetonide and institute alternative therapy.
- Continued or Recurrent Otorrhea: If otorrhea persists after a full course of therapy, or if two or more episodes of otorrhea occur within six months, further evaluation is recommended to exclude an underlying condition such as cholesteatoma, foreign body, or a tumor.

Adverse Reactions: The most common adverse reactions that occurred in up to 5.4% of patients during clinical trials include:

- Otorrhea
- Excessive Granulation Tissue
- Ear Infection
- Ear Pruritus
- Tympanic Membrane Disorder
- Auricular Swelling
- Balance Disorder

Use in Special Populations:

- Pregnancy: Ciprofloxacin/fluocinolone acetonide is negligibly absorbed following otic administration and maternal use is not expected to result in fetal exposure to ciprofloxacin and fluocinolone acetonide.

- Lactation: Ciprofloxacin/fluocinolone acetonide is negligibly absorbed following otic administration and breastfeeding is not expected to result in infant exposure to ciprofloxacin and fluocinolone acetonide.
- Pediatric Use: Ciprofloxacin/fluocinolone acetonide has been studied in patients as young as 6 months of age in adequate and well-controlled clinical trials. No major differences in safety and effectiveness have been observed between adult and pediatric patients.
- Geriatric Use: Clinical studies of ciprofloxacin/fluocinolone acetonide did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Efficacy: Two Phase 3 multicenter, randomized, double-blind, active-controlled trials were conducted in 662 pediatric patients in total (6 months to 12 years of age) with AOMT, to assess the efficacy and safety of Otovel® compared to ciprofloxacin otic solution and to fluocinolone acetonide otic solution (Trial 1 and Trial 2). The primary endpoint was time to cessation of otorrhea. In both trials, the Otovel® treatment arms showed significantly shorter times to cessation of otorrhea in comparison to both the ciprofloxacin and fluocinolone acetonide alone arms demonstrating the contribution of both components of Otovel®.

- Trial 1: In the Otovel® treatment arm, 78.6% of the patients had cessation of otorrhea by Day 22. In the ciprofloxacin and fluocinolone treatment arms, the percentage of patients with cessation of otorrhea at Day 22 was 67.0% and 48.2% respectively. Additionally, in the Otovel® arm the median time to cessation was 3.75 days. In the ciprofloxacin arm, the median time to cessation was 7.69 days.
- Trial 2: In the Otovel® treatment arm, 78.4% of the patients had cessation of otorrhea by Day 22. In the ciprofloxacin and fluocinolone treatment arms, the percentage of patients with cessation of otorrhea at Day 22 was 68.8% and 43.5% respectively. Additionally, in the Otovel® arm the median time to cessation was 4.94 days. In the ciprofloxacin arm, the median time to cessation was 6.83 days.
- The median time to cessation was not estimable for the fluocinolone arm due to the number of patients without cessation of otorrhea at 22 days being greater than the number of patients with cessation of otorrhea.

Cost Comparison:

Medication	Cost per Vial or mL	Cost per Treatment
Otovel® (ciprofloxacin/fluocinolone 0.3%/0.025%)	**$14.14**	**$197.96**
Ciprodex® (ciprofloxacin/dexamethasone 0.3%/0.1%)	$24.86	$186.45
Cipro® HC (ciprofloxacin/hydrocortisone 0.2%/1%)	$25.16	$251.60
Coly-Mycin® S (colistin/neomycin/thonzonium/hydrocortisone)	$16.69	$166.90

Costs do not reflect rebated prices or net costs.
Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendations

The College of Pharmacy recommends the placement of Otovel® (ciprofloxacin/fluocinolone 0.3%/0.025%) into Tier-2 of the Otic Anti-Infective Medications Product Based Prior Authorization category (PBPA). Current Tier-2 criteria for this category will apply.

Otic Anti-Infectives Medications*		
Tier-1	**Tier-2**	**Special PA**
acetic acid (VoSol®, Acetasol®)	ciprofloxacin (Cetraxal®)	acetic acid/HC (Acetasol® HC, VoSol® HC)
ciprofloxacin/dexamethasone (Ciprodex®)	**ciprofloxacin/fluocinolone (Otovel®)**	
ciprofloxacin/HC (Cipro® HC)	finafloxacin (Xtoro™)	
neomycin/colistin/HC/ thonzonium (Coly-Mycin® S)	neomycin/polymyxin B/HC (Cortisporin®, Pediotic®)	
	ofloxacin (Floxin® Otic)	

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable; HC = hydrocortisone
*The Otic Anti-infective Medications tier chart was updated to reflect the FDA recommendations to remove unapproved products.

Utilization Details of Otic Anti-Infective Medications: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
TIER-1 PRODUCTS						
CIPRODEX SUS 0.3-0.1%	21,580	17,495	$3,999,148.34	1.23	$17.15	$185.32
ACETIC ACID SOL 2% OTIC	489	454	$14,386.38	1.08	$0.98	$29.42
CIPRO HC SUS OTIC	335	327	$85,485.17	1.02	$18.55	$255.18
CORTISPORIN SUS -TC OTIC	325	318	$57,485.88	1.02	$16.31	$176.88
COLY-MYCIN S SUS OTIC	177	174	$24,164.40	1.02	$12.59	$136.52
TIER-1 SUBTOTAL	**22,906**	**18,768**	**$4,180,670.17**	**1.22**	**$16.21**	**$182.51**
TIER-2 PRODUCTS						
NEO/POLY/HC SOL 1% OTIC	4,657	4,409	$185,617.37	1.06	$3.47	$39.86
NEO/POLY/HC SUS 1% OTIC	3,863	3,664	$155,689.06	1.05	$3.83	$40.30
OFLOXACIN DRO 0.3% OTIC	479	462	$46,091.91	1.04	$9.90	$96.23
TIER-2 SUBTOTAL	**8,999**	**8,535**	**$387,398.34**	**1.05**	**$3.92**	**$43.05**
TOTAL	**31,905**	**25,936***	**$4,568,068.51**	**1.23**	**$12.80**	**$143.18**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- Some Tier-1 products are supplementally rebated products; therefore, the Tier-1 cost shown does not reflect the Tier-1 net cost.
- Neomycin/polymyxin B/hydrocortisone solution and suspension were moved to Tier-2 of the Otic Anti-Infective Medications Product Based Prior Authorization category in fiscal year 2016 (FY16). This change was implemented in June 2016. Therefore, the majority of utilization for FY16 occurred when these two medications were Tier-1 products. The FY16

utilization is shown under the Tier-2 products in the chart above, to reflect the current tier placement.

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[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?resetfields=1. Last revised 09/2016. Last accessed 11/08/2016.

[2] Clinical Practice Guideline: Otitis Media with Effusion (Update). *Otolaryngology Head Neck Surgery*. February 2016; 154 (suppl 1):S1-S41. Available online at: http://www.entnet.org/content/clinical-practice-guideline-otitis-media-effusion-ome. Issued 02/2016. Last accessed 11/2016.

[3] U.S. Food and Drug Administration (FDA) News Release: FDA takes action against unapproved prescription ear drop products. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm453348.htm. Issued 07/01/2015. Last accessed: 11/14/2016.

[4] Otovel® Prescribing Information. Arbor Pharmaceuticals, LLC. Available online at: https://www.otovel.com/hcp. Last revised 04/2016. Last accessed 11/11/2016.

Appendix J

Fiscal Year 2016 Annual Review of Maintenance Asthma & Chronic Obstructive Pulmonary Disease (COPD) Medications & 30-Day Notice to Prior Authorize Cinqair® (Reslizumab) and Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate)

Oklahoma Health Care Authority
December 2016

Current Prior Authorization Criteria

Advair®, Symbicort®, and Dulera® Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); or
2. An FDA approved diagnosis of asthma:
    a. Medication must be indicated for member's age; and
    b. Member must have used an inhaled corticosteroid (ICS) product for at least one month immediately prior to request for authorization; and
    c. Member's asthma must be considered uncontrolled by prescriber:
        i. Member requires rescue inhaler more than two days per week for reasons other than prevention of exercise induced bronchospasms; or
        ii. Member requires oral systemic corticosteroids; or
    d. Clinical situation warranting initiation with combination therapy due to severity of asthma.

Anoro® Ellipta® (Umeclidinium/Vilanterol) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); and
3. A patient-specific, clinically significant reason why the member cannot use Tier-1 long-acting beta$_2$ agonist (LABA) and long-acting muscarinic antagonist (LAMA) individual components.

Daliresp® (Roflumilast) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) with history of chronic bronchitis; and
2. Forced expiratory volume (FEV) less than or equal to 50% of predicted; and
3. Inadequately controlled symptoms on long-acting beta$_2$ agonist (LABA) therapy (must have three or more claims for a LABA in the previous six months).

Stiolto® Respimat® (Tiotropium/Olodaterol) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); and
3. A patient-specific, clinically significant reason why the member cannot use Tier-1 long-acting beta$_2$ agonist (LABA) and long-acting muscarinic antagonist (LAMA) individual components.

Arnuity™ Ellipta® (Fluticasone Furoate) Approval Criteria:

1. An FDA approved diagnosis of asthma; and
2. Member must be 12 years of age or older; and
3. A patient-specific, clinically significant reason why Flovent® (fluticasone propionate) is not an option for the member.

Breo® Ellipta® (Fluticasone Furoate/Vilanterol) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) or chronic bronchitis and/or emphysema associated with COPD; or
2. An FDA approved diagnosis of asthma in patients 18 years and older; and
3. Trials of Advair® and Symbicort®, consisting of at least 30 days each within the last 90 days that did not adequately control COPD or asthma symptoms.

Spiriva® Respimat® (Tiotropium Bromide Soft Mist Inhaler) Approval Criteria for Asthma Diagnosis:

1. Member must have an FDA approved diagnosis of asthma; and
2. Member must be 12 years of age or older; and
3. Member must have used a high-dose inhaled corticosteroid and long-acting $beta_2$ agonist (ICS/LABA) product for at least one month immediately prior to request for authorization; and
4. Member must have had a trial of a leukotriene receptor antagonist for at least one month in the last 90 days; and
5. Member must have a history of exacerbations despite required trials; and
6. Member must remain on an ICS or ICS/LABA while on tiotropium therapy; and
    a. Member's asthma must be considered uncontrolled by prescriber:
        i. Member requires rescue inhaler more than two days per week for reasons other than prevention of exercise induced bronchospasms; or
        ii. Member requires oral systemic corticosteroids; or
    b. Clinical situation warranting initiation of tiotropium therapy in addition to an ICS/LABA due to severity of asthma; and
7. A clinically significant reason the member is unable to use Spiriva® Handihaler® (tiotropium) which does not require prior authorization.

Nucala® (Mepolizumab Injection) Approval Criteria:

1. An FDA approved indication for add-on maintenance treatment of patients with severe eosinophilic phenotype asthma; and
2. Member must be age 12 years or older; and
3. Member must have a baseline blood eosinophil count of 150 cell/mcL or greater within the last six weeks of initiation of dosing; and
4. Member must have had at least two asthma exacerbations requiring systemic corticosteroids within the last 12 months or require daily systemic corticosteroids despite compliant use of high-dose inhaled corticosteroid (ICS) plus at least one additional controller medication; and
5. Member must have failed a high-dose ICS (≥880 mcg/day fluticasone propionate or equivalent daily dose or ≥440 mcg/day in ages 12 to 17 years) used compliantly for at

least the past 12 months (for ICS/LABA combination products, the highest approved dose meets this criteria); and

6. Member must have failed at least one other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past three months; and
7. Nucala® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
8. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval; and
9. A quantity limit of 1 vial per 28 days will apply.

Utibron™ Neohaler® (Indacaterol/Glycopyrrolate) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); and
3. A patient-specific, clinically significant reason why the member cannot use Tier-1 long-acting beta$_2$ agonist (LABA) and long-acting muscarinic antagonist (LAMA) individual components.

Xolair® (Omalizumab) Approval Criteria for Asthma:

1. Member must be between 6 and 75 years of age; and
2. Member must have a diagnosis of severe persistent asthma [as per National Asthma Education and Prevention Program (NAEPP) guidelines]; and
3. Member must have a positive skin test to at least one perennial aeroallergen. Positive perennial allergens must be listed on the prior authorization request; and
4. Member must have a pretreatment serum IgE level between 30 and 1,300 IU/mL (depending on member age); and
5. Member's weight must be between 30kg and 150kg; and
6. Member must have been on high-dose inhaled corticosteroids (ICS) (as per NAEPP guidelines) for at minimum the past three months; and
7. Prescribed Xolair® dose must be an FDA approved regimen per Xolair® prescribing information; and
8. Xolair® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
9. Member must have been in the emergency room (ER) or hospitalized, due to an asthma exacerbation, twice in the past six months (date of visits must be listed on the prior authorization request), or member must have been determined to be dependent on systemic steroids to prevent serious exacerbations; and
10. Both the prior authorization request form and statement of medical necessity form must be submitted for processing.
11. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval.

Xolair® (Omalizumab) Approval Criteria for Chronic Idiopathic Urticaria:

1. Member must be 12 years of age or older; and
2. Other forms of urticaria must be ruled out; and
3. Other potential causes of urticaria must be ruled out; and
4. Member must have an Urticaria Activity Score (UAS) ≥16; and
5. Prescriber must be an allergist, immunologist, dermatologist, or be an advanced care practitioner with a supervising physician that is an allergist, immunologist, or dermatologist; and
6. Member must have tried and failed to obtain relief from other treatments including the following trials within the last six months (member must fail all classes unless contraindicated):
    a. At least two different H_1-antihistamine trials for a minimum duration of two weeks each:
        i. One trial must be a second generation antihistamine dosed four times the maximum FDA dose; and
        ii. One trial must be tried in combination with an H_2-antihistamine; and
    b. A 4-week trial of a leukotriene receptor antagonist in combination with a 4-week trial of doxepin 10 to 50mg daily; and
7. Initial dosing will only be approved for 150mg every four weeks. If inadequate results at this dose, then the dose may be increased to 300mg every four weeks.

Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonist (LAMA)	
Tier-1	**Tier-2**
Long Acting Beta$_2$ Agonists (LABA)	
Foradil® (formoterol aerosolized powder)	Brovana® (arformoterol nebulizer solution)
Serevent® (salmeterol inhalation powder)	Perforomist® (formoterol nebulizer solution)
	Arcapta® (indacaterol inhalation powder)
	Striverdi® Respimat® (olodaterol inhalation spray)
Long Acting Muscarinic Antagonists (LAMA)	
Spiriva® (tiotropium inhalation powder)	Tudorza® (aclidinium inhalation powder)
	Seebri™ Neohaler® (glycopyrrolate)
	Spiriva® Respimat® (tiotropium soft mist inhaler)*
	Incruse® Ellipta® (umeclidinium inhalation powder)

Combination agents that contain a Tier-1 ingredient qualify as Tier-1 agents.
*See Spiriva® Respimat® (tiotropium soft mist inhaler) Approval Criteria for Asthma. Respimat® for COPD diagnosis requires reason for use in place of the Handihaler®.

Long-Acting Beta$_2$ Agonists (LABA) & Long-Acting Muscarinic Antagonist (LAMA) Approval Criteria:

1. Tier-1 medications do not require prior authorization with a chronic obstructive pulmonary disease (COPD) diagnosis.

2. Tier-2 Approval Criteria:
    a. Member must be 18 years of age or older; and
    b. An FDA approved diagnosis of COPD, chronic bronchitis, or emphysema; and
    c. A four week trial of at least one long-acting beta$_2$ agonist (LABA) and a four week trial of one long-acting muscarinic antagonist (LAMA) within the past 90 days; or
    d. A documented adverse effect, drug interaction, or contraindication to all available Tier-1 products.
    e. A clinical exception may apply for members who are unable to effectively use hand-actuated devices, such as Spiriva® Handihaler®, or who are stable on nebulized therapy.

Utilization of Maintenance Asthma and COPD Medications: Fiscal Year 2016

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	6,766	32,374	$9,741,019.50	$300.89	$9.84	1,129,233	989,712
2016	6,700	32,454	$10,655,133.20	$328.31	$10.73	1,038,983	992,706
% Change	**-1.00%**	**0.20%**	**9.40%**	**9.10%**	**9.00%**	**-8.00%**	**0.30%**
Change	**-66**	**80**	**$914,113.70**	**$27.42**	**$0.89**	**-90,250**	**2,994**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Data excludes monoclonal antibodies and monotherapy inhaled corticosteroids (see end of report for details).

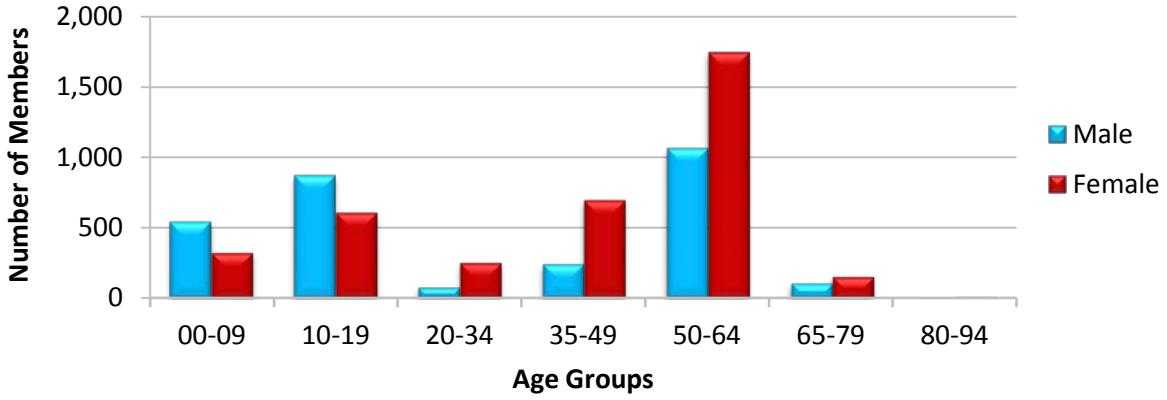
Comparison of Fiscal Years: Monoclonal Antibodies¥

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	13	81	$269,672.99	$3,329.30	$118.69	324	2,272
2016	17	82	$293,332.51	$3,577.23	$127.65	318	2,298
% Change	**30.80%**	**1.20%**	**8.80%**	**7.40%**	**7.50%**	**-1.90%**	**1.10%**
Change	**4**	**1**	**$23,659.52**	**$247.93**	**$8.96**	**-6**	**26**

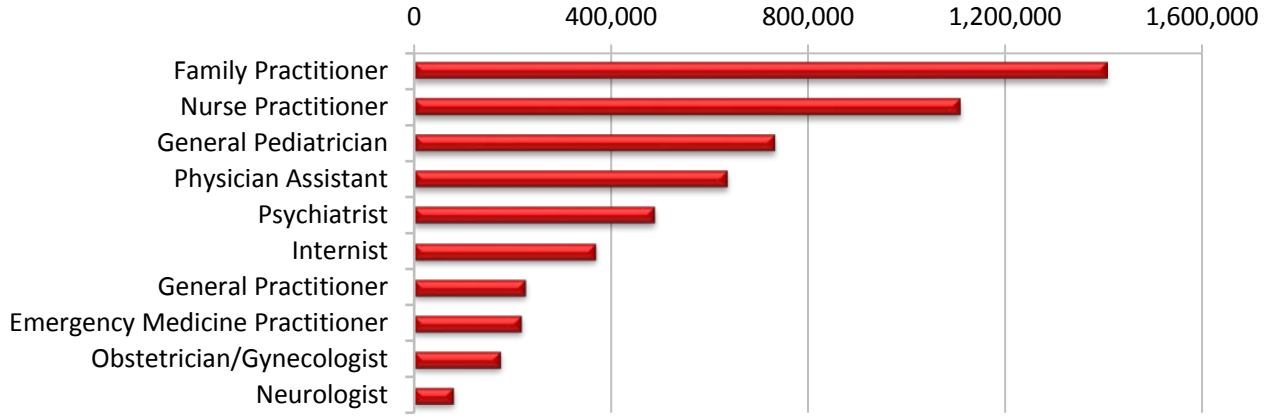
¥Pharmacy claims data only.
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- Please note Cinqair® (reslizumab) is billed by medical claims only and not reflected in the above pharmacy claims data; however, there were no paid or denied medical claims for Cinqair® (reslizumab) or Nucala® (mepolizumab) during fiscal year 2016. Xolair® (omalizumab) medical claims utilization details can be found at the end of this report.

Demographics of Members Utilizing Maintenance Asthma and COPD Medications



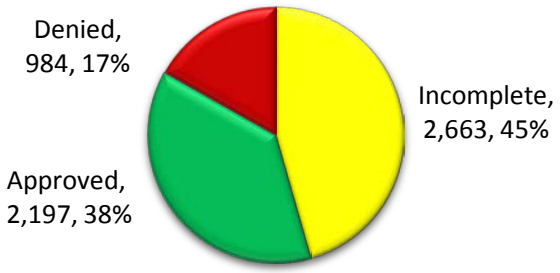
Top Prescriber Specialties of Maintenance Asthma and COPD Medications by Number of Claims



Prior Authorization of Maintenance Asthma and COPD Medications

There were 5,844 prior authorization requests submitted for maintenance asthma and COPD medications during fiscal year 2016. Of those prior authorization requests, 150 were submitted for monoclonal antibody medications. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23]

Anticipated Patent Expiration(s):

- Dulera® (mometasone/formoterol): May 2020
- Foradil® (formoterol aerosolized powder): November 2020
- Perforomist® (formoterol nebulizer solution): June 2021
- Brovana® (arformoterol nebulizer solution): November 2021
- Daliresp® (roflumilast oral tablet): March 2024
- Spiriva® HandiHaler® (tiotropium inhalation powder): March 2027
- Tudorza® (aclidinium inhalation powder): April 2027
- Arcapta® (indacaterol inhalation powder): October 2028
- Seebri™ Neohaler® (glycopyrrolate inhalation powder): October 2028
- Utibron™ Neohaler® (indacaterol/glycopyrrolate inhalation powder): October 2028
- Symbicort® (budesonide/formoterol): April 2029
- Spiriva® Respimat® (tiotropium soft mist inhaler): December 2029
- Striverdi® Respimat® (olodaterol inhalation spray): December 2029
- Stiolto® Respimat® (tiotropium bromide/olodaterol inhalation spray): December 2029
- Breo® Ellipta® (fluticasone furoate/vilanterol inhalation powder): October 2030
- Anoro® Ellipta® (umeclidinium/vilanterol inhalation powder): October 2030
- Incruse® Ellipta® (umeclidinium inhalation powder): October 2030
- Arnuity™ Ellipta® (fluticasone furoate inhalation powder): October 2030

News:

- **December 2015:** Mylan submitted an abbreviated new drug application (ANDA) to the U.S. Food and Drug Administration (FDA) for generic fluticasone/salmeterol inhalation powder, brand name Advair Diskus®, and a response is anticipated by March 2017. Vectura also submitted an ANDA for generic Advair Diskus® in April of 2016 and is expecting an FDA response by May 2017. Both companies are confident they can share the market without vastly undercutting one another on price.
- **February 2016:** Genentech provided an update on two identical Phase 3 studies of lebrikizumab, an interleukin (IL)-13 antagonist monoclonal antibody, in people with severe asthma with only one of the two studies meeting primary end points. LAVOLTA I met its primary endpoint, showing a significant reduction in the rate of asthma exacerbations in people with higher levels of serum periostin or blood eosinophils, both biomarkers of airway inflammation. In addition, this study demonstrated a significant improvement in lung function as measured by forced expiratory volume in one second (FEV_1). The observed effect in the primary and secondary endpoints, however, was less than seen in the lebrikizumab Phase 2 trials. In contrast, the exacerbation reduction results observed in LAVOLTA II did not meet statistical significance. No new safety signals were observed in either study. Clinical studies with lebrikizumab in asthma, COPD, atopic dermatitis, and idiopathic pulmonary fibrosis are ongoing.
- **April 2016:** The European Medicines Agency (EMA) completed a review of the known risk of pneumonia in patients who take inhaled corticosteroid (ICS) medications to treat COPD and the review confirmed the risk of pneumonia with these products. However, the EMA found the benefits of ICS medications in treating COPD continue to outweigh

their risks and there should be no change in how these medications are currently used. The agency advised patients with COPD and their doctors to be alert for signs and symptoms of pneumonia.

- **May 2016:** Sorrento Therapeutics, Inc. announced STI-004, a biosimilar humanized monoclonal antibody (MAB) for omalizumab (Xolair®), has successfully completed a combined Phase 2 & 3 clinical study in China demonstrating clinical efficacy and safety. In the 32-week study, asthma exacerbation was experienced by 21% of patients taking STI-004 as compared to 55% in the placebo group. When compared to the currently marketed product, Xolair®, the types and incidence rates of adverse events were similar. Xolair® is an anti-IgE antibody indicated for moderate-to-severe persistent asthma in patients six years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS. Sorrento is aiming to advance this product as well as several other biosimilar products toward regulatory approval and commercialization, however, has not announced a goal date for FDA submission.
- **May 2016:** GlaxoSmithKline (GSK) presented new data at the American Thoracic Society (ATS) conference on two pre-specified analyses from the SUMMIT trial for Breo® Ellipta® (fluticasone furoate/vilanterol). One analysis demonstrated that patients with COPD and moderate airflow limitation receiving Breo® Ellipta® achieved improvements in exacerbations compared with placebo. The second analysis demonstrated these patients reported similar rates of pneumonia when taking Breo® Ellipta® compared to placebo.
- **June 2016:** The *New England Journal of Medicine* (*NEJM*) published results of the Phase 3 FLAME head-to-head trial funded by Novartis showing once daily Ultibro® Breezhaler® (indacaterol/glycopyrronium 110/50mcg) met the primary endpoint and demonstrated superiority to Advair® (salmeterol/fluticasone 50/500mcg) in reducing the COPD exacerbation rate during the 52 week trial in patients with a history of exacerbation during the previous year. The rate of exacerbations was 11% lower in high-risk patients treated with indacaterol/glycopyrronium, a LABA/LAMA combination product, than in those receiving salmeterol/fluticasone, a LABA/ICS combination product. Once-daily Ultibro® Breezhaler® (indacaterol/glycopyrronium 110/50mcg) is not approved by the FDA in the United States; however, twice-daily Utibron™ Neohaler® (indacaterol/ glycopyrrolate 27.5mcg/15.6mcg) is FDA approved and currently available in the United States.
- **June 2016:** GSK announced results from the Phase 3 FULFIL study of investigational, once-daily, 'closed', triple, combination therapy, fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI), a combination ICS/LAMA/LABA, in patients with COPD. The study met its two co-primary endpoints, demonstrating statistically significant improvements compared with twice-daily Symbicort® Turbohaler® (budesonide/formoterol 400mcg/ 12mcg) in both lung function as measured by trough FEV_1 (171mL, 95% confidence interval [148, 194], $p<0.001$), and health-related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ) (-2.2 units, 95% confidence interval [-3.5, -1.0], $p<0.001$), at the end of the 24-week study period. The proportion of patients who responded with the minimum clinically important difference in SGRQ (-4 units) was 50% on FF/UMEC/VI and 41% on budesonide/formoterol. GSK submitted a New Drug

Application (NDA) for the closed, triple, combination therapy for the treatment of COPD to the FDA on November 21, 2016.

- **August 2016:** Vectura Group announced that the Phase 3 trial of Flutiform® (fluticasone propionate/formoterol) did not meet the primary endpoint demonstrating statistically significant superiority in the reduction of annualized rates of moderate and severe COPD exacerbations when compared to mono-component LABA treatment alone. The failed primary endpoint result will not allow a regulatory filing for the COPD indication in Europe. Flutiform® (fluticasone propionate/formoterol) is currently approved in Europe for the maintenance treatment of asthma.
- **September 2016:** Results from AstraZeneca's Phase 3 trials presented at the European Respiratory Society (ERS) International Congress demonstrated that adding benralizumab to standard-of-care medicine significantly reduced exacerbations and improved lung function and asthma symptoms in severe asthma patients with an eosinophilic phenotype, as indicated by the presence of eosinophils in their blood. The SIROCCO and CALIMA trials evaluated the effect of two dosing regimens of benralizumab 30mg administered in 4-week and 8-week regimens as add-on therapy to standard-of-care medicine across primary and key secondary endpoints. The results demonstrated reductions in the annual rate of asthma exacerbations (up to 51%), improvement in lung function (change in FEV_1 of up to 159mL), which was seen at four weeks after the first benralizumab dose and sustained throughout the treatment period, and improvement in asthma symptoms, such as wheeze, cough, chest tightness, and shortness of breath. The outcomes were demonstrated for the 8-week dosing regimen, with no additional benefit observed with 4-week dosing, which may support less-frequent dosing. AstraZeneca plans on submitting SIROCCO and CALIMA trial data for benralizumab for FDA approval by the end of 2016.
- **September 2016:** GSK announced results for Breo® Ellipta® (fluticasone furoate/vilanterol) from the COPD Salford Lung Study published in the *NEJM* and presented at the ERS International Congress. The study evaluated the safety and effectiveness of Breo® Ellipta® (fluticasone furoate/vilanterol) in patients with COPD compared with their 'usual care' administered in an everyday clinical practice setting across the town of Salford in England. For the primary endpoint in patients, who had exacerbated in the year before the study, treated with fluticasone furoate/vilanterol 100mcg/25mcg there was a statistically significant reduction of 8.4% (p=0.025; 95% CI 1.1 to 15.2) in the rate of moderate or severe exacerbations compared with patients receiving 'usual care'. The majority of these patients in the study on usual care were taking an ICS containing regimen (88%).
- **September 2016:** Regeneron Pharmaceuticals, Inc. and Sanofi announced the FDA has accepted dupilumab, an investigational antibody that inhibits signaling of IL-4 and IL-13, two key cytokines required for the type 2 (including Th2) immune response, for priority review for the treatment of adult patients with uncontrolled moderate-to-severe atopic dermatitis. A response from the FDA is expected by March 2017. Dupilumab is also being studied for the treatment of asthma and data results from the Phase 3 study, QUEST, are predicted to be more than a year away.

- **October 2016:** Positive results were announced from two replicate Phase 3 efficacy studies of revefenacin, an investigational LAMA and the first once-daily, nebulized bronchodilator in development for the treatment of COPD. Top-line results across more than 1,250 moderate-to-very-severe COPD patients confirmed that both Phase 3 studies met their primary efficacy endpoint, demonstrating statistically significant improvements over placebo in trough FEV_1 after 12 weeks of dosing for each of the revefenacin doses studied (88mcg once daily and 175mcg once daily). In addition to the two efficacy trials, the revefenacin Phase 3 program includes an ongoing twelve-month, open-label, active comparator safety study in more than 1,050 patients, which is expected to be completed in 2017. Together, the three studies enrolled approximately 2,300 patients. Should outcomes from the safety study be supportive, Theravance Biopharma expects to file a NDA for revefenacin with the FDA by the end of 2017.

New FDA Approval(s):

- **March 2016:** Cinqair® (reslizumab)
- **April 2016:** Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate)

Guideline Update(s):

- The 2017 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for the Diagnosis, Management, and Prevention of COPD was recently released and reflects the latest evidence and published scientific research. The latest update recommends pharmacological treatment that is tailored to patients based on symptoms and exacerbation history. The new strategy still uses the A, B, C, D system, with each category having its own treatment algorithm supporting a more tailored approach addressing patient needs. The 2017 Gold Strategy for COPD now recommends LAMA/LABA combination therapy as a mainstay treatment choice for patients with COPD in GOLD groups B-D which is a significant change from previous GOLD guidelines. The added benefits of treatment with a LAMA/LABA beyond the individual components alone, and versus LABA/ICS for people with COPD, have been confirmed by a number of randomized, clinical trials.

Cinqair® (Reslizumab) Product Summary[24,25]

Indications: Cinqair® (reslizumab) is an IL-5 antagonist monoclonal antibody indicated for the add-on maintenance treatment of patients with severe asthma age 18 years and older with an eosinophilic phenotype.

Limitations of use:

- Reslizumab is not indicated for the treatment of other eosinophilic conditions.
- Reslizumab is not indicated for the relief of acute bronchospasm or status asthmaticus.

Dosing:

- Cinqair® is available as a 100mg/10mL (10mg/mL) single-use vial for injection.
- Reslizumab is for intravenous (IV) infusion only. It should not be administered as an IV push or bolus.
- Reslizumab should be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis.

- The recommended dosing of reslizumab is 3mg/kg once every four weeks by IV infusion over 20 to 50 minutes.

Mechanism of Action:

- Reslizumab is an IL-5 antagonist (IgG4, kappa) monoclonal antibody. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Reslizumab binds to IL-5, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil surface. Inflammation is an important component in the pathogenesis of asthma. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Reslizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of reslizumab action in asthma has not been definitively established.

Contraindications:

- Patients with known hypersensitivity to Cinqair® or any of its excipients.

Safety:

- Malignancy: Malignancies were observed in clinical studies. The observed malignancies in reslizumab-treated patients in placebo-controlled clinical trials were diverse in nature and without clustering of any particular tissue type. The majority of malignancies were diagnosed within less than six months of reslizumab exposure.
- Reduction of Corticosteroid Dosage: Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of therapy with reslizumab. Corticosteroids should be decreased gradually, if appropriate.
- Parasitic (Helminth) Infection: Patients with pre-existing helminth infections should be treated before therapy with reslizumab. If patients become infected while receiving reslizumab and do not respond to anti-helminth treatment, reslizumab should be discontinued until the parasitic infection resolves.

Adverse Reactions: The most commonly reported adverse reaction (≥2%) during clinical trials was oropharyngeal pain.

Efficacy: The efficacy of reslizumab was evaluated in four double-blind, randomized trials enrolling 981 patients with severe asthma on currently available therapies. Reslizumab or a placebo was administered to patients every four weeks as an add-on asthma treatment.

- Compared with placebo, patients with severe asthma receiving reslizumab had fewer asthma attacks (95% CI 0.5, 0.41), and a longer time to the first attack. Also, treatment with reslizumab resulted in significant lung function improvement as measured by $FEV_{1.}$ (137mL FEV_1 change from baseline over 16 weeks).

Cost Comparison:

Medication	Cost Per Unit*	Cost Per Month[+]	Cost Per Year[¥]
Cinqair® (reslizumab) 100mg/10mL vial	$83.50/mL	$1,670.00	$20,040.00
Nucala® (mepolizumab) 100mg vial	$2,575.00/vial	$2,575.00	$30,900.00

Costs do not reflect rebated prices or net costs.
*Costs are based on WAC (wholesale acquisition cost) pricing.
[+]Cinqair® cost based on recommended dosing of 3mg/kg for a 66.6kg patient (2 vials) once every 4 weeks. Nucala® cost based on recommended dosing of 100mg once (1 vial) every 4 weeks.
[¥]Cost per year based on twelve 28-day months.

Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate) Product Summary[5,26]

Indications: Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate) is a combination of glycopyrrolate, an anticholinergic, and formoterol fumarate, a long-acting beta$_2$-adrenergic agonist (LABA) indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD.

Limitation of use:

- Glycopyrrolate/formoterol fumarate is not indicated for the relief of acute bronchospasm or for the treatment of asthma.

Dosing:

- Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate) is available as a pressurized metered dose inhaler containing a combination of glycopyrrolate (9mcg) and formoterol fumarate (4.8mg) as an inhalation aerosol. Each canister contains 120 inhalations and has a net fill weight of 10.7grams.
- Glycopyrrolate/formoterol fumarate is for oral inhalation only.
- The recommended dosing for glycopyrrolate/formoterol fumarate for the maintenance treatment of COPD is two inhalations twice daily.

Mechanism of Action:

- Bevespi Aerosphere® contains both glycopyrrolate and formoterol fumarate. The mechanism of action described below for the individual components apply to Bevespi Aerosphere®. These drugs represent two different classes of medications (a long-acting muscarinic antagonist and a long-acting selective beta$_2$-adrenoceptor agonist) that have different effects on clinical and physiological indices.
- Glycopyrrolate is a long-acting antimuscarinic agent which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. In the airways, it exhibits pharmacological effect through inhibition of the M3 receptor at the smooth muscle leading to bronchodilation. The bronchodilation following inhalation of glycopyrrolate is predominately a site-specific effect.
- Formoterol fumarate is a long-acting selective beta$_2$-adrenergic agonist (beta$_2$-agonist) with a rapid onset of action. Inhaled formoterol has more than 200-fold greater agonist activity at beta$_2$-receptors than at beta$_1$-receptors. The in vitro binding selectivity to beta$_2$- over beta$_1$-adrenoceptors is higher for formoterol than for albuterol (five times), whereas salmeterol has a higher (three times) beta$_2$-selectivity ratio than formoterol. The pharmacological effects of beta$_2$-adrenoceptor agonist drugs, including formoterol

fumarate, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3', 5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Contraindications:

- All LABAs are contraindicated in patients with asthma without use of a long-term asthma controller medication. Glycopyrrolate/formoterol fumarate is not indicated for the treatment of asthma.
- Hypersensitivity to glycopyrrolate, formoterol fumarate, or to any component of Bevespi Aerosphere®.

Safety:

- Glycopyrrolate/formoterol fumarate should not be initiated in acutely deteriorating COPD or to treat acute symptoms.
- Glycopyrrolate/formoterol fumarate should not be used in combination with an additional medicine containing a LABA because of risk of overdose.
- If paradoxical bronchospasm occurs, glycopyrrolate/formoterol fumarate should be discontinued and alternative therapy instituted.
- Glycopyrrolate/formoterol fumarate should be used with caution in patients with cardiovascular disorders.
- Glycopyrrolate/formoterol fumarate should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis.
- Prescribers should be alert for hypokalemia and hyperglycemia.
- Worsening of narrow-angle glaucoma may occur. Glycopyrrolate/formoterol fumarate should be used with caution in patients with narrow-angle glaucoma and patients should be instructed to contact a physician immediately if symptoms occur.
- Worsening urinary retention may occur. Glycopyrrolate/formoterol fumarate should be used with caution in patients with prostatic hyperplasia or bladder-neck obstruction and patients should be instructed to contact a physician immediately if symptoms occur.

Adverse Reactions: The most common adverse reactions during clinical trials (incidence ≥2% and more common than with placebo) include urinary tract infection and cough.

Efficacy: The FDA approval of glycopyrrolate/formoterol fumarate was based on results of the PINNACLE Phase 3 pivotal studies (PINNACLE 1, PINNACLE 2, and a safety extension study, PINNACLE 3) which included over 3,700 patients with moderate-to-very-severe COPD. The studies demonstrated that glycopyrrolate/formoterol fumarate achieved statistically significant improvements in lung function as measured by change from baseline in morning pre-dose trough FEV_1 at 24 weeks ($p<0.001$) versus its individual components (glycopyrrolate 9mcg and formoterol fumarate 4.8mcg) and placebo, all dosed twice daily.

Availability: Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate) is currently unavailable with a launch date set for early 2017.

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month[+]	Cost Per Year
Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate)	$29.50/gram*	$315.65	$3,787.80
Anoro® Ellipta® (umeclidinium/vilanterol)	$5.08[€]	$304.80	$3,657.60

Costs do not reflect rebated prices or net costs.
*Costs are based on WAC (wholesale acquisition cost) pricing.
[€]Cost based on National Average Drug Acquisition Costs (NADAC).
[+]Bevespi Aerosphere® cost based on recommended dosing of two inhalations twice daily (120 inhalations/month) or one inhaler. Anoro® Ellipta® cost based on one inhalation once daily which is equivalent to one inhaler (60 blisters).

Recommendations

The College of Pharmacy recommends the prior authorization of Cinqair® (reslizumab) and Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate) with the following criteria:

Cinqair® (Reslizumab) Approval Criteria:

1. An FDA approved indication of add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype; and
2. Member must be 18 years of age or older; and
3. Member must have a blood eosinophil count of at least 400/mcL (within three to four weeks of dosing); and
4. Member must have had at least two asthma exacerbations requiring systemic corticosteroids within the last 12 months or require daily systemic corticosteroids despite compliant use of high-dose inhaled corticosteroid (ICS) plus at least one additional controller medication; and
5. Member must have failed a high-dose ICS used compliantly for at least the past 12 months (for ICS/LABA combination medications, the highest approved dose meets this criteria); and
6. Member must have failed at least one other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past three months; and
7. Cinqair® must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis; and
8. Cinqair® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
9. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval.
10. Member's weight should be provided on prior authorization requests. Weights should have been taken within the last four weeks to provide accurate weight-based dosing.

Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); and
3. A patient-specific, clinically significant reason why the member cannot use Tier-1 long-acting beta$_2$ agonist (LABA) and long-acting muscarinic antagonist (LAMA) individual components.

Utilization Details of Maintenance Asthma and COPD Medications: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
COMBINATION LABA/ICS PRODUCTS						
ADVAIR DISKU AER 250/50	5,545	1,427	$1,849,722.47	$11.04	$333.58	17.36%
SYMBICORT AER 160-4.5	4,793	1,190	$1,408,997.55	$9.34	$293.97	13.22%
ADVAIR HFA AER 115/21	2,989	821	$967,073.87	$10.54	$323.54	9.08%
ADVAIR DISKU AER 500/50	2,204	488	$976,885.85	$14.77	$443.23	9.17%
ADVAIR DISKU AER 100/50	1,775	504	$472,294.66	$8.80	$266.08	4.43%
DULERA AER 200-5MCG	1,143	315	$313,523.70	$8.88	$274.30	2.94%
SYMBICORT AER 80-4.5	1,016	283	$256,910.05	$7.87	$252.86	2.41%
ADVAIR HFA AER 230/21	892	239	$391,664.00	$14.29	$439.09	3.68%
DULERA AER 100-5MCG	801	237	$220,186.29	$8.83	$274.89	2.07%
ADVAIR HFA AER 45/21	399	132	$106,142.38	$8.70	$266.02	1.00%
BREO ELLIPTA INH 100-25	71	14	$21,843.37	$10.26	$307.65	0.21%
SUBTOTAL	**21,628**	**5,650**	**$6,985,244.19**	**$10.30**	**$322.97**	**65.57%**
INDIVIDUAL COMPONENT LABA PRODUCTS						
TIER-1						
SEREVENT DIS AER 50MCG	508	206	$160,064.43	$10.43	$315.09	1.50%
FORADIL CAP AEROLIZE	196	61	$47,333.21	$7.99	$241.50	0.44%
SUBTOTAL	**704**	**267**	**$207,397.64**	**$9.21**	**$294.60**	**1.94%**
TIER-2						
BROVANA NEB 15MCG	101	23	$78,685.43	$25.34	$779.06	0.74%
PERFOROMIST NEB 20MCG	48	7	$28,517.69	$20.44	$594.12	0.27%
SUBTOTAL	**149**	**30**	**$107,203.12**	**$22.89**	**$719.48**	**1.01%**
INDIVIDUAL COMPONENT LAMA PRODUCTS						
TIER-1						
SPIRIVA CAP HANDIHLR	8,469	2,131	$2,860,847.08	$11.16	$337.80	26.85%
SUBTOTAL	**8,469**	**2,131**	**$2,860,847.08**	**$11.16**	**$337.80**	**26.85%**
TIER-2						
SPIRIVA SPR 2.5MCG	1,171	316	$396,595.74	$11.07	$338.68	3.72%
TUDORZA PRES AER	44	14	$12,954.15	$9.60	$294.41	0.12%
INCRUSE ELPT INH 62.5MCG	6	2	$1,614.74	$8.97	$269.12	0.02%
SUBTOTAL	**1,221**	**332**	**$411,164.63**	**$9.88**	**$336.74**	**3.86%**
COMBINATION LABA/LAMA PRODUCTS						
ANORO ELLIPT AER 62.5-25	38	10	$12,311.78	$10.52	$323.99	0.12%
STIOLTO AER 2.5-2.5	13	7	$4,343.59	$11.14	$334.12	0.04%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
SUBTOTAL	**51**	**17**	**$16,655.37**	**$10.83**	**$326.58**	**0.16%**
PHOSPHODIESTERASE-4 ENZYME INHIBITOR PRODUCTS						
DALIRESP TAB 500MCG	228	34	$65,508.23	$9.49	$287.32	0.61%
SUBTOTAL	**228**	**34**	**$65,508.23**	**$9.49**	**$287.32**	**0.61%**
SPECIAL PRIOR AUTHORIZATION INHALED CORTICOSTEROID PRODUCTS						
ARNUITY ELPT 100MCG	2	1	$323.92	$5.40	$161.96	0.00%
ARNUITY ELPT 200MCG	2	1	$789.02	$13.15	$394.51	0.01%
SUBTOTAL	**4**	**2**	**$1,112.94**	**$18.55**	**$278.24**	**0.01%**
TOTAL	**32,454**	**6,700***	**$10,655,133.20**	**$10.73**	**$328.31**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
LABA = long-acting beta$_2$ agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid

Utilization Details of Asthma Monoclonal Antibodies (Pharmacy Claims): Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
MONOCLONAL ANTIBODY PRODUCTS						
XOLAIR SOL 150MG	78	16	$282,758.11	$129.35	$3,625.10	96.40%
NUCALA INJ 100MG	4	1	$10,574.40	$94.41	$2,643.60	3.60%
TOTAL	**82**	**17***	**$293,332.51**	**$127.65**	**$3,577.23**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Utilization Details of Asthma Monoclonal Antibodies (Medical Claims): Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	TOTAL UNITS	COST/ CLAIM	% COST
MONOCLONAL ANTIBODY PRODUCTS						
OMALIZUMAB INJ 5MG (J2357)	70	10	$198,033.30	6,630	$2,829.05	100%
TOTAL	**70**	**10***	**$198,033.30**	**6,630**	**$2,829.05**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Utilization Details of Inhaled Corticosteroids: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
INHALED CORTICOSTEROID PRODUCTS						
FLOVENT HFA AER 110MCG	20,028	8,734	$4,319,260.16	$6.30	$215.66	27.33%
FLOVENT HFA AER 44MCG	18,367	8,494	$2,970,896.62	$5.09	$161.75	18.80%
QVAR AER 40MCG	7,832	3,771	$1,159,695.63	$4.12	$148.07	7.34%
BUDESONIDE SUS 0.25MG/2	6,045	3,648	$1,337,468.96	$8.69	$221.25	8.46%
BUDESONIDE SUS 0.5MG/2	5,137	2,665	$1,543,070.94	$11.21	$300.38	9.77%
QVAR AER 80MCG	4,769	2,092	$927,454.81	$5.52	$194.48	5.87%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
FLOVENT HFA AER 220MCG	2,858	1,340	$966,339.07	$9.62	$338.12	6.12%
PULMICORT INH 90MCG	1,423	678	$221,661.62	$5.57	$155.77	1.40%
PULMICORT INH 180MCG	1,379	717	$279,401.41	$5.39	$202.61	1.77%
ASMANEX 60 AER 220MCG	1,180	412	$242,565.16	$6.48	$205.56	1.54%
ASMANEX 30 AER 220MCG	1,171	431	$207,293.83	$5.89	$177.02	1.31%
FLOVENT DISK AER 100MCG	1,171	529	$200,284.71	$5.46	$171.04	1.27%
ASMANEX 30 AER 110MCG	939	350	$151,638.61	$5.37	$161.49	0.96%
AEROSPAN AER 80MCG	706	362	$131,238.00	$5.49	$185.89	0.83%
FLOVENT DISK AER 250MCG	686	279	$153,062.24	$7.23	$223.12	0.97%
PULMICORT SUS 0.25MG/2	657	438	$153,285.59	$8.65	$233.31	0.97%
FLOVENT DISK AER 50MCG	459	200	$72,332.50	$5.04	$157.59	0.46%
ALVESCO AER 80MCG	388	138	$87,743.45	$6.88	$226.14	0.56%
ASMANEX HFA AER 100 MCG	328	173	$53,131.29	$4.72	$161.99	0.34%
BUDESONIDE SUS 1MG/2ML	309	163	$237,894.65	$27.77	$769.89	1.51%
ASMANEX 120 AER 220MCG	256	141	$67,080.26	$6.04	$262.03	0.42%
ALVESCO AER 160MCG	244	105	$54,745.48	$7.05	$224.37	0.35%
PULMICORT SUS 0.5MG/2	242	162	$74,357.13	$11.98	$307.26	0.47%
ASMANEX HFA AER 200 MCG	218	114	$40,903.57	$5.49	$187.63	0.26%
PULMICORT SUS 1MG/2ML	148	63	$147,586.16	$33.28	$997.20	0.93%
ARNUITY ELPT INH 100MCG	2	1	$323.92	$5.40	$161.96	0.00%
ARNUITY ELPT INH 200MCG	2	1	$789.02	$13.15	$394.51	0.00%
TOTAL	**76,944**	**32,032***	**$15,801,504.79**	**$6.35**	**$205.36**	**100.00%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

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[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?resetfields=1. Last revised 09/2016. Last accessed 11/2016.

[2] PR Newswire: "Mylan Confirms FDA Submission of ANDA for Generic Advair Diskus®." Available online at: http://www.prnewswire.com/news-releases/mylan-confirms-fda-submission-of-anda-for-generic-advair-diskus-300202571.html. Issued 01/2016. Last accessed 11/2016.

[3] FiercePharma: "Wannabe generic Advair makers Mylan, Vectura aim for 'rational' drug pricing." Available online at: http://www.fiercepharma.com/pharma/wannabe-generic-advair-makers-mylan-vectura-aim-for-rational-drug-pricing. Issued 06/2016. Last accessed 11/2016.

[4] Vectura Latest News. "VR315US- ANDA for Generic Advair Diskus® accepted for filing by FDA and milestone payment." Available online at: http://www.vectura.com/news/vr315-us-anda-generic-advair-diskus-accepted-filing-fda-and-milestone-payment/#. Issued 04/2016. Last accessed 11/2016.

[5] AstraZeneca. "Bevespi Aerosphere™ Approved by the US FDA for Patients with COPD." Available online at: https://www.astrazeneca.com/media-centre/press-releases/2016/bevespi-aerosphere-approved-by-the-us-fda-for-patients-with-copd-25042016.html. Issued 04/2016. Last accessed 11/2016.

[6] Genentech. "Genentech Provides Update on Two Identical Phase III Studies of Lebrikizumab in People with Severe Asthma." Available online at: https://www.gene.com/media/press-releases/14619/2016-02-28/genentech-provides-update-on-two-identic. Issued 02/2016. Last accessed 11/2016.

[7] European Medicines Agency. "EMA Completes Review of Inhaled Corticosteroids for Chronic Obstructive Pulmonary Disease." Available online at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Inhaled_corticosteroids_for_chronic_obstructive_pulmonary_disease/human_referral_prac_000050.jsp&mid=WC0b01ac05805c516f. Issued 04/2016. Last accessed 11/2016.

[8] Boyles, S. "LABA-LAMA Combo Tops Advair for Cutting COPD Flares." *MedPage Today*. Available online at: http://www.medpagetoday.com/meetingcoverage/ats/57928. Issued 05/2016. Last accessed 11/2016.
[9] Wedzicha, J, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *The New England Journal of Medicine.* Available online at: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1516385. Issued 06/2016. Last accessed 11/2016.
[10] AstraZeneca. "Benralizumab phase III trials show positive results in severe asthma." Available online at: https://www.astrazeneca.com/media-centre/press-releases/2016/benralizumub-phase-III-trials-show-positive-results-in-severe-asthma-05092016.html. Issued 09/2016. Last accessed 11/2016.
[11] PR Newswire: "Sorrento Announced Positive Data from a Combined Phase 2 & 3 Clinical Study of STI-004, an Anti-IgE Biosimilar Antibody." Available online at: http://www.prnewswire.com/news-releases/sorrento-announces-positive-data-from-a-combined-phase-2--3-clinical-study-of-sti-004-an-anti-ige-biosimilar-antibody-300268834.html. Issued 05/2016. Last accessed 11/2016.
[12] Xolair® Prescribing Information. Genentech USA, Inc. Available online at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Last revised 07/2016. Last accessed 11/2016.
[13] GlaxoSmithKline. "GSK presents new data from Breo® Ellipta® SUMMIT study in patients with COPD at ATS Conference." Available online at: http://www.gsk.com/en-gb/media/press-releases/2016/gsk-presents-new-data-from-breo-ellipta-summit-study-in-patients-with-copd-at-ats-conference/. Issued 05/2016. Last accessed 11/2016.
[14] GlaxoSmithKline. "GSK announce positive results from the COPD Salford Lung Study published in the NEJM and presented at European Respiratory Congress." Available online at: hhttp://www.gsk.com/en-gb/media/press-releases/2016/gsk-announce-positive-results-from-the-copd-salford-lung-study-published-in-the-nejm-and-presented-at-european-respiratory-congress/. Issued 09/2016. Last accessed 11/2016.
[15] GlaxoSmithKline. "FULFIL study shows superiority of closed triple combination therapy FF/UMEC/VI versus Symbicort® Turbohaler® in improving lung function and health related quality of life in COPD patients." Available online at: http://www.gsk.com/en-gb/media/press-releases/2016/fulfil-study-shows-superiority-of-closed-triple-combination-therapy-ffumecvi-versus-symbicort-turbohaler-in-improving-lung-function-and-health-related-quality-of-life-in-copd-patients/. Issued 06/2016. Last accessed 11/2016.
[16] Vectura. "Update on Mundipharma's European Phase III trial of Flutiform® in COPD and latest Flutiform® in-market sales." Available online at: http://www.vectura.com/news/update-mundipharmas-european-phase-iii-trial-flutiform-copd-and-latest-flutiform-market-sales/. Issued 08/2016. Last accessed 11/2016.
[17] PR Newswire: "Regeneron and Sanofi Announce Dupilumab Biologics License Application Accepted for Priority Review by the U.S. FDA." Available online at: http://www.prnewswire.com/news-releases/regeneron-and-sanofi-announce-dupilumab-biologics-license-application-accepted-for-priority-review-by-us-fda-300333529.html. Issued 09/2016. Last accessed 11/2016.
[18] BioPharma Dive: "Regeneron and Sanofi tout dupilumab success." Available online at: http://www.biopharmadive.com/news/regeneron-and-sanofi-tout-dupilumab-success/427474/. Issued 10/2016. Last accessed 11/2016.
[19] Theravance® Biopharma. "Theravance Biopharma and Mylan Announce Positive Results from Two Pivotal Phase 3 Studies of Revefenacin (TD-4208) for the treatment of Chronic Obstructive Pulmonary Disease (COPD)." Available online at: http://investor.theravance.com/releasedetail.cfm?releaseid=994556. Issued 10/2016. Last accessed 11/2016.
[20] C. Vogelmeier, Chair, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2017 Report. Available online at: http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/. Updated 2017 version. Last accessed 11/2016.
[21] Business Wire® A Berkshire Hathaway Company: "Boehringer Ingelheim Welcomes Central Role of LAMA/LABA therapy within 2017 GOLD Strategy for COPD." Available online at: http://www.businesswire.com/news/home/20161116006085/en/Boehringer-Ingelheim-welcomes-central-role-LAMALABA-therapy. Issued 11/2016. Last accessed 11/2016.
[22] Boyles, S. et al. "Novel LAMA/LABA Combo Shines for COPD." Available online at: http://www.medpagetoday.com/clinical-context/copd/59789. Issued 08/2016. Last accessed 11/2016.
[23] GlaxoSmithKline. "GSK files regulatory submission in US for once-daily closed triple combination therapy FF/UMEC/VI for patients with COPD." Available online at: http://www.gsk.com/en-gb/media/press-releases/2016/gsk-files-regulatory-submission-in-us-for-once-daily-closed-triple-combination-therapy-ffumecvi-for-patients-with-copd/. Issued 11/2016. Last accessed 11/2016.
[24] Cinqair® Prescribing Information. Teva Respiratory, LLC. Available online at: http://www.cinqair.com/pdf/PrescribingInformation.pdf. Last revised 05/2016. Last accessed 11/2016.
[25] Cinqair® New Drug Approval. OptumRx. Available online at: https://hcp-prod.optumrx.com/vgnlive/HCP/Assets/RxNews/Drug%20approvals_Cinqair_2016-0324.pdf. Issued 2016. Last accessed 11/2016.
[26] Bevespi Aerosphere™ Prescribing Information. AstraZeneca Pharmaceuticals. Available online at: http://www.azpicentral.com/bevespi/bevespi_pi.pdf. Last revised 04/2016. Last accessed 11/2016.

Appendix K

Fiscal Year 2016 Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Syndros™ (Dronabinol), Sustol® (Granisetron), and Bonjesta® (Doxylamine/Pyridoxine)

Oklahoma Health Care Authority
December 2016

Current Prior Authorization Criteria

Kytril® and Sancuso® (Granisetron), Anzemet® (Dolasetron), and Emend® (Aprepitant) Approval Criteria:

1. An FDA approved diagnosis; and
2. A recent trial of ondansetron (within the past six months) used for at least three days or one cycle that resulted in an inadequate response is required for authorization in members receiving moderately emetogenic chemotherapy; and
3. No ondansetron trial is required for authorization of Emend® (aprepitant) in members receiving highly emetogenic chemotherapy; and
4. Approval length will be based on duration of need.
5. For Emend® (aprepitant) oral suspension, an age restriction of six years and younger will apply. Members older than six years of age will require a patient-specific, clinically significant reason why the oral capsule formulation cannot be used.

Akynzeo® (Netupitant/Palonosetron) Approval Criteria:

1. An FDA approved diagnosis for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy; and
2. A previously failed trial of aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why aprepitant cannot be used must be provided; and
3. Approval length will be based on duration of need.
4. A quantity limit of one capsule per chemotherapy cycle will apply.

Varubi™ (Rolapitant) Approval Criteria:

1. An FDA approved indication for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy; and
2. A previously failed trial of aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why aprepitant cannot be used must be provided; and
3. Approval length will be based on duration of need.
4. A quantity limit of two tablets per chemotherapy cycle will apply.

Marinol® (Dronabinol) and Cesamet® (Nabilone) Approval Criteria:

1. Approval can be granted for six months for the diagnosis of HIV related loss of appetite.
2. The diagnosis of chemotherapy induced nausea and vomiting requires the following:

a. A recent trial of ondansetron (within the past six months) used for at least three days or one cycle that resulted in inadequate response.

3. Approval length will be based on duration of need.
4. A quantity limit of 60 capsules per 30 days will apply.

Zuplenz® (Ondansetron) Approval Criteria:

1. An FDA approved diagnosis; and
2. A patient-specific, clinically significant reason why the member cannot take all other available formulations of generic ondansetron.

Diclegis® (Doxylamine/Pyridoxine) Approval Criteria:

1. An FDA approved diagnosis of nausea and vomiting associated with pregnancy that is not responsive to conservative management; and
2. Trials with at least two non-pharmacological therapies that have failed to relieve nausea and vomiting; and
3. A patient-specific, clinically significant reason why member cannot use over-the-counter (OTC) doxylamine and OTC Vitamin B_6 (pyridoxine).

Utilization of Anti-Emetic Medications: Fiscal Year 2016

Comparison of Fiscal Years for Anti-Emetic Medications: Pharmacy Claims

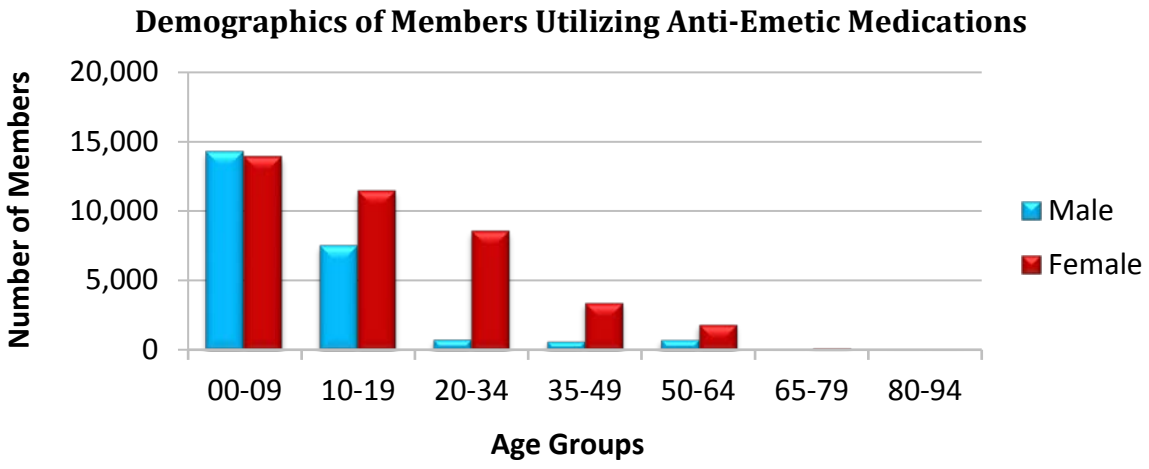
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	65,281	89,376	$1,182,418.86	$13.23	$1.61	1,392,353	734,260
2016	63,563	85,738	$941,711.39	$10.98	$1.47	1,334,097	641,184
% Change	**-2.60%**	**-4.10%**	**-20.40%**	**-17.00%**	**-8.70%**	**-4.20%**	**-12.70%**
Change	**-1,718**	**-3,638**	**-$240,707.47**	**-$2.25**	**-$0.14**	**-58,256**	**-93,076**

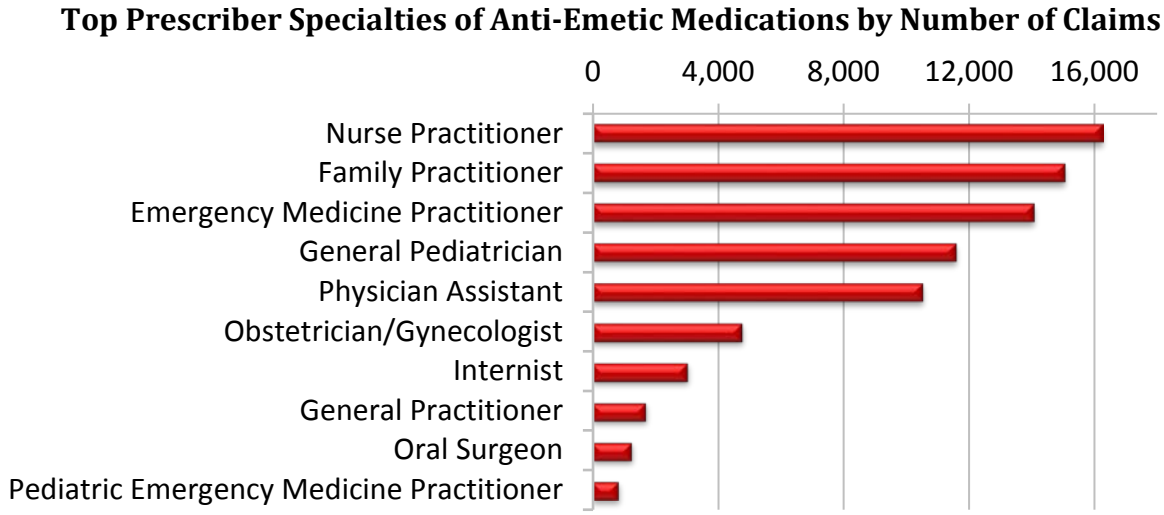
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Fiscal Year 2016 Utilization of Anti-Emetic Medications: Medical Claims

*Total Members	Total Claims	Total Cost	Cost/Claim	Claims/Member
281	1,015	$263,694.54	$259.80	3.61

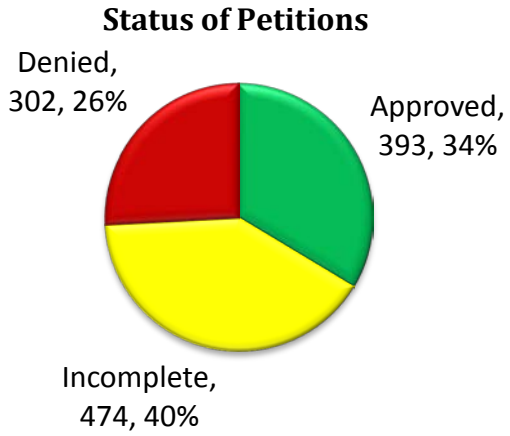
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.





Prior Authorization of Anti-Emetic Medications

There were 1,169 prior authorization requests submitted for anti-emetic medications during fiscal year 2016. The following chart shows the status of the submitted petitions.



Market News and Updates[1,2,3,4,5,6,7]

Anticipated Patent Expiration(s):

- Diclegis® (doxylamine/pyridoxine): June 2021
- Sancuso® (granisetron transdermal patch): January 2025
- Emend® (aprepitant): September 2027
- Varubi™ (rolapitant): October 2029
- Zuplenz® (ondansetron oral soluble film): July 2030
- Akynzeo® (netupitant/palonosetron): September 2031

New FDA Approval(s) and Indication(s):

- **February 2016:** The U.S. Food and Drug Administration (FDA) approved a supplemental new drug application (sNDA) for the single-dose, intravenous (IV) formulation of Emend® (fosaprepitant), in combination with other anti-emetic agents, for the prevention of delayed nausea and vomiting in adults receiving initial and repeat courses of moderately emetogenic chemotherapy (MEC). Fosaprepitant is a prodrug of aprepitant and was first FDA approved in 2008 for the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV) in adults receiving highly emetogenic chemotherapy (HEC). With this new indication, fosaprepitant is the first IV, single-dose substance P/neurokinin-1 (NK_1) receptor antagonist approved in the United States for both HEC and MEC.
- **July 2016:** The FDA approved Syndros™ (dronabinol oral solution) for the treatment of anorexia associated with weight loss in adult patients with acquired immunodeficiency syndrome (AIDS) and for the treatment of nausea and vomiting associated with cancer chemotherapy in adult patients who have failed to respond adequately to conventional antiemetic treatments. Dronabinol is also available generically as oral capsules, with the same FDA approved indications as Syndros™.
- **August 2016:** The FDA approved Sustol® (granisetron extended-release injection for subcutaneous use) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens, in combination with other anti-emetic medications in adult patients.
- **August 2016:** The FDA approved an abbreviated new drug application (ANDA) for doxylamine/pyridoxine 10mg/10mg tablets (generic Diclegis®) for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management; however, the anticipated release date and cost information is not currently available.
- **November 2016:** The FDA approved Bonjesta® (doxylamine/pyridoxine 20mg/20mg tablets) for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Other News:

- **October 2016:** Aprepitant failed to meet its primary endpoint in a trial for the symptoms of gastroparesis. Compared with placebo, aprepitant did not meet the patient-reported 100mm visual analog scale (VAS) for nausea (met by 46% aprepitant vs 40% placebo;

P=0.43). However, the study did find that aprepitant use resulted in a greater decline in nausea over four weeks, mean 4-week Gastroparesis Cardinal Symptom Index (GCSI) score, and greater improvement in multiple other measures of symptom severity, indicating that future research on aprepitant as a treatment for gastroparesis is imperative.

Syndros™ (Dronabinol) Product Summary[8,9]

Indications: Syndros™ (dronabinol) is a cannabinoid indicated in adults for the treatment of:

- Anorexia associated with weight loss in patients with AIDS; and
- Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatments.

Dosing:

- Syndros™ (dronabinol) is available as a 5mg/mL oral solution.
- For anorexia associated with weight loss in patients with AIDS, the recommended starting dosage is 2.1mg orally twice daily, one hour before lunch and dinner.
  - The maximum dosage for this indication is 8.4mg twice daily.
- For nausea and vomiting associated with chemotherapy, the recommended starting dosage is 4.2mg/m^2, administered one to three hours prior to chemotherapy, then every two to four hours after chemotherapy for a total of four to six doses per day. The first dose should be administered on an empty stomach at least 30 minutes prior to eating; subsequent doses can be taken without regard to meals.
  - The maximum dosage for this indication is 12.6mg/m^2 per dose for four to six doses per day.
- The enclosed calibrated dosing syringe should always be used to measure the dose.
- Syndros™ should be taken with a full glass of water (six to eight ounces).
- Syndros™ should be stored in the refrigerator prior to opening. After the bottle is opened, Syndros™ can be stored at room temperature for up to 28 days. Syndros™ should not be used 28 days after opening the bottle.

Comparison to Currently Available Products: Dronabinol is currently available as oral capsules (Marinol®), and Marinol® is indicated for the same indications as Syndros™ oral solution (*see above indications*). Marinol® was granted orphan drug designation for use in the stimulation of appetite and prevention of weight loss in patients with a confirmed diagnosis of AIDS, and was first FDA approved in 1985. The effectiveness of Syndros™ was established based on clinical studies of Marinol®. Dronabinol oral capsules are currently available as a generic product.

Cost: Cost information for Syndros™ is not currently available at this time.

Sustol® (Granisetron) Product Summary[10,11]

Indications: Sustol® (granisetron) is a serotonin-3 (5-HT$_3$) receptor antagonist indicated in combination with other anti-emetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic

chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

Dosing:

- Sustol® (granisetron) is available as a 10mg/0.4mL extended-release injection in a single-dose, pre-filled syringe.
- The recommended dosage is 10mg administered as a single subcutaneous injection at least 30 minutes before the start of emetogenic chemotherapy on day one.
- Sustol® should not be administered more frequently than once every seven days.
- Use of Sustol® with successive emetogenic chemotherapy cycles for more than six months is not recommended.
- Sustol® is for subcutaneous injection only and is intended for administration by a healthcare provider. Due to the viscosity of Sustol®, administration requires a slow, sustained injection over 20 to 30 seconds.

Comparison to Currently Available Products: Granisetron is currently available as oral tablets and vials for IV infusion (Kytril®), and as extended-release transdermal patches (Sancuso®), and is indicated for similar indications as Sustol® (*see above indications*). Kytril® vials for IV infusion were first FDA approved in 1993, followed by Kytril® oral tablets in 1995, and Sancuso® transdermal patches in 2008. Granisetron oral tablets and vials for IV infusion are currently available as generic products.

Cost Comparison of Granisetron Products:

Medication	Dosing Regimen	Cost/Unit*	Cost/Chemo Cycle+
Sustol® 10mg/0.4mL ER injection	**10mg SubQ at least 30 minutes prior to chemo**	**$495.00**	**$495.00**
granisetron 1mg/mL vial (generic Kytril®)	10mcg/kg IV at least 30 minutes prior to chemo	$18.87	$18.87
granisetron 1mg tablet (generic Kytril®)	2mg PO one hour prior to chemo	$1.56	$3.12
Sancuso® 3.1mg/24hr transdermal patch	Apply 1 patch at least 24 hours prior to chemo	$442.19	$442.19

ER = Extended-release; PO = By mouth; SubQ = Subcutaneous; IV = Intravenous; Chemo = Chemotherapy
*Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable, and recommended dosing regimen for prophylaxis of chemotherapy-induced nausea and vomiting in a 70kg adult patient. Costs do not reflect rebated prices or net costs.
+Cost/Chemo Cycle is based on one chemotherapy treatment per week (every 7 days).

Bonjesta® (Doxylamine/Pyridoxine) Product Summary[12,13]

Indications: Bonjesta® is a fixed-dose combination product of doxylamine, an antihistamine, and pyridoxine, a vitamin B_6 analog, indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Dosing:

- Bonjesta® (doxylamine/pyridoxine) is available as extended-release oral tablets containing 20mg doxylamine and 20mg pyridoxine.

- The recommended dosage is one tablet orally at bedtime on day one. On day two, if symptoms are not adequately controlled, the dose can be increased to one tablet in the morning and one tablet at bedtime.
- The maximum recommended dose is two tablets daily (40mg doxylamine and 40mg pyridoxine per day).
- Bonjesta® tablets should be taken daily and not on an as needed basis. Each patient should be reassessed for the continued need for Bonjesta® as her pregnancy progresses.
- Bonjesta® tablets should be taken whole on an empty stomach with a glass of water.
- Bonjesta® has not been studied in women with hyperemesis gravidarum.

Comparison to Currently Available Products: Doxylamine/pyridoxine is currently available as oral tablets containing 10mg doxylamine and 10mg pyridoxine in each tablet (Diclegis®). Diclegis® is indicated for the same indications as Bonjesta®, and also has the same recommended dosing with regard to total milligram dose per day (*see above indications and dosing*). Generic Diclegis® was recently FDA approved, but is not yet available. Doxylamine 25mg is also available as an over-the-counter (OTC) product (available generically and as brand name Unisom® SleepTabs®), and pyridoxine (vitamin B_6) is available as an OTC product in multiple strengths, including 25mg, 50mg, and 100mg. The effectiveness of Bonjesta® was established based on clinical studies of Diclegis®; there have been no efficacy and safety trials conducted with Bonjesta®.

Cost: Cost information for Bonjesta® is not currently available at this time.

Recommendations

The College of Pharmacy recommends the prior authorization of Syndros™ (dronabinol oral solution), Sustol® (granisetron subcutaneous injection), and Bonjesta® (doxylamine/pyridoxine 20mg/20mg oral tablets) with the following criteria:

Marinol® and Syndros™ (Dronabinol) and Cesamet® (Nabilone) Approval Criteria:

1. Approval can be granted for six months for the diagnosis of HIV related loss of appetite.
2. The diagnosis of chemotherapy induced nausea and vomiting requires the following:
   a. A recent trial of ondansetron (within the past six months) used for at least three days or one cycle that resulted in inadequate response.
3. Approval length will be based on duration of need.
4. For Marinol® and Cesamet®, a quantity limit of 60 capsules per 30 days will apply.
5. For Syndros™, the quantity approved will be patient-specific depending on patient diagnosis, maximum recommended dosage, and manufacturer packaging.
6. For Syndros™ (dronabinol) oral solution, an age restriction of six years and younger will apply. Members older than six years of age will require a patient-specific, clinically significant reason why dronabinol oral capsules cannot be used.

Sustol® (Granisetron Subcutaneous Injection) Approval Criteria:

1. An FDA approved indication for use in the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens; and
2. Chemotherapy regimen must be listed on the prior authorization request; and
3. A recent trial of ondansetron (within the past six months) used for at least three days or one cycle that resulted in inadequate response is required for authorization in members receiving MEC; or
4. No ondansetron trial is required for authorization of granisetron in members receiving AC combination chemotherapy regimens; and
5. A patient-specific, clinically significant reason why the member cannot use Kytril® (granisetron hydrochloride injection); and
6. A quantity limit of one injection every seven days will apply.

Diclegis® and Bonjesta® (Doxylamine/Pyridoxine) Approval Criteria:

1. An FDA approved diagnosis of nausea and vomiting associated with pregnancy that is not responsive to conservative management; and
2. Trials with at least two non-pharmacological therapies that have failed to relieve nausea and vomiting; and
3. A patient-specific, clinically significant reason why member cannot use over-the-counter (OTC) doxylamine and OTC Vitamin B_6 (pyridoxine).
4. If the daily net cost of Bonjesta® (doxylamine/pyridoxine 20mg/20mg) is greater than the daily net cost of Diclegis® (doxylamine/pyridoxine 10mg/10mg), authorization of Bonjesta® would also require a patient-specific, clinically significant reason why member cannot use Diclegis®.

Utilization Details of Anti-Emetic Medications: Fiscal Year 2016

Anti-Emetic Medications: Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
ONDANSETRON PRODUCTS						
ONDANSETRON TAB 4MG ODT	51,561	43,028	$459,602.45	$1.34	$8.91	48.81%
ONDANSETRON TAB 4MG	12,562	9,321	$87,612.96	$0.79	$6.97	9.30%
ONDANSETRON TAB 8MG ODT	10,328	7,533	$107,629.98	$1.38	$10.42	11.43%
ONDANSETRON SOL 4MG/5ML	5,785	5,202	$153,482.33	$2.78	$26.53	16.30%
ONDANSETRON TAB 8MG	4,724	3,034	$40,273.86	$0.86	$8.53	4.28%
ONDANSETRON INJ 4MG/2ML	28	19	$332.63	$2.41	$11.88	0.04%
ONDANSETRON INJ 40/20ML	22	6	$679.22	$2.36	$30.87	0.07%
SUBTOTAL	**85,010**	**63,509***	**$849,613.43**	**$1.34**	**$9.99**	**90.22%**
GRANISETRON PRODUCTS						
GRANISETRON INJ 4MG/4ML	489	77	$14,888.48	$22.49	$30.45	1.58%
GRANISETRON TAB 1MG	20	8	$2,005.88	$9.16	$100.2	0.21%
SANCUSO DIS 3.1MG	15	11	$11,915.27	$35.25	$794.3	1.27%
SUBTOTAL	**524**	**94***	**$28,809.63**	**$23.63**	**$54.98**	**3.06%**
DRONABINOL PRODUCTS						
DRONABINOL CAP 5MG	96	31	$31,242.76	$11.30	$325.4	3.32%
DRONABINOL CAP 2.5MG	63	32	$10,282.89	$5.51	$163.2	1.09%
DRONABINOL CAP 10MG	22	9	$12,047.69	$16.73	$547.6	1.28%
SUBTOTAL	**181**	**65***	**$53,573.34**	**$10.01**	**$295.9**	**5.69%**
DOXYLAMINE/PYRIDOXINE PRODUCTS						
DICLEGIS TAB 10-10MG	18	10	$5,517.42	$11.03	$306.5	0.59%
SUBTOTAL	**18**	**10***	**$5,517.42**	**$11.03**	**$306.5**	**0.59%**
APREPITANT PRODUCTS						
EMEND PAK 80 & 125	4	3	$4,102.02	$39.07	$1,025.	0.44%
EMEND CAP 40MG	1	1	$95.55	$95.55	$95.55	0.01%
SUBTOTAL	**5**	**4***	**$4,197.57**	**$39.60**	**$839.5**	**0.45%**
TOTAL	**85,738**	**63,563***	**$941,711.39**	**$1.47**	**$10.98**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Anti-Emetic Medications: Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER
EMEND (FOSAPREPITANT) INJ J1453	998	273	$260,805.00	$261.33	3.66
EMEND (APREPITANT) CAPS J8501	17	8	$2,889.54	$169.97	2.13
TOTAL	**1,015**	**281**	**$263,694.54**	**$259.80**	**3.61**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 09/2016. Last accessed 11/17/2016.
[2] Merck News Release: FDA Approves Merck's Single-Dose Emend® (fosaprepitant dimeglumine) for Injection, in Combination with Other Antiemetic Agents, for the Prevention of Delayed Nausea and Vomiting in Adults Receiving Moderately Emetogenic Chemotherapy (MEC). Available online at: http://www.mercknewsroom.com/news-release/corporate-news/fda-approves-mercks-single-dose-emend-fosaprepitant-dimeglumine-injectio. Issued 02/04/2016. Last accessed 11/17/2016.
[3] Globe Newswire: Insys Therapeutics Announces FDA Approval of Syndros™. Available online at: https://globenewswire.com/news-release/2016/07/05/853588/0/en/Insys-Therapeutics-Announces-FDA-Approval-of-Syndros.html. Issued 07/05/2016. Last accessed 11/17/2016.
[4] Business Wire: Heron Therapeutics Announces U.S. FDA Approval of Sustol® (granisetron) Extended-Release Injection for the Prevention of Chemotherapy-Induced Nausea and Vomiting. Available online at: http://www.businesswire.com/news/home/20160810005389/en/Heron-Therapeutics-Announces-U.S.-FDA-Approval-SUSTOL%C2%AE. Issued 08/10/2016. Last accessed 11/17/2016.
[5] FDA ANDA Approval: Doxylamine/Pyridoxine Oral Tablets. Available online at: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=205811. Issued 08/19/2016. Last accessed 11/17/2016.
[6] FDA NDA Approval: Bonjesta (Doxylamine/Pyridoxine 20mg/20mg) Oral Tablets. Available online at: http://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=209661. Issued 11/07/2016. Last accessed 11/17/2016.
[7] Bachert A. Aprepitant Trial in Gastroparesis Misses the Primary Mark – But Positive Findings in Secondary Outcomes May Save the Day. *Medpage Today*. Available online at: http://www.medpagetoday.com/meetingcoverage/acg/60848. Issued 10/18/2016. Last accessed 11/17/2016.
[8] Syndros™ Prescribing Information. Drugs@FDA. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/205525s000lbl.pdf. Last revised 07/2016. Last accessed 11/17/2016.
[9] Marinol® Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/marinol-2/. Last revised 08/12/2015. Last accessed 11/17/2016.
[10] Sustol® Prescribing Information. Heron Therapeutics. Available online at: http://sustol.com/public/pdfs/PI.pdf. Last revised 08/2016. Last accessed 11/17/2016.
[11] Micromedex 2.0: Granisetron Drug Information. Available online at: http://www.micromedexsolutions.com/micromedex2/librarian/. Last revised 11/11/2016. Last accessed 11/17/2016.
[12] Bonjesta® Prescribing Information. Drugs@FDA. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209661lbl.pdf. Last revised 11/2016. Last accessed 11/17/2016.
[13] Diclegis® Package Insert. Medlibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/diclegis-1/. Last revised 05/18/2016. Last accessed 11/17/2016.

Appendix L

Fiscal Year 2016 Annual Review of Phosphate Binders and 30-Day Notice to Prior Authorize Fosrenol® (Lanthanum Carbonate), Velphoro® (Sucroferric Oxyhydroxide), and Auryxia™ (Ferric Citrate)

Oklahoma Health Care Authority
December 2016

Introduction[1,2,3,4]

Patients with chronic kidney disease (CKD) are unable to effectively excrete phosphate. High serum levels of phosphorus may lead to renal bone disease, vascular calcification, hyperparathyroidism, and mortality. The National Kidney Foundation released guidelines regarding the management of hyperphosphatemia in patients with renal impairment. For CKD patients who are not on dialysis, moderate restriction of phosphate intake is recommended, provided this can be done without compromising nutritional status. In nondialysis CKD patients who have a high serum phosphorus level despite dietary phosphate restriction, administration of phosphate binders to maintain serum phosphorus levels in the normal range is suggested. For patients on dialysis (5D), the three most common methods to treat hyperphosphatemia include restricting dietary phosphate intake, administering phosphate binders, and increasing dialysis.

Phosphate binders are classified as calcium-containing and noncalcium-containing. The calcium-containing binders include calcium carbonate and calcium acetate. Examples of noncalcium-containing binders include sevelamer and lanthanum. There is no consensus on which phosphate binder should be used in CKD patients; all are effective at lowering phosphate. An extensive systematic review and meta-analysis published online in *Nephrology Dialysis Transplantation* revealed few important advantages for any particular agent.

Calcium-based agents have traditionally been used, however these products are associated with adverse effects such as vascular calcification and arterial stiffening secondary to hypercalcemia. Calcium-free phosphate binders, such as sevelamer and lanthanum, were developed to manage patients with CKD and to avoid hypercalcemia. Current National Kidney Foundation guidelines recommend that for patients with CKD stages 3 to 5 and 5D, it is reasonable that the choice of phosphate binder takes into account the patient's CKD stage, concomitant therapies, adverse effects profile, and the presence of other components of mineral and bone disorders.

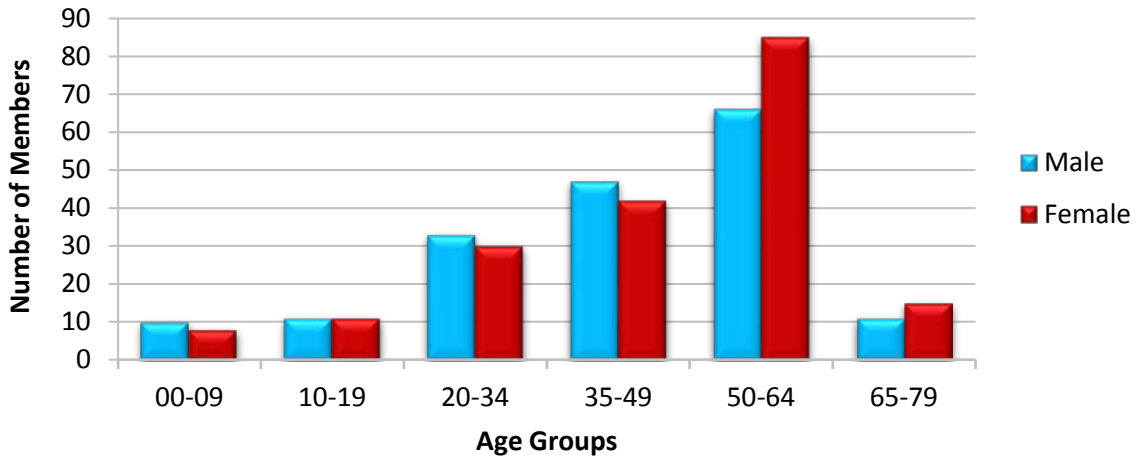
Utilization of Phosphate Binders: Fiscal Year 2016

Comparison of Fiscal Years for Phosphate Binders

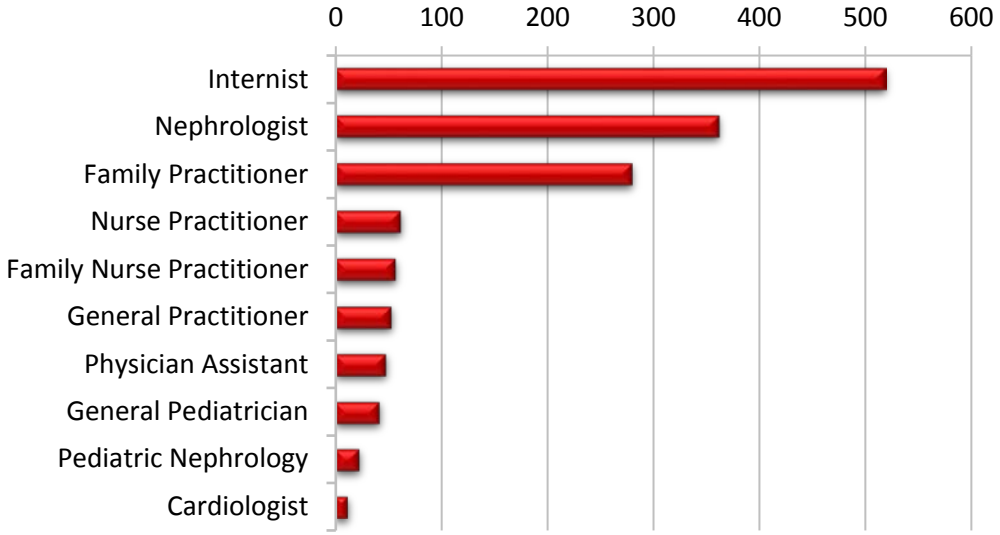
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	354	1,460	$1,204,035.33	$824.68	$28.80	389,757	41,808
2016	369	1,497	$1,332,715.72	$890.26	$30.81	401,269	43,261
% Change	**4.20%**	**2.50%**	**10.70%**	**8.00%**	**7.00%**	**3.00%**	**3.50%**
Change	**15**	**37**	**$128,680.39**	**$65.58**	**$2.01**	**11,512**	**1,453**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Phosphate binders do not currently require prior authorization.

Demographics of Members Utilizing Phosphate Binders



Top Prescriber Specialties of Phosphate Binders by Number of Claims



Market News and Updates[5,6]

Anticipated Patent Expiration(s):

- Velphoro® (sucroferric oxyhydroxide): December 2017
- Renagel® (sevelamer hydrochloride): October 2020
- PhosLo® (calcium acetate): July 2021
- Fosrenol® (lanthanum carbonate) tablet: August 2024
- Renvela® (sevelamer carbonate) tablet: October 2025
- Phoslyra® (calcium acetate): February 2030
- Auryxia™ (ferric citrate): July 2030
- Fosrenol® (lanthanum carbonate) powder: December 2030
- Renvela® (sevelamer carbonate) packet for suspension: December 2030

Safety Update(s):

- **February 2016:** The U.S. Food and Drug Administration (FDA) approved safety labeling changes for Fosrenol® (lanthanum carbonate). The *Warnings and Precautions* section was revised to include information regarding serious cases of gastrointestinal (GI) obstruction, ileus, subileus, GI perforation, and fecal impaction that have been reported in patients taking lanthanum, some requiring surgery or hospitalization. Risk factors for GI obstruction and perforation identified from post-marketing reports in patients taking Fosrenol® chewable tablets include altered GI anatomy, hypomotility disorders, and concomitant medications. Some cases were reported in patients with no history of GI disease. Patients who are prescribed Fosrenol® chewable tablets should be advised to completely chew the tablet to reduce the risk of serious adverse GI events.

Phosphate Binder Product Comparison[1]

Comparison of Phosphate Binders

Phosphate Binder	Available Products	RPBC	Initial Dose	Estimated Cost per Month*
calcium carbonate	Various products available as tablets; suspension in various strengths (e.g., Tums®)	1.0	500mg TID with meals	<$10 (generic)
calcium acetate	PhosLo® 667mg capsule; Phoslyra® 667mg/5mL solution; Others	1.0	1,334mg TID with meals	$57.46 (generic calcium acetate capsules); $207.00 (Phoslyra® 667mg/5mL solution)
sevelamer carbonate	Renvela® 800mg tablet; Renvela® 800mg, 2,400mg powder packet for oral suspension	0.75	800mg to 1,600mg TID with meals	$490.50 (Renvela® 800mg tablet); $1,469.70 (Renvela® 800mg powder packet)
sevelamer hydrochloride	Renagel® 400mg, 800mg tablet	0.75	800mg to 1,600mg TID with meals	$612.00

Phosphate Binder	Available Products	RPBC	Initial Dose	Estimated Cost per Month*
lanthanum carbonate	Fosrenol® 500mg, 750mg, 1,000mg chewable tablet; Fosrenol® 750mg, 1,000mg oral powder	2.0	500mg TID with meals	$951.30 (Fosrenol® 500mg chewable tablet); $981.00 (Fosrenol® 750mg oral powder)
sucroferric oxyhydroxide	Velphoro® 500mg chewable tablet	Not known	500mg TID with meals	$943.11
ferric citrate	Auryxia™ 1g tablet	Not known	2g TID with meals	$874.80

Table modified from: Comparison of Phosphate Binders. *Pharmacist's Letter/Prescriber's Letter.*
*Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. Costs do not reflect rebated prices or net costs.
RPBC = Relative Phosphate-Binding Coefficients (calcium carbonate as index); TID = Three times daily

Fosrenol® (Lanthanum Carbonate) Product Summary[7]

Initial FDA Approval: 2004

Indications: Fosrenol® (lanthanum carbonate) is a phosphate binder indicated to reduce serum phosphate in patients with end stage renal disease (ESRD).

Dosing:

- Fosrenol® is available as chewable tablets in the following strengths: 500mg, 750mg, and 1,000mg. It is also available as an oral powder in the following strengths: 750mg and 1,000mg.
- The recommended initial total daily dose is 1,500mg in divided doses. The dose can be titrated every 2 to 3 weeks based on serum phosphate levels.
- It is recommended to take lanthanum carbonate with or immediately after meals.
- Fosrenol® chewable tablets should be chewed or crushed completely prior to swallowing.
- Fosrenol® oral powder can be sprinkled on a small quantity of applesauce or other similar food and consumed immediately. It is suggested to consider the powder formulation in patients with poor dentition or who have difficulty chewing tablets.

Mechanism of Action: Lanthanum carbonate is a phosphate binder that reduces absorption of phosphate by forming insoluble lanthanum phosphate complexes that pass through the gastrointestinal (GI) tract unabsorbed. Serum phosphate and calcium phosphate are both reduced as a consequence of the decreased dietary phosphate absorption.

Contraindications:

- Bowel obstruction, ileus, and fecal impaction.

Warnings and Precautions:

- Gastrointestinal Adverse Effects: Serious cases of GI obstruction, ileus, subileus, GI perforation, and fecal impaction have been reported in patients taking lanthanum, some requiring hospitalization or surgery. Patients prescribed the chewable tablets should be

advised to chew the tablet completely to reduce the risk of serious adverse GI events. Risk factors for GI obstruction and GI perforation identified from post-marketing reports include altered GI anatomy (e.g., history of GI surgery, diverticular disease, GI ulceration), hypomotility disorders (e.g., constipation, ileus, diabetic gastroparesis), and concomitant medications (e.g., calcium channel blockers).

- Diagnostic Tests: Lanthanum carbonate has radio-opaque properties and therefore may give the appearance typical of an imaging agent during abdominal X-ray procedures.

Adverse Reactions: The most common adverse reactions reported in controlled trials with lanthanum carbonate (≥5% difference vs. placebo) include the following:

- Vomiting
- Nausea
- Abdominal Pain

The following adverse reactions have been identified during post-approval use of lanthanum carbonate:

- Constipation
- Dyspepsia
- Allergic Skin Reactions
- Tooth Injury While Chewing the Tablet

Drug Interactions:

- Drugs Binding to Antacids: Lanthanum carbonate may interact with compounds which bind to cationic antacids (i.e., aluminum-, magnesium-, or calcium-based). It is recommended patients not take such compounds within two hours of dosing with lanthanum carbonate.
- Quinolone Antibiotics: Co-administration of quinolone antibiotics with lanthanum carbonate may reduce the extent of antibiotic absorption. Oral quinolone antibiotics should be administered at least one hour before or four hours after lanthanum carbonate. When oral quinolones are given for short courses, it is recommended to consider eliminating the doses of lanthanum carbonate that would be normally scheduled near the time of quinolone administration to improve quinolone absorption.
- Levothyroxine: Levothyroxine bioavailability was decreased by approximately 40% when taken with lanthanum carbonate. Thyroid hormone replacement therapy should be administered at least two hours before or two hours after dosing with lanthanum carbonate. It is recommended that thyroid stimulating hormone (TSH) levels also be monitored.

Use in Special Populations:

- Pregnancy: Lanthanum carbonate is Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. Use is not recommended in pregnancy.
- Labor and Delivery: The effects of lanthanum carbonate on labor and delivery in humans is unknown.
- Lactation: It is not known whether lanthanum carbonate is excreted in human milk. The possibility of infant exposure should be considered when lanthanum carbonate is administered to a nursing woman as many drugs are excreted in human milk.

- Pediatric Use: The safety and efficacy of lanthanum carbonate in pediatric patients have not been established. Lanthanum was deposited into developing bone including growth plates and the consequences of such deposition in developing bone in pediatric patients are unknown. The use of lanthanum carbonate is not recommended in this population.
- Geriatric Use: Of the total number of patients in clinical studies for lanthanum carbonate, 32% (538) were ≥65 years of age and 9.3% (159) were ≥75 years of age. No overall differences in safety or effectiveness were observed between patients ≥65 years of age and younger patients.

Efficacy: The effectiveness of lanthanum carbonate in reducing serum phosphorus levels in ESRD patients was demonstrated in two placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies.

- Double-Blind Placebo Controlled Studies: In the placebo-controlled, randomized withdrawal studies, 185 patients with ESRD undergoing either hemodialysis (n=146) or peritoneal dialysis (n=39) were enrolled. After titration of lanthanum carbonate to achieve a phosphate level between 4.0 and 5.6mg/dL in one study (doses up to 2,250mg/day) or ≤5.9mg/dL in the second study (doses up to 3,000mg/day) and maintenance through six weeks, patients were randomized to lanthanum carbonate or placebo. The phosphorus concentration rose in the placebo group by 1.7mg/dL in one study and 1.9mg/dL in the other study relative to patients who remained on lanthanum carbonate.
- Open-Label Active Controlled Studies: Two long-term, open-label studies were conducted, involving a total of 2,028 patients with ESRD undergoing hemodialysis. Patients were randomized to receive lanthanum carbonate or alternative phosphate binders for up to six months in one study and two years in another study. The daily lanthanum carbonate doses ranged from 375mg to 3,000mg divided and taken with meals. Doses were titrated to reduce serum phosphate levels to a target level. The daily doses of alternative therapy was based on current prescribing information for those commonly utilized. Both treatment groups had similar reductions in serum phosphate of about 1.8mg/dL. Maintenance of the reduction was observed for up to three years in patients treated with lanthanum carbonate in long-term, open-label extensions. Furthermore, no effects on serum levels of 25-dihydroxyvitamin D3, vitamin A, vitamin B12, vitamin E, and vitamin K were observed in patients taking lanthanum carbonate who were monitored for six months. Paired bone biopsies (at baseline and at one or two years) in 69 patients randomized to either lanthanum carbonate or calcium carbonate in one study and 99 patients randomized to either lanthanum carbonate or alternative therapy in a second study showed no differences in the development of mineralization defects between the groups.

Velphoro® (Sucroferric Oxyhydroxide) Product Summary[8]

Initial FDA Approval: 2013

Indications: Velphoro® (sucroferric oxyhydroxide) is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis.

Dosing:

- Velphoro® is available as a 500mg chewable tablet. Each tablet contains 500mg iron (equivalent to 2,500mg sucroferric oxyhydroxide).
- The recommended initial dose is 1,500mg per day, administered as one tablet three times daily with meals. The dose can be titrated as often as weekly in decrements or increments of 500mg per day as needed until an acceptable serum phosphorus level is reached.
- The tablets must be chewed and not swallowed whole. To aid with chewing and swallowing, the tablets may be crushed.

Mechanism of Action: In the aqueous environment of the GI tract, phosphate binding takes place by ligand exchange between hydroxyl groups and/or water in sucroferric oxyhydroxide and the phosphate in the diet. The bound phosphate is eliminated in the feces. As a consequence of the reduced dietary phosphate absorption both serum phosphorus levels and calcium-phosphorus levels are reduced.

Contraindications:

- None.

Warnings and Precautions:

- Monitoring in Patients with GI Disorders or Iron Accumulation Disorders: In patients with peritonitis during peritoneal dialysis, significant gastric or hepatic disorders, following major GI surgery, or with a history of hemochromatosis or other diseases with iron accumulation the effect and iron homeostasis should be monitored as such patients have not been included in clinical studies with sucroferric oxyhydroxide.

Adverse Reactions: The most common adverse reactions reported in controlled trials of sucroferric oxyhydroxide (≥5% of patients) include the following:

- Diarrhea
- Nausea
- Discolored Feces

Drug Interactions:

- Doxycycline: If doxycycline and sucroferric oxyhydroxide must be used concurrently, doxycycline should be taken at least one hour before sucroferric oxyhydroxide.
- Levothyroxine: The concomitant use of levothyroxine and sucroferric oxyhydroxide is not recommended.
- There are no empirical data on avoiding drug interactions between sucroferric oxyhydroxide and most concomitant oral medications. For oral medications where a reduction in the bioavailbility of that medication would have a clinically significant effect on its safety or efficacy, separating the administration of the two medications should be considered.

Use in Special Populations:

- Pregnancy: Sucroferric oxyhydroxide is Pregnancy Category B. No adequate and well-controlled studies have been conducted in pregnant women. Reproduction studies in rats and rabbits at doses up to 16 and 4 times, respectively, the human maximum

recommended clinical dose on a body weight basis have not revealed evidence of impaired fertility or harm to the fetus due to sucroferric oxyhydroxide.

- Labor and Delivery: The effects of sucroferric oxyhydroxide on labor and delivery in humans is unknown. In animal studies with doses up to 16 times the maximum recommended clinical dose on a body weight basis, no sucroferric oxyhydroxide treatment-related effects on labor and delivery were seen.
- Lactation: Since the absorption of iron from sucroferric oxyhydroxide is minimal, excretion of sucroferric oxyhydroxide in breast milk is unlikely.
- Pediatric Use: The safety and effectiveness of sucroferric oxyhydroxide in pediatric patients have not been established.
- Geriatric Use: No overall differences in safety or effectiveness were observed between patients ≥65 years of age and younger patients in two active-controlled clinical studies of sucroferric oxyhydroxide.

Efficacy: The ability of sucroferric oxyhydroxide to lower serum phosphorus in ESRD patients was demonstrated in two randomized clinical trials: one six-week, open-label, active-controlled (sevelamer hydrochloride), dose-finding study and one 55-week, open-label, active-controlled (sevelamer carbonate), parallel-group, safety and efficacy study.

- Fixed-Dose Study: In one study, 154 ESRD patients on hemodialysis who were hyperphosphatemic (serum phosphorus >5.5mg/dL but <7.75mg/dL) following a two-week phosphate binder washout period were randomized to receive sucroferric oxyhydroxide at 250mg/day, 1,000mg/day, 1,500mg/day, 2,000mg/day, or 2,500mg/day or active-control (sevelamer hydrochloride). Sucroferric oxyhydroxide treatment was divided across meals and no dose titration was allowed. Within each of the groups, the serum phosphorus level at the end of treatment was compared to baseline value. Sucroferric oxyhydroxide was shown to be efficacious ($p \leq 0.016$) for all doses except 250mg/day.
- Dose Titration Study: In one 55-week, open-label, active-controlled, parallel-group, safety and efficacy study, 1,054 patients on hemodialysis (N=968) or peritoneal dialysis (N=87) with serum phosphorus ≥6mg/dL following a two to four week phosphate binder washout period were randomized and treated with either sucroferric oxyhydroxide or active-control (sevelamer carbonate) for 24 weeks. At the end of week 24, 93 patients on hemodialysis whose serum phosphorus levels were controlled (<5.5mg/dL) with sucroferric oxyhydroxide in the first part of the study were re-randomized to continue treatment with their week 24 maintenance dose of sucroferric oxyhydroxide or a non-effective low-dose control of 250mg/day for a further three weeks. At week 27, a superiority analysis of the sucroferric oxyhydroxide maintenance dose versus low-dose was performed. The maximum dose of sucroferric oxyhydroxide was 3,000mg/day and the minimum dose was 1,000mg/day. The sucroferric oxyhydroxide maintenance dose was statistically significantly superior in sustaining the phosphorus lowering effect in hemodialysis patients at week 27 ($p<0.001$) compared with the non-effective low-dose control. Following completion of the 27 weeks, 658 patients were treated in a 28-week extension study with either sucroferric oxyhydroxide (N=391) or sevelamer carbonate (N=267) according to their original randomization. Serum phosphorus levels declined

rapidly during the first few weeks of treatment and remained relatively constant thereafter. The phosphorus lowering effect of sucroferric oxyhydroxide was consistently maintained through twelve months of treatment. Serum iron level increases from baseline were not clinically meaningful and did not differ significantly compared to the active control. There was no evidence of iron accumulation during one year of treatment.

Auryxia™ (Ferric Citrate) Product Summary[9]

Initial FDA Approval: 2014

Indications: Auryxia™ (ferric citrate) is a phosphate binder indicated for the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis.

Dosing:

- Auryxia™ is available as a 210mg ferric iron tablet, equivalent to 1g ferric citrate.
- The recommended initial dose is two tablets orally three times per day with meals. The dose should be adjusted by one to two tablets as needed to maintain serum phosphorus at target levels. The maximum recommended dose is twelve tablets daily. The dose should be titrated at one week or longer intervals.

Mechanism of Action: Ferric iron binds dietary phosphate in the GI tract and precipitates as ferric phosphate. This compound is excreted in the stool. By binding phosphate in the GI tract and decreasing absorption, ferric citrate lowers the phosphate concentration in the serum.

Contraindications:

- Iron overload syndromes (e.g., hemochromatosis).

Warnings and Precautions:

- Iron Overload: Iron absorption from ferric citrate may lead to excessive elevations in iron stores. Increases in serum ferritin and transferrin saturation (TSAT) levels were observed in clinical trials. Iron parameters (e.g., serum ferritin and TSAT) should be assessed prior to initiating ferric citrate and monitored while on therapy. Patients receiving intravenous (IV) iron may require a reduction in dose or discontinuation of IV iron therapy.
- Accidental Overdose of Iron-Containing Products: A leading cause of fatal poisoning in children under 6 years of age is accidental overdose of iron-containing products. This product should be kept out of the reach of children. In case of accidental overdose, a doctor or poison control center should be contacted immediately.
- Patients with GI Bleeding or Inflammation: Patients with inflammatory bowel disease or active, symptomatic GI bleeding were excluded from clinical trials. Safety has not been established in these patients.

Adverse Reactions: The most common adverse reactions reported in clinical trials with ferric citrate include the following:

- Diarrhea
- Nausea

- Constipation
- Vomiting
- Discolored Feces

Drug Interactions:

- Doxycycline: If doxycycline and ferric citrate must be used concurrently, doxycycline should be taken at least one hour before ferric citrate.
- Ciprofloxacin: If ciprofloxacin and ferric citrate must be used concurrently, ciprofloxacin should be taken at least two hours before or after ferric citrate.
- When clinically significant drug interactions are expected, it is recommended to consider separation of the timing of administration. Consideration should be given to monitoring clinical responses or blood levels of the concomitant medication.

Use in Special Populations:

- Pregnancy: Ferric citrate is Pregnancy Category B. No adequate and well-controlled studies have been conducted in pregnant women. It is not known whether ferric citrate can cause fetal harm when administered to a pregnant woman. No animal reproduction studies have been conducted. An overdose of iron in pregnant women may carry a risk for spontaneous abortion, gestational diabetes, and fetal malformation.
- Labor and Delivery: The effects of ferric citrate on labor and delivery are unknown.
- Nursing Mothers: Data from rat studies have shown the transfer of iron into milk by divalent metal transporter-1 (DMT-1) and ferroportin-1 (FPN-1). Hence, there is a possibility of infant exposure when ferric citrate is administered to a nursing woman.
- Pediatric Use: The safety and effectiveness of ferric citrate in pediatric patients have not been established.
- Geriatric Use: Clinical studies of ferric citrate included 106 patients 65 years of age and older. The clinical study experience has not identified any obvious differences in responses between the elderly and younger patients in the tolerability or efficacy of ferric citrate.

Efficacy: The safety and efficacy of ferric citrate was studied in a multicenter, randomized, open-label, Phase 3 trial of 441 hyperphosphatemia patients with CKD on hemodialysis and peritoneal dialysis over 56 weeks. The primary endpoint of the trial was change in serum phosphorus from baseline (Week 52) to Week 56 between ferric citrate and placebo in a 4-week efficacy assessment (Placebo-Controlled Period), which followed a 52-week safety assessment (Active Control Period). At the final Active Control Period visit, ferric citrate patients were re-randomized to either continue ferric citrate treatment or receive placebo as part of the Placebo-Controlled Period. Ferric citrate brought patients to goal (3.5 to 5.5mg/dL), with serum phosphorus reductions comparable to sevelamer carbonate and/or calcium acetate, and maintained significant reductions compared to placebo. In the 52-week Active Control Period (selected secondary endpoint), the treatment difference was 0.02mg/dL at Week 52 ($P=0.89$) and in the 4-week Placebo-Controlled Period (primary endpoint), the treatment difference at Week 56 was -2.18mg/dL ($P<0.0001$).

Recommendations

The College of Pharmacy recommends the prior authorization of Velphoro® (sucroferric oxyhydroxide) and Auryxia™ (ferric citrate) with the following criteria:

Velphoro® (Sucroferric Oxyhydroxide) and Auryxia™ (Ferric Citrate) Approval Criteria:

1. A diagnosis of hyperphosphatemia in patients with chronic kidney disease (CKD) on dialysis; and
2. Documented trials of inadequate response to at least two of the phosphate binders available without a prior authorization or a patient-specific, clinically significant reason why the member cannot use a phosphate binder available without a prior authorization.
3. For Auryxia™, a quantity limit of 12 tablets per day will apply.

Additionally, the College of Pharmacy recommends the prior authorization of Fosrenol® (lanthanum carbonate) 1,000mg chewable tablets, 750mg packets, and 1,000mg packets with the following criteria:

Fosrenol® (Lanthanum Carbonate) 1,000mg Chewable Tablets, 750mg Oral Powder, and 1,000mg Oral Powder Approval Criteria:

1. An FDA approved diagnosis of hyperphosphatemia in patients with end stage renal disease (ESRD); and
2. Documented trials of inadequate response to at least two of the phosphate binders available without a prior authorization or a patient-specific, clinically significant reason why the member cannot use a phosphate binder available without a prior authorization; and
3. For the approval of Fosrenol® oral powder, a patient-specific, clinically significant reason why a special formulation is needed over a phosphate binder available without a prior authorization, such as Fosrenol® 500mg or 750mg chewable tablets which can be crushed, must be provided; and
4. For the approval of Fosrenol® 1,000mg chewable tablets, a patient-specific, clinically significant reason why the member cannot use a phosphate binder available without a prior authorization, such as Fosrenol® 500mg or 750mg chewable tablets, must be provided.

Based on the lower net cost of generic calcium acetate containing products, Phoslyra®, Renvela®, Renagel®, and Fosrenol® 500mg and 750mg chewable tablets, the College of Pharmacy does not recommend the prior authorization of these products at this time.

Utilization Details of Phosphate Binders: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
CALCIUM ACETATE PRODUCTS						
CALC ACETATE CAP 667MG	654	202	$62,923.64	$3.30	$96.21	4.72%
PHOSLYRA SOL	29	4	$8,460.23	$11.80	$291.73	0.63%
CALC ACETATE TAB 667MG	26	10	$3,451.75	$4.47	$132.76	0.26%
PHOSLO CAP 667MG	3	3	$445.14	$4.95	$148.38	0.03%
SUBTOTAL	**712**	**219**	**$75,280.76**	**$3.65**	**$105.73**	**5.64%**
SEVELAMER PRODUCTS						
RENVELA TAB 800MG	577	165	$942,000.26	$56.84	$1,632.58	70.68%
RENVELA PAK 0.8GM	49	16	$84,796.21	$63.90	$1,730.53	6.36%
RENVELA PAK 2.4GM	46	13	$83,746.41	$58.98	$1,820.57	6.28%
RENAGEL TAB 800MG	39	14	$51,777.55	$46.86	$1,327.63	3.89%
RENAGEL TAB 400MG	7	3	$2,090.25	$9.95	$298.61	0.16%
SUBTOTAL	**718**	**211**	**$1,164,410.68**	**$56.43**	**$1,621.74**	**87.37%**
LANTHANUM CARBONATE PRODUCTS						
FOSRENOL CHW 1000MG	27	7	$35,598.76	$44.22	$1,318.47	2.67%
FOSRENOL CHW 500MG	3	2	$3,110.21	$34.56	$1,036.74	0.23%
SUBTOTAL	**30**	**9**	**$38,708.97**	**$43.25**	**$1,290.30**	**2.90%**
SUCROFERRIC OXYHYDROXIDE PRODUCTS						
VELPHORO CHW 500MG	37	11	$54,315.31	$48.93	$1,467.98	4.08%
SUBTOTAL	**37**	**11**	**$54,315.31**	**$48.93**	**$1,467.98**	**4.08%**
TOTAL	**1,497**	**369***	**$1,332,715.72**	**$30.81**	**$890.26**	**100%**

*Total number of unduplicated members.
Costs listed in the table above do not take into account federal or supplemental rebate participation; therefore, do not reflect net costs.
Phosphate binders do not currently require prior authorization.

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[1] PL Detail-Document, Comparison of Phosphate Binders. *Pharmacist's Letter/Prescriber's Letter*. August 2015.
[2] Hutchison, Alastair. Oral Phosphate Binders. *Kidney International.* 2009: 75(9): 906-914.
[3] Berkoben M, Quarles L. Treatment of Hyperphosphatemia in Chronic Kidney Disease. *UpToDate*. Available online at: http://www.uptodate.com/contents/treatment-of-hyperphosphatemia-in-chronic-kidney-disease?source=search_result&search=phosphate+binders&selectedTitle=1%7E150. Last revised 05/04/2016. Last accessed 11/09/2016.
[4] Foote E. Few advantages proven for a particular phosphate binder in patients with kidney disease. APHA DrugInfoLine®. Available online at: http://www.aphadruginfoline.com/nephrology/few-advantages-proven-particular-phosphate-binder-patients-kidney-disease. Issued 11/01/2016. Last accessed 11/09/2016.
[5] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 10/2016. Last accessed 12/02/2016.
[6] U.S. Food and Drug Administration (FDA). FDA Safety Labeling Changes: Fosrenol® (lanthanum carbonate) Chewable Tablets. Available online at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm254564.htm. Issued 02/2016. Last accessed 11/14/2016.
[7] Fosrenol® Package Insert. Shire US, Inc. Available online at: https://pi.shirecontent.com/PI/PDFs/Fosrenol_USA_ENG.pdf. Last revised 02/2016. Last accessed 10/27/2016.
[8] Velphoro® Prescribing Information. Daily Med. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=237da26c-f38c-4faa-93ad-735e71c9d0c1. Last revised 09/10/2014. Last accessed 11/10/2016.
[9] Auryxia™ Prescribing Information. Keryx Biopharmaceuticals, Inc. Available online at: https://www.auryxia.com/wp-content/uploads/Auryxia_PI_Keryx.pdf. Last revised 11/2016. Last accessed 11/11/2016.

Appendix M

30-Day Notice to Prior Authorize Defitelio® (Defibrotide Sodium)

Oklahoma Health Care Authority
December 2016

Hepatic Veno-Occlusive Disease (VOD) Background Information[1,2,3,4,5,6]

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), is a potentially life-threatening complication that occurs most commonly following hematopoietic stem-cell transplant (HSCT). VOD may also occur less commonly following the use of chemotherapeutic agents in non-transplant settings, following ingestion of alkaloid toxins, after high-dose radiation therapy, or following liver transplantation. VOD is characterized by ascites, right upper quadrant pain, rapid weight gain, jaundice, and hepatomegaly. Clinically, the disease resembles the Budd-Chiari syndrome; however, in VOD the hepatic venous outflow obstruction is due to occlusion of the terminal hepatic venules and hepatic sinusoids rather than the hepatic veins and inferior vena cava. The occurrence of VOD has been reported in up to 60% of patients following HSCT, ranging in severity from a mild, reversible disease to a severe syndrome associated with multi-organ failure and death.

The management of VOD depends at least partially on the severity of the disease. Severe VOD predicts a poor outcome and warrants more aggressive therapy. Supportive care is a key component in the management of all patients with VOD. Supportive measures that should be considered include maintaining euvolemia (daily weights and measures of fluid intake and output are critical), minimizing exposure to hepatotoxic agents (e.g., alcohol, nonsteroidal anti-inflammatory drugs, excessive use of acetaminophen, certain herbal remedies), pain control, and paracentesis. However, patients with severe VOD have high mortality rates with supportive care alone. In March 2016, the U.S. Food and Drug Administration (FDA) approved Defitelio® (defibrotide sodium) to treat adult and pediatric patients who develop VOD with additional kidney or lung abnormalities after HSCT. Defitelio® is the first FDA-approved therapy for the treatment of this rare and life-threatening liver condition. The FDA granted the Defitelio® application priority review status which expedites the development and review of certain drugs due to their potential to benefit patients with serious or life-threatening conditions. The medication also received orphan drug designation, which provides incentives such as tax credits and eligibility for exclusivity to assist and encourage the development of drugs for rare diseases.

Defitelio® (Defibrotide Sodium) Product Summary[7]

Indications: Defitelio® (defibrotide sodium) is indicated for the treatment of adult and pediatric patients with hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with pulmonary or renal dysfunction following hematopoietic stem-cell transplantation (HSCT).

Dosing:

- Defitelio® is available in a single-patient-use vial containing 200mg/2.5mL of defibrotide sodium.
- The recommended dose for adult and pediatric patients is 6.25mg/kg every six hours given as a 2-hour intravenous infusion.
- The dose should be based on the patient's baseline body weight, defined as the weight prior to the preparative regimen for HSCT.
- Defibrotide sodium is administered for a minimum of 21 days. If after 21 days the signs and symptoms of hepatic VOD have not resolved, defibrotide sodium is continued until resolution of VOD or up to a maximum of 60 days.

Mechanism of Action: The mechanism of action of defibrotide sodium has not been fully elucidated. In vitro, defibrotide sodium enhances the enzymatic activity of plasmin to hydrolyze fibrin clots. Defibrotide sodium increased tissue plasminogen activator and thrombomodulin expression, and decreased von Willebrand factor and plasminogen activator inhibitor-1 expression, thereby reducing endothelial cell activation and increasing endothelial cell mediated fibrinolysis. Defibrotide sodium protected endothelial cells from damage caused by chemotherapy, tumor necrosis factor-α, serum starvation, and perfusion.

Contraindications:

- Concomitant administration with systemic anticoagulant or fibrinolytic therapy.
- Known hypersensitivity to Defitelio® or to any of its excipients.

Warnings and Precautions:

- <u>Hemorrhage:</u> Defibrotide sodium increased the activity of fibrinolytic enzymes in vitro and it may increase the risk of bleeding in patients with VOD following HSCT. Defibrotide sodium should not be initiated in patients with active bleeding. Patients should be monitored for signs of bleeding.
- <u>Hypersensitivity Reactions:</u> Hypersensitivity reactions occurred in less than 2% of patients treated with defibrotide sodium. These reactions include rash, urticaria, and angioedema. One case of an anaphylactic reaction was reported in a patient who had previously been treated with defibrotide sodium. It is recommended that patients be monitored for hypersensitivity reactions, especially if there is a history of previous exposure. If a severe hypersensitivity reaction occurs, defibrotide sodium should be discontinued and the patient should be treated according to the standard of care and monitored until symptoms resolve.

Adverse Reactions: The most common adverse reactions associated with defibrotide sodium treatment (incidence ≥10% and independent of causality) include the following:

- Hypotension
- Diarrhea
- Vomiting
- Nausea
- Epistaxis

Drug Interactions:

- Antithrombotic Agents: Defibrotide sodium may enhance the pharmacodynamic activity of antithrombotic/fibrinolytic drugs such as heparin or alteplase. The concomitant use of defibrotide sodium with antithrombotics or fibrinolytic drugs is contraindicated due to increased risk of hemorrhage.

Use in Special Populations:

- Pregnancy: There are no available data on the use of defibrotide sodium in pregnant women. When pregnant rabbits were administered defibrotide sodium during the period of organogenesis at doses that were comparable to the recommended human dose based on body surface area, defibrotide sodium decreased the number of implantations and viable fetuses. Pregnant women should be advised of the potential risk of miscarriage.
- Lactation: There is no information on the presence of defibrotide sodium in human milk, the effects on the breastfed infant, or the effects on milk production. Breastfeeding is not recommended during treatment with defibrotide sodium due to the potential for serious adverse reactions, including bleeding in a breastfed infant.
- Pediatric Use: The safety and effectiveness of defibrotide sodium in pediatric patients have been established. Use of defibrotide sodium in adult and pediatric patients with VOD with evidence of renal or pulmonary dysfunction following HSCT is supported by evidence from an adequate and well-controlled study and a dose finding study. The clinical trials enrolled 66 pediatric patients in the following age groups: 22 infants (1 month up to less than 2 years of age), 30 children (3 years of age up to less than 12 years of age), and 14 adolescents (12 years of age to less than 17 years of age). The efficacy and safety outcomes were consistent across pediatric and adult patients in the clinical trials.
- Geriatric Use: Clinical studies did not include a sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Efficacy: The efficacy of defibrotide sodium was investigated in three studies: two prospective clinical trials (Study 1 and 2) and an expanded access study (Study 3).

- Study 1 enrolled 102 adult and pediatric patients in the defibrotide sodium treatment group with a diagnosis of VOD according to the following criteria (bilirubin of at least 2mg/dL and at least two of the following findings: hepatomegaly, ascites, and weight gain greater than 5% by Day 21 post HSCT) with an associated diagnosis of multi-organ dysfunction (pulmonary, renal, or both) by day 28 post-HSCT. Defibrotide sodium was administered to the treatment group at a dose of 6.25mg/kg infused every six hours for a minimum of 21 days and continued until the patient was discharged from the hospital. Patients enrolled in the treatment group were not permitted to receive concomitant medications such as heparin, warfarin, or alteplase because of the increased risk of bleeding.

- Study 2 included adult and pediatric patients with a diagnosis of hepatic VOD and multi-organ dysfunction following HSCT. A total of 75 patients were treated with defibrotide sodium at a dose of 6.25mg/kg infused every six hours. The planned minimum duration of treatment was 14 days. The treatment could be continued until signs of hepatic VOD resolved.
- Study 3 was an expanded access program for defibrotide sodium for the treatment of adult and pediatric patients with hepatic VOD. The efficacy of defibrotide sodium was evaluated in 351 patients who had received a HSCT and developed hepatic VOD with renal or pulmonary dysfunction. All patients received defibrotide sodium at a dose of 6.25mg/kg infused every six hours. The efficacy of defibrotide sodium was based on survival at Day 100 after HSCT.
- In study 1, 2, and 3 the survival rate 100 days after transplantation was 38% (95% CI: 29%, 48%), 44% (95% CI: 33%, 55%), and 45% (95% CI: 40%, 51%), respectively. Based on published reports and analyses of patient level data for individuals with hepatic VOD with renal or pulmonary dysfunction who received supportive care or interventions other than defibrotide sodium, the expected Day 100 survival rates are 21% to 31%.

Cost:

Medication	WAC Per Vial	WAC for 21 Days of Therapy*	WAC for 60 Days of Therapy*
Defitelio® (defibrotide sodium) 200mg/2.5mL vial	**$825.00**	**$138,600.00**	**$396,000.00**

WAC = wholesale acquisition cost; costs do not reflect rebated prices or net costs.
*Dosing based on 64kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Defitelio® (defibrotide sodium) with the following criteria:

Defitelio® (Defibrotide Sodium) Approval Criteria:

1. An FDA approved diagnosis of hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome (SOS), with renal or pulmonary dysfunction following hematopoietic stem-cell transplantation.
2. Initial approvals will be for one month of therapy. An additional month of therapy (maximum of 60 days) may be granted if the physician documents the continued need for therapy.

[1] Negrin R, Bonis P. Diagnosis of hepatic sinusoidal obstruction syndrome (veno-occlusive disease) following hematopoietic cell transplantation. *Up-To-Date*. Available online at: http://www.uptodate.com/contents/diagnosis-of-hepatic-sinusoidal-obstruction-syndrome-veno-occlusive-disease-following-hematopoietic-cell-transplantation?source=see_link. Last revised 09/14/2016. Last accessed 10/12/2016.

[2] Mohty M, Malard F, Abecassis M, et al. Sinusoidal obstruction syndrome/veno-occlusive disease: current situation and perspectives—a position statement from the European Society for Blood and Marrow Transplantation (EBMT). *Bone Marrow Transplantation*. 2015; 50(6):781-789. doi:10.1038/bmt.2015.52. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4456788/. Published online 03/23/2015. Last accessed 11/04/2016.

[3] Coppell JA, Richardson PG, Soiffer R, et al. Hepatic Veno-Occlusive Disease following Stem Cell Transplantation: Incidence, Clinical Course, and Outcome. *Biology of Blood and Marrow Transplantation: Journal of the American Society for Blood and Marrow Transplantation*. 2010; 16(2):157-168. doi:10.1016/j.bbmt.2009.08.024. Available online at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3018714/. Published online 02/2010. Last accessed 11/04/2016.

[4] Negrin, Robert. Treatment and prevention of hepatic sinusoidal obstruction syndrome following hematopoietic cell transplantation. *Up-To-Date*. Available online at: http://www.uptodate.com/contents/treatment-and-prevention-of-hepatic-sinusoidal-obstruction-syndrome-following-hematopoietic-cell-transplantation?source=search_result&search=vod&selectedTitle=2%7E104. Last revised 04/01/2016. Last accessed 10/12/2016.

[5] Jazz Pharmaceuticals Announces FDA Approval of Defitelio® (defibrotide sodium) for the Treatment of Hepatic Veno-Occlusive Disease (VOD) with Renal or Pulmonary Dysfunction Following Hematopoietic Stem-Cell Transplantation (HSCT). Jazz Pharmaceuticals. Available online at: http://www.prnewswire.com/news-releases/jazz-pharmaceuticals-announces-fda-approval-of-defitelio-defibrotide-sodium-for-the-treatment-of-hepatic-veno-occlusive-disease-vod-with-renal-or-pulmonary-dysfunction-following-hematopoietic-stem-cell-transplantation-hsct-300243563.html. Issued 03/30/2016. Last accessed 11/04/2016.

[6] U.S. Food and Drug Administration (FDA). FDA approves first treatment for rare disease in patients who receive stem cell transplant from blood or bone marrow. Available online at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm493225.htm. Issued 03/30/2016. Last accessed 10/12/2016.

[7] Defitelio® Prescribing Information. Jazz Pharmaceuticals. Available online at: https://defitelio.com/DefitelioPI.pdf. Last revised 03/2016. Last accessed 10/12/2016.

Appendix N

Fiscal Year 2016 Annual Review of Testosterone Products

Oklahoma Health Care Authority
December 2016

Current Prior Authorization Criteria

Testosterone Products		
Tier-1*	**Tier-2**	**Special PA**
methyltestosterone powder	testosterone nasal gel (Natesto®)	fluoxymesterone oral tablet (Androxy®)
testosterone cypionate injection (Depo-Testosterone®)	testosterone patch (Androderm®)	methyltestosterone oral tablet/capsule (Android®, Methitest®, Testred®)
testosterone enanthate injection	testosterone topical gel (Fortesta®, Testim®, Vogelxo™)	testosterone buccal tablet (Striant®)
testosterone topical gel (Androgel®)+	testosterone topical solution (Axiron®)	testosterone pellets (Testopel®)
	testosterone undecanoate injection (Aveed®)	

*Tier-1 products include generic injectable products and supplemental rebated topical products.
+Brand name preferred
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Initial Approval Criteria for All Testosterone Products:

1. An FDA approved diagnosis:
    a. Testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, or orchidectomy; or
    b. Idiopathic gonadotropin or luteinizing-hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation; or
    c. Delayed puberty; or
    d. Advanced inoperable metastatic mammary cancer in females one to five years postmenopausal, or premenopausal females with breast cancer benefitting from oophorectomy and have been determined to have a hormone-responsive tumor; and
2. Must include two labs showing pre-medication, morning testosterone (total testosterone) levels below 300ng/dL; and
3. Must include one lab showing abnormal gonadotropins and/or other information necessary to demonstrate diagnosis; or
4. Testosterone and gonadotropin labs are not required for authorization of testosterone therapy if documentation is provided for established hypothalamic pituitary or gonadal disease, if the pituitary gland or testes has/have been removed, or for postmenopausal females with advanced inoperable metastatic mammary cancer or premenopausal

females with breast cancer benefitting from oophorectomy and that have been determined to have a hormone-responsive tumor.

Testosterone Products Tier-2 Authorization Criteria:

1. All diagnoses and laboratory requirements listed in the initial approval criteria for all testosterone products must be met; and
2. A trial of at least two Tier-1 products (must include at least one injectable and one topical formulation) at least 12 weeks in duration; or
3. A patient-specific, clinically significant reason why member cannot use all available Tier-1 medications; or
4. Prior stabilization on a Tier-2 medication (within the past 180 days).
5. Approvals will be for the duration of one year.

Testosterone Products Special Prior Authorization (PA) Criteria:

1. All diagnoses and laboratory requirements listed in the initial approval criteria for all testosterone products must be met; and
2. A patient-specific, clinically significant reason why member cannot use all other available formulations of testosterone.
3. Approvals will be for the duration of one year.

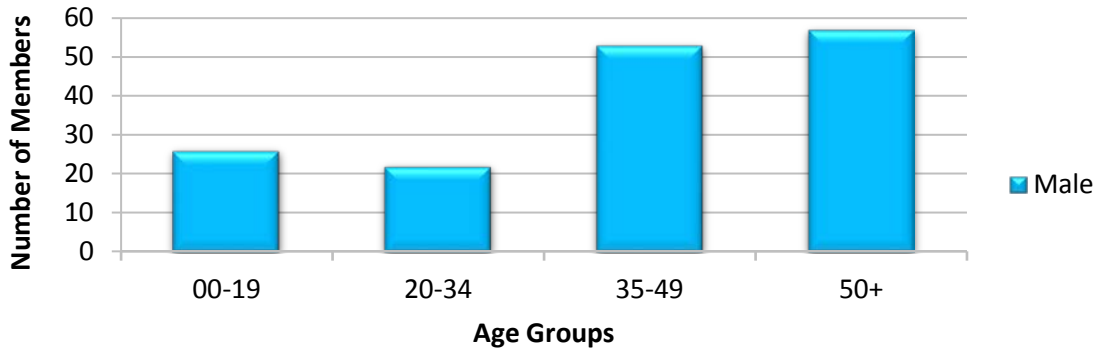
Utilization of Testosterone Products: Fiscal Year 2016

Comparison of Fiscal Years

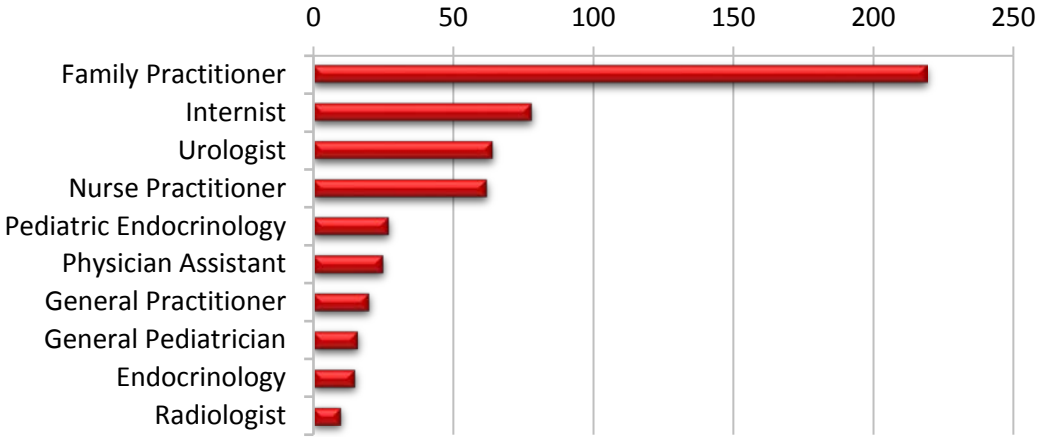
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	175	613	$152,245.33	$248.36	$5.20	32,475	29,261
2016	158	551	$146,405.85	$265.71	$5.36	29,513	27,305
% Change	**-9.70%**	**-10.10%**	**-3.80%**	**7.00%**	**3.10%**	**-9.10%**	**-6.70%**
Change	**-17**	**-62**	**-$5,839.48**	**$17.35**	**$0.16**	**-2,962**	**-1,956**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Demographics of Members Utilizing Testosterone Products



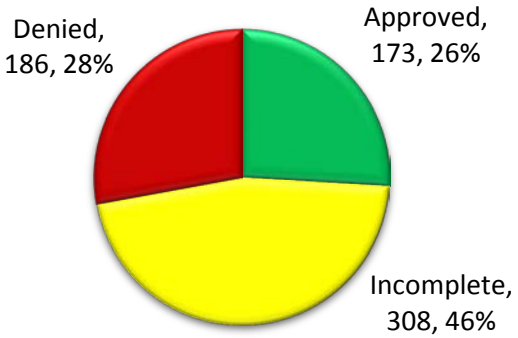
Top Prescriber Specialties of Testosterone Products by Number of Claims



Prior Authorization of Testosterone Products

There were 667 prior authorization requests submitted for 341 unique members for the testosterone products category during fiscal year 2016. All products regardless of tier status require prior authorization in order to evaluate submitted labs. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8]

Anticipated Patent Expiration(s):

- Fortesta® (testosterone topical gel): November 2018
- Striant® (testosterone buccal tablets): August 2019
- Natesto® (testosterone nasal gel): February 2024
- Testim® (testosterone topical gel): January 2025
- Androgel® 1.62% (testosterone topical gel): October 2026
- Aveed® (testosterone undecanoate injection): March 2027
- Axiron® (testosterone topical solution): September 2027
- Vogelxo™ (testosterone topical gel): February 2034

News:

- **March 2015:** A University of Texas study of 61,474 men age 40 years or older treated with testosterone from 2001 to 2010 found that 20 percent of men were prescribed testosterone despite having normal testosterone levels. Normal testosterone levels were based on the Endocrine Society guidelines.

Safety Alert(s):

- **March 2015:** In January 2014, the U.S. Food and Drug Administration (FDA) announced that they were investigating the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products. Based on available evidence from published studies and expert input from an Advisory Committee meeting, the FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. The FDA cautions the use of testosterone products for low testosterone due to aging and is requiring labeling changes for all prescription testosterone products to reflect the possible increased risk of heart attacks and strokes associated with testosterone use. The FDA is also requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products.
- **May 2016:** A retrospective cohort study of more than 250,000 medical records in Sweden did not reveal an increased risk of prostate cancer in men prescribed testosterone for longer than a year. The risk did not differ between dosage formulations (e.g., topical, injection).
- **October 2016:** The FDA approved labeling changes for all prescription testosterone products, adding a new *Warning* and updating the *Abuse and Dependence* section to include new safety information regarding the risks associated with abuse and dependence of testosterone. Testosterone is currently a Schedule III medication due to its abuse potential as a performance enhancing medication in athletes. Abuse of testosterone at high doses is associated with heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, and male infertility. Prescribers are advised to measure serum testosterone concentration if abuse is suspected.

Updated Treatment Guidelines:

- **October 2015:** The Canadian Men's Health Foundation published clinical practice guidelines regarding the diagnosis and management of testosterone deficiency syndrome in men. Significant recommendations and conclusions include:
    - The initial biochemical test should be total testosterone level measured in serum samples taken in the morning between 7:00am and 11:00am, or within 3 hours after waking in the case of shift workers.
    - Measurement of sex hormone-binding globulin with calculated free or bioavailable testosterone should be restricted to men with symptoms of testosterone deficiency and equivocally low testosterone levels.
    - Investigation for secondary or reversible causes of hypogonadism is recommended in all men with testosterone deficiency syndrome.

- Men with documented testosterone deficiency syndrome and no contraindications should receive treatment with testosterone.
- Men with testosterone deficiency syndrome and stable cardiovascular disease are candidates for testosterone treatment.
- Testosterone replacement therapy is not recommended in men more interested in maintaining fertility over symptomatic improvement.
- Response and adverse effects should be assessed at three and six months after onset of therapy, and testosterone levels should be assessed at three and six months after onset of therapy and annually thereafter if stable.

Pipeline Update(s):

- **May 2016:** Clarus Therapeutics Inc. announced it has begun a Phase 3 study of their oral testosterone product Jatenzo™. Clarus launched the trial after receiving a Complete Response Letter (CRL) from the FDA for Jatenzo™; the trial is intended to "provide supplemental data requested by the FDA" and will compare Jatenzo™ to a topical testosterone formulation.
- **October 2016:** Lipocine Inc. participated in a Post Action meeting with the FDA following receipt of a CRL for their oral testosterone candidate, LPCN1021. Lipocine was seeking approval of LPCN1021 for testosterone replacement therapy but was not approved based on "deficiencies related to the dosing algorithm for the label." Lipocine is working with the FDA to determine actions needed for approval of LPCN1021.

Recommendations

The College of Pharmacy does not recommend any changes to the Testosterone Product Based Prior Authorization (PBPA) category at this time.

Utilization Details of Testosterone Products: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TESTOSTERONE INJECTABLE PRODUCTS					
TESTOST CYP INJ 200MG/ML	232	83	$15,913.14	2.8	$68.59
DEPO-TESTOST INJ 200MG/ML	53	23	$3,122.43	2.3	$58.91
TESTOST ENAN INJ 200MG/ML	13	7	$1,321.54	1.86	$101.66
TESTOST CYP INJ 100MG/ML	8	8	$441.32	1	$55.17
DEPO-TESTOST INJ 100MG/ML	2	2	$158.53	1	$79.27
SUBTOTAL	**308**	**113**	**$20,956.96**	**2.73**	**$68.04**
TESTOSTERONE TOPICAL PRODUCTS					
ANDROGEL GEL 1.62%	142	27	$80,248.69	5.26	$565.13
TESTOSTERONE GEL 1%(50MG)	43	7	$16,683.89	6.14	$388.00
ANDROGEL GEL 1%(50MG)	34	5	$20,180.18	6.8	$593.53
ANDROGEL GEL 1.62%	7	1	$1,042.13	7	$148.88
ANDRODERM DIS 2MG/24HR	6	2	$2,398.40	3	$399.73
ANDROGEL GEL 1.62%	4	2	$1,918.97	2	$479.74
TESTOSTERONE GEL PUMP 1%	3	3	$980.28	1	$326.76
TESTIM GEL 1%(50MG)	2	1	$940.62	2	$470.31
AXIRON SOL 30MG/ACT	2	2	$1,055.73	1	$527.87
SUBTOTAL	**243**	**47**	**$125,448.89**	**5.17**	**$516.25**
TOTAL	**551**	**158***	**$146,405.85**	**3.49**	**$265.71**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

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[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 09/01/2016. Last accessed 11/07/2016.
[2] University of Texas Branch at Galveston. Testosterone being prescribed when not medically needed. *ScienceDaily*. Available online at: https://sciencedaily.com/releases/2015/03/150303153517.htm. Issued 03/03/2015. Last accessed 11/07/2016.
[3] U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: FDA Cautions About Using Testosterone Products for Low Testosterone Due to Aging; Requires Labeling Change to Inform of Possible Increased Risk of Heart Attack and Stroke with Use. Available online at: http://www.fda.gov/drugs/drugsafety/ucm436259.htm. Issued 03/03/2015. Last accessed 11/07/2016.
[4] NYU Langone Medical Center, New York University School of Medicine. Testosterone therapy does not raise risk of aggressive prostate cancer. *ScienceDaily*. Available online at: https://sciencedaily.com/releases/2016/05/160507143326.htm. Issued 05/07/2016. Last accessed 11/07/2016.
[5] U.S. Food and Drug Administration (FDA). FDA approves new changes to testosterone labeling regarding the risks associated with abuse and dependence of testosterone and other anabolic androgenic steroids (AAS). Available online at: http://www.fda.gov/Drugs/DrugSafety/ucm526206.htm. Issued 10/25/2016. Last accessed 11/07/2016.
[6] Morales A, Bebb RA, Manjoo P, et al. Diagnosis and Management of Testosterone Deficiency Syndrome in Men: Clinical Practice Guideline. *CMAJ* 2015. DOI:10.1503/cmaj.150033.
[7] Clarus Therapeutics Inc. Clarus Therapeutics Initiates Phase 3 Clinical Trial of Oral Testosterone Replacement Therapy. *Globe Newswire*. Available online at: https://globenewswire.com/news-release/2016/05/17/840736/0/en/Clarus-Therapeutics-Initiates-Phase-3-Clinical-Trial-of-Oral-Testosterone-Replacement-Therapy.html. Issued 05/17/2016. Last accessed 11/07/2016.
[8] Lipocine Inc. Lipocine Completes Post Action Meeting With FDA for LPCN 1021 New Drug Application. Available online at: http://ir.lipocine.com/releasedetail.cfm?releaseid=993826. Issued 10/17/2016. Last accessed 11/07/2016.

Appendix O

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

FDA NEWS RELEASE

For Immediate Release: November 17th, 2016

FDA approves Intrarosa for postmenopausal women experiencing pain during sex

The U.S. Food and Drug Administration approved Intrarosa (prasterone) to treat women experiencing moderate to severe pain during sexual intercourse (dyspareunia), a symptom of vulvar and vaginal atrophy (VVA), due to menopause. Intrarosa is the first FDA approved product containing the active ingredient prasterone, which is also known as dehydroepiandrosterone (DHEA).

During menopause, levels of estrogen decline in vaginal tissues, which may cause a condition known as VVA, leading to symptoms such as pain during sexual intercourse.

Efficacy of Intrarosa, a once-daily vaginal insert, was established in two 12-week placebo-controlled clinical trials of 406 healthy postmenopausal women, 40 to 80 years of age, who identified moderate to severe pain during sexual intercourse as their most bothersome symptom of VVA. Women were randomly assigned to receive Intrarosa or a placebo vaginal insert. Intrarosa, when compared to placebo, was shown to reduce the severity of pain experienced during sexual intercourse.

The safety of Intrarosa was established in four 12-week placebo-controlled trials and one 52-week open-label trial. The most common adverse reactions were vaginal discharge and abnormal Pap smear.

Although DHEA is included in some dietary supplements, the efficacy and safety of those products have not been established for diagnosing, curing, mitigating, treating or preventing any disease.

Intrarosa is marketed by Quebec-based Endoceutics Inc.

Current Drug Shortages Index (as of December 5th, 2016):

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

Acetohydroxamic Acid (Lithostat) Tablets	***Currently in Shortage***
Ammonium Chloride Injection	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Bleomycin Sulfate for Injection	***Currently in Shortage***
Caffeine Anhydrous (125mg/mL); Sodium Benzoate (125mg/mL) Injection	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Ceftazidime and Avibactam (AVYCAZ) for Injection, 2.5g	***Currently in Shortage***
Chloramphenicol Sodium Succinate Injection	***Currently in Shortage***
Dexamethasone Sodium Phosphate Injection	***Currently in Shortage***
Dihydroergotamine Mesylate Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Doxorubicin Lyophilized Powder for Injection	***Currently in Shortage***
Epinephrine Injection	***Currently in Shortage***
Estradiol Valerate Injection, USP	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fomepizole Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Indigotindisulfonate Sodium (Indigo Carmine) Injection	***Currently in Shortage***
Ketoprofen Capsules	***Currently in Shortage***

L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Mecasermin [rDNA origin] (Increlex) Injection	***Currently in Shortage***
Methyldopate Hydrochloride Injection	***Currently in Shortage***
Methylprednisolone Sodium Succinate for Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nimodipine (Nymalize) Oral Solution	***Currently in Shortage***
Penicillin G Benzathine (Bicillin L-A) Injection	***Currently in Shortage***
Penicillin G Benzathine and Penicillin G Procaine (Bicillin C-R) Injection	***Currently in Shortage***
Penicillin G Procaine Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Scopolamine (Transderm Scop) Transdermal System Patch	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sufentanil Citrate (Sufenta) Injection	***Currently in Shortage***
Sumatriptan (Imitrex) Nasal Spray	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***
Tigecycline (Tygacil) Injection	***Currently in Shortage***
Tobramycin Injection	***Currently in Shortage***
Trimipramine Maleate (SURMONTIL) Capsules	***Currently in Shortage***