Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
October 4, 2017
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 (DUR) Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – October 4, 2017

DATE: September 27, 2017

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 October 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

Action Item – Vote on 2018 Meeting Dates – Appendix B

Update on Medication Coverage Authorization Unit/Menopausal Hormone Therapy (MHT) for Vasomotor Symptoms Safety Mailing Update – Appendix C

Action Item – Vote to Prior Authorize Afstyla® [Antihemophilic Factor (Recombinant), Single Chain] and Rebinyn® [Coagulation Factor IX (Recombinant), GlycoPEGylated] – Appendix D

Action Item – Vote to Prior Authorize Endari™ (L-Glutamine) – Appendix E

Action Item – Vote to Prior Authorize Namenda XR® (Memantine Extended-Release Capsules) and Update Namzaric® (Memantine Extended-Release/Donepezil Capsules) Criteria – Appendix F

Action Item – Vote to Prior Authorize Zypitamag™ (Pitavastatin Magnesium) and Nikita™ (Pitavastatin Sodium) – Appendix G

Action Item – Vote to Prior Authorize Fabrazyme® (Agalsidase Beta) – Appendix H

Action Item – Vote to Prior Authorize Kisqali® (Ribociclib), Kisqali® Femara® Co-Pack (Ribociclib/Letrozole), and Nerlynx™ (Neratinib) – Appendix I

Annual Review of Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) Medications and 30-Day Notice to Prior Authorize Blincyto® (Blinatumomab), Besponsa® (Inotuzumab Ozogamicin), Bosulif® (Bosutinib), Gleevec® (Imatinib), Iclusig® (Ponatinib), Kymriah™ (Tisagenlecleucel), Synribo® (Omacetaxine), Sprycel® (Dasatinib), and Tasigna® (Nilotinib) – Appendix J

Annual Review of Skin Cancer Medications and 30-Day Notice to Prior Authorize Bavencio® (Avelumab) – Appendix K

Annual Review of Hereditary Angioedema Medications and 30-Day Notice to Prior Authorize Haegarda® [C1 Esterase Inhibitor (Human)] – Appendix L

Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Kevzara® (Sarilumab), Siliq™ (Brodalumab), Tremfya™ (Guselkumab), Cyltezo™ (Adalimumab-adbm), and Renflexis™ (Infliximab-abda) – Appendix M

Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Trulance™ (Plecanatide), Xermelo™ (Telotristat Ethyl), Symproic® (Naldemedine), and Motofen® (Difenoxin/Atropine) – Appendix N

Annual Review of Thrombopoietin (TPO) Receptor Agonists and 30-Day Notice to Prior Authorize Promacta® (Eltrombopag) – Appendix O

Annual Review of Allergen Immunotherapies and 30-Day Notice to Prior Authorize Odactra™ (House Dust Mite Allergen Extract) – Appendix P

Annual Review of Topical Corticosteroids and 30-Day Notice to Prior Authorize MiCort™ HC (Hydrocortisone Acetate 2.5% Cream) – Appendix Q

Annual Review of Bladder Control Medications and 30-Day Notice to Prior Authorize Noctiva™ (Desmopressin Acetate Nasal Spray) – Appendix R

Annual Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and 30-Day Notice to Prior Authorize Sprix® (Ketorolac Tromethamine Nasal Spray) and Cataflam® (Diclofenac Potassium Tablets) – Appendix S

Annual Review of Anti-Ulcer Medications and 30-Day Notice to Prior Authorize Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets) – Appendix T

Industry News and Updates – Appendix U

U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates – Appendix V

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – October 4, 2017 @ 4:00 p.m.

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call to Order

A. Roll Call – Dr. Cothran

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. September 13, 2017 DUR Minutes – Vote
B. September 13, 2017 DUR Recommendations Memorandum

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

4. Action Item – Vote on 2018 Meeting Dates – See Appendix B

A. Meetings are held the second Wednesday of every month at 4:00 PM

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

5. Update on Medication Coverage Authorization Unit/Menopausal Hormone Therapy (MHT) for Vasomotor Symptoms Safety Mailing Update – See Appendix C

A. Medication Coverage Activity for September 2017
B. Pharmacy Help Desk Activity for September 2017
C. Menopausal Hormone Therapy (MHT) for Vasomotor Symptoms Safety Mailing Update

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

6. Action Item – Vote to Prior Authorize Afstyla® [Antihemophilic Factor (Recombinant), Single Chain] and Rebinyn® [Coagulation Factor IX (Recombinant), GlycoPEGylated] – See Appendix D

A. Introduction
B. Recommendations

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

7. Action Item – Vote to Prior Authorize Endari™ (L-Glutamine) – See Appendix E

A. Introduction
B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Namenda XR® (Memantine Extended-Release Capsules) and Update Namzaric® (Memantine Extended-Release/Donepezil Capsules) Criteria – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize Zypitamag™ (Pitavastatin Magnesium) and Nikita™ (Pitavastatin Sodium) – See Appendix G

A. Introduction

B. College of Pharmacy Recommendations

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

10. Action Item – Vote to Prior Authorize Fabrazyme® (Agalsidase Beta) – See Appendix H

A. Introduction
B. College of Pharmacy Recommendations

Items to be presented by Dr. Schmidt, Dr. Borders, Dr. Medina, Dr. Muchmore, Chairman:

11. Action Item – Vote to Prior Authorize Kisqali® (Ribociclib), Kisqali® Femara® Co-Pack (Ribociclib/Letrozole), and Nerlynx™ (Neratinib) – See Appendix I

A. Introduction
B. Recommendations

Items to be presented by Dr. Schmidt, Dr. Borders, Dr. Medina, Dr. Muchmore, Chairman:

12. Annual Review of Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) Medications and 30-Day Notice to Prior Authorize Blincyto® (Blinatumomab), Besponsa® (Inotuzumab Ozogamicin), Bosulif® (Bosutinib), Gleevec® (Imatinib), Iclusig® (Ponatinib), Kymriah™ (Tisagenlecleucel), Synribo® (Omacetaxine), Sprycel® (Dasatinib), and Tasigna® (Nilotinib) – See Appendix J

A. Introduction
B. Utilization of ALL/CML Medications
C. Market News and Updates
D. Product Summaries
E. Recommendations
F. Utilization Details of ALL/CML Medications

Items to be presented by Dr. Schmidt, Dr. Borders, Dr. Medina, Dr. Muchmore, Chairman:

13. Annual Review of Skin Cancer Medications and 30-Day Notice to Prior Authorize Bavencio® (Avelumab) – See Appendix K

A. Introduction
B. Previously Voted Prior Authorization Criteria
C. Utilization of Skin Cancer Medications
D. Prior Authorization of Skin Cancer Medications
E. Market News and Updates
F. Bavencio® (Avelumab) Product Summary
G. Recommendations
H. Utilization Details of Skin Cancer Medications

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

14. Annual Review of Hereditary Angioedema Medications and 30-Day Notice to Prior Authorize Haegarda® [C1 Esterase Inhibitor (Human)] – See Appendix L

A. Current Prior Authorization Criteria
B. Utilization of Hereditary Angioedema Medications
C. Market News and Updates
D. Prior Authorization of Hereditary Angioedema Medications
E. Haegarda® [C1 Esterase Inhibitor (Human)] Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Hereditary Angioedema Medications

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

15. Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Kevzara® (Sarilumab), Siliq™ (Brodalumab), Tremfya™ (Guselkumab), Cyltezo™ (Adalimumab-adbm), and Renflexis™ (Infliximab-abda) – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of Targeted Immunomodulator Agents
C. Prior Authorization of Targeted Immunomodulator Agents
D. Market News and Updates
E. Kevzara® (Sarilumab) Product Summary

F. Siliq™ (Brodalumab) Product Summary
G. Tremfya™ (Guselkumab) Product Summary
H. Biosimilar Product Summaries
I. Giant Cell Arteritis (GCA) Summary
J. College of Pharmacy Recommendations
K. Utilization Details of Targeted Immunomodulator Agents

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

16. Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Trulance™ (Plecanatide), Xermelo™ (Telotristat Ethyl), Symproic® (Naldemedine), and Motofen® (Difenoxin/Atropine) – See Appendix N

A. Current Prior Authorization Criteria
B. Utilization of Constipation and Diarrhea Medications
C. Prior Authorization of Constipation and Diarrhea Medications
D. Market News and Updates
E. Trulance™ (Plecanatide) Product Summary
F. Xermelo™ (Telotristat Ethyl) Product Summary
G. Symproic® (Naldemedine) Product Summary
H. Cost Comparison: Constipation Medications
I. College of Pharmacy Recommendations
J. Utilization Details of Constipation and Diarrhea Medications

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

17. Annual Review of Thrombopoietin (TPO) Receptor Agonists and 30-Day Notice to Prior Authorize Promacta® (Eltrombopag) – See Appendix O

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of TPO Receptor Agonists
D. Prior Authorization of TPO Receptor Agonists
E. Market News and Updates
F. Promacta® (Eltrombopag) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of TPO Receptor Agonists

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

18. Annual Review of Allergen Immunotherapies and 30-Day Notice to Prior Authorize Odactra™ (House Dust Mite Allergen Extract) – See Appendix P

A. Current Prior Authorization Criteria
B. Utilization of Allergen Immunotherapies
C. Prior Authorization of Allergen Immunotherapies
D. Market News and Updates
E. Odactra™ (House Dust Mite Allergen Extract) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Allergen Immunotherapies

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

19. Annual Review of Topical Corticosteroids and 30-Day Notice to Prior Authorize MiCort™ HC (Hydrocortisone Acetate 2.5% Cream) – See Appendix Q

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

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

20. Annual Review of Bladder Control Medications and 30-Day Notice to Prior Authorize Noctiva™ (Desmopressin Acetate Nasal Spray) – See Appendix R

A. Current Prior Authorization Criteria
B. Utilization of Bladder Control Medications
C. Prior Authorization of Bladder Control Medications
D. Market News and Updates
E. Nocturnal Polyuria
F. Noctiva™ (Desmopressin Acetate Nasal Spray) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Bladder Control Medications

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

21. Annual Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and 30-Day Notice to Prior Authorize Sprix® (Ketorolac Tromethamine Nasal Spray) and Cataflam® (Diclofenac Potassium Tablets) – See Appendix S

A. Current Prior Authorization Criteria
B. Utilization of NSAIDs
C. Prior Authorization of NSAIDs
D. Market News and Updates
E. Sprix® (Ketorolac Tromethamine Nasal Spray) Product Summary
F. Cost Comparison
G. College of Pharmacy Recommendations
H. Utilization Details of NSAIDs

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

22. Annual Review of Anti-Ulcer Medications and 30-Day Notice to Prior Authorize Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets) – See Appendix T

A. Current Prior Authorization Criteria
B. Utilization of Anti-Ulcer Medications
C. Prior Authorization of Anti-Ulcer Medications
D. Market News and Updates
E. Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Anti-Ulcer Medications

Non-Presentation; Questions Only:

23. Industry News and Updates – See Appendix U

A. Introduction
B. News and Updates

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

24. U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates – See Appendix V

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

25. Future Business* (Upcoming Product and Class Reviews)

A. Hepatitis C Medications
B. Ophthalmic Anti-Inflammatories
C. Pancreatic Enzymes
D. Chronic Iron Overload Medications
E. Various Antibiotics
F. Cystic Fibrosis Medications

**Future business subject to change.*

26. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF SEPTEMBER 13, 2017

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	
Lee Munoz, Pharm.D.	x	
James Osborne, Pharm.D.		x
Paul Louis Preslar, D.O., MBA; Vice Chairman	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	
Stephanie Nichols, Pharm.D., BCGP; 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): Not applicable		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Melody Anthony, Deputy State Medicaid Director		x
Marlene Asmussen, R.N.; Population Care Management Director		x
Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.; Assistant Pharmacy Director	x	
Kelli Brodersen, Marketing Coordinator		x
Robert Evans, M.D.; Sr. Medical Director		x
Michael Herndon, D.O.; Chief Medical Officer	x	
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Thomas Nunn, D.O.; Medical 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, J.D.; Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Jean Ritter, Quintiles IMS	Edie Dodson, Sanofi Genzyme	Heather Dehlin, Pfizer
Nikki Goff, Novo Nordisk	Bill Streitenberger, Novo Nordisk	Tyler Craddock, MDCO
Quynhchau Doan, AbbVie	John Brunson, Impax	Marc Parker, Sunovion
Mark DeClerk, Lilly	Mary Stewart Crane, J&J	Jim Chapman, AbbVie
Denise Hill, Astellas	Jason Schwier, Amgen	Melvin Nwamadi, Abbott
Alex Bitting, Bioverativ	Mai Duong, Novartis	Jason Russell, Bioverativ
Kristen Rowe, Bioverativ	Matt Forney, Merck	Ron Schnare, Shire
Jonathan Kendter, Amgen	Lance Burcham, Medimmue	Clarence L. Wiley, M.D.

PRESENT FOR PUBLIC COMMENT:	
Clarence L. Wiley, M.D.	Beauty Thru Health Dermatology
Jonathan Kendter	Amgen

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 ITEM NO. 6 SPEAKER: CLARENCE L. WILEY, M.D.

2B: AGENDA ITEM NO. 8 SPEAKER: JONATHAN KENDTER

ACTION: NONE REQUIRED

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

3A: JULY 12, 2017 DUR MINUTES – VOTE

3B: JULY 12, 2017 DUR RECOMMENDATIONS MEMORANDUM

3C: CORRESPONDENCE

Materials included in agenda packet; presented by Dr. Cothran

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/MEDICAID OPIOID UTILIZATION COMPARISON

4A: MEDICATION COVERAGE ACTIVITY FOR JULY 2017

4B: PHARMACY HELP DESK ACTIVITY FOR JULY 2017

4C: MEDICATION COVERAGE ACTIVITY FOR AUGUST 2017

4D: PHARMACY HELP DESK ACTIVITY FOR AUGUST 2017

4E: MEDICAID OPIOID UTILIZATION COMPARISON

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE RADICAVA™ (EDARAVONE)

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Adams

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE EUCRISA™ (CRISABOROLE 2% OINTMENT), DUPIXENT® (DUPILUMAB INJECTION), AND PRUDOXIN™ AND ZONALON® (DOXEPIN 5% CREAM)

6A: INTRODUCTION

6B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Abbott

Dr. Muchmore recommends requests for concurrent use of dupilumab and other biologic medications be reviewed on a case-by-case basis.
Dr. Munoz moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE VIMIZIM® (ELOSULFASE ALFA)
7A: INTRODUCTION
7B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
Dr. Harrell moved to approve; seconded by Dr. Munoz
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE RAYALDEE® (CALCIFEDIOL), PARSABIV™ (ETELCALCETIDE), ZEMPLAR® (PARICALCITOL CAPSULES), AND HECTOROL® (DOXERCALCIFEROL CAPSULES)
8A: INTRODUCTION
8B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nawaz
Dr. Hardzog-Britt moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE MARPLAN® (ISOCARBOXAZID) AND DESYREL® (TRAZODONE 300MG TABLETS)
9A: INTRODUCTION
9B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Garton moved to approve; seconded by Ms. Varalli-Claypool
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: VOTE TO PRIOR AUTHORIZE CHOLINE FENOFIBRATE DELAYED-RELEASE (TRILIPIX®) 135MG CAPSULES AND FENOFIBRATE MICRONIZED (LOFIBRA®) 200MG CAPSULES
10A: COST COMPARISON
10B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nichols
Dr. Preslar moved to approve; seconded by Dr. Munoz
ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: VOTE TO PRIOR AUTHORIZE ARYMO™ ER (MORPHINE SULFATE EXTENDED-RELEASE), TROXYCA® ER (OXYCODONE/NALTREXONE EXTENDED-RELEASE), VANTRELA™ ER (HYDROCODONE EXTENDED-RELEASE), OXAYDO® (OXYCODONE), AND ROXYBOND™ (OXYCODONE)
11A: INTRODUCTION
11B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Garton moved to approve; seconded by Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 12: VOTE TO PRIOR AUTHORIZE BRINEURA™ (CERLIPONASE ALFA)
12A: INTRODUCTION
12B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Harrell moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF BREAST CANCER MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE KISQALI® (RIBOCICLIB), KISQALI® FEMARA® CO-PACK (RIBOCICLIB/LETROZOLE), AND NERLYNX™ (NERATINIB)

13A: INTRODUCTION
13B: CURRENT PRIOR AUTHORIZATION CRITERIA
13C: UTILIZATION OF BREAST CANCER MEDICATIONS
13D: PRIOR AUTHORIZATION OF BREAST CANCER MEDICATIONS
13E: MARKET NEWS AND UPDATES
13F: PRODUCT SUMMARIES
13G: RECOMMENDATIONS
13H: UTILIZATION DETAILS OF BREAST CANCER MEDICATIONS
Materials included in agenda packet; presented by Dr. Schmidt
ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: ANNUAL REVIEW OF FACTOR REPLACEMENT PRODUCTS AND 30-DAY NOTICE TO PRIOR AUTHORIZE AFSTYLA® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), SINGLE CHAIN] AND REBINYN® [COAGULATION FACTOR IX (RECOMBINANT), GLYCOPEGYLATED])
14A: CURRENT PRIOR AUTHORIZATION CRITERIA
14B: UTILZATION OF FACTOR REPLACEMENT PRODUCTS
14C: PRIOR AUTHORIZATION OF FACTOR REPLACEMENT PRODUCTS
14D: MARKET NEWS AND UPDATES
14E: AFSTYLA® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), SINGLE CHAIN] PRODUCT SUMMARY
14F: REBINYN® [COAGULATION FACTOR IX (RECOMBINANT), GLYCOPEGYLATED] PRODUCT SUMMARY
14G: RECOMMENDATIONS
14H: UTILIZATION DETAILS OF FACTOR REPLACEMENT PRODUCTS
Materials included in agenda packet; presented by Dr. Ratterman
ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: ANNUAL REVIEW OF GROWTH HORMONE
15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF GROWTH HORMONE
15C: PRIOR AUTHORIZATION OF GROWTH HORMONE
15D: MARKET NEWS AND UPDATES
15E: COLLEGE OF PHARMACY RECOMMENDATIONS
15F: UTILIZATION DETAILS OF GROWTH HORMONE
Materials included in agenda packet; presented by Dr. Holderread
Dr. Garton moved to approve; seconded by Dr. Hardzog-Britt
ACTION: MOTION CARRIED

AGENDA ITEM NO. 16: ANNUAL REVIEW OF SYNAGIS® (PALIVIZUMAB)
16A: CURRENT PRIOR AUTHORIZATION CRITERIA
16B: UTILIZATION OF SYNAGIS® (PALIVIZUMAB)
16C: PRIOR AUTHORIZATION OF SYNAGIS® (PALIVIZUMAB)
16D: SEASON COMPARISON
16E: MARKET NEWS AND UPDATES
16F: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: 30-DAY NOTICE TO PRIOR AUTHORIZE ENDARI™ (L-GLUTAMINE)
17A: INTRODUCTION
17B: MARKET NEWS AND UPDATES
17C: ENDARI™ (L-GLUTAMINE) PRODUCT SUMMARY
17D: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: **ANNUAL REVIEW OF INSOMNIA MEDICATIONS**

18A: CURRENT PRIOR AUTHORIZATION CRITERIA
18B: UTILIZATION OF INSOMNIA MEDICATIONS
18C: PRIOR AUTHORIZATION OF INSOMNIA MEDICATIONS
18D: MARKET NEWS AND UPDATES
18E: NON-24-HOUR SLEEP-WAKE RHYTHM DISORDER
18F: COLLEGE OF PHARMACY RECOMMENDATIONS
18G: UTILIZATION DETAILS OF INSOMNIA MEDICATIONS

Materials included in agenda packet; presented by Dr. Nichols
Dr. Munoz moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 19: **30-DAY NOTICE TO PRIOR AUTHORIZE FABRAZYME® (AGALSIDASE BETA)**

19A: INTRODUCTION
19B: UTILIZATION OF FABRAZYME® (AGALSIDASE BETA)
19C: MARKET NEWS AND UPDATES
19D: FABRAZYME® (AGALSIDASE BETA) PRODUCT SUMMARY
19E: COVERAGE INFORMATION
19F: COLLEGE OF PHARMACY RECOMMENDATIONS

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

AGENDA ITEM NO. 20: **ANNUAL REVIEW OF ANTIHYPERLIPIDEMICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ZYPITAMAG™ (PITAVASTATIN MAGNESIUM) AND NIKITA™ (PITAVASTATIN SODIUM)**

20A: CURRENT PRIOR AUTHORIZATION CRITERIA
20B: UTILIZATION OF ANTIHYPERLIPIDEMICS
20C: PRIOR AUTHORIZATION OF ANTIHYPERLIPIDEMICS
20D: MARKET NEWS AND UPDATES
20E: COLLEGE OF PHARMACY RECOMMENDATIONS
20F: UTILIZATION DETAILS OF ANTIHYPERLIPIDEMICS

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

AGENDA ITEM NO. 21: **ANNUAL REVIEW OF ALZHEIMER'S DISEASE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE NAMENDA XR® (MEMANTINE EXTENDED-RELEASE CAPSULES)**

21A: CURRENT PRIOR AUTHORIZATION CRITERIA
21B: UTILIZATION OF ALZHEIMER'S DISEASE MEDICATIONS
21C: PRIOR AUTHORIZATION OF ALZHEIMER'S DISEASE MEDICATIONS
21D: MARKET NEWS AND UPDATES
21E: NAMENDA XR® (MEMANTINE EXTENDED-RELEASE CAPSULES) PRODUCT SUMMARY
21F: COLLEGE OF PHARMACY RECOMMENDATIONS
21G: UTILIZATION DETAILS OF ALZHEIMER'S DISEASE MEDICATIONS

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

AGENDA ITEM NO. 22: **ANNUAL REVIEW OF ANTICOAGULANTS AND PLATELET AGGREGATION INHIBITORS**

22A: CURRENT PRIOR AUTHORIZATION CRITERIA
22B: UTILIZATION OF ANTICOAGULANTS AND PLATELET AGGREGATION INHIBITORS
22C: PRIOR AUTHORIZATION OF ANTICOAGULANTS AND PLATELET AGGREGATION INHIBITORS
22D: MARKET NEWS AND UPDATES
22E: COLLEGE OF PHARMACY RECOMMENDATIONS

22F: UTILIZATION DETAILS OF ANTICOAGULANTS
22G: UTILIZATION DETAILS OF PLATELET AGGREGATION INHIBITORS
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 23: INDUSTRY NEWS AND UPDATES
23A: INTRODUCTION
23B: NEWS AND UPDATES
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 24: U.S. FOOD AND DRUG ADMINISTRATION (FDA) AND DRUG ENFORCEMENT ADMINISTRATION (DEA) UPDATES
Materials included in agenda packet; presented by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 25: FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)
OCTOBER MEETING RESCHEDULED TO OCTOBER 4, 2017 AT 4PM.
25A: TOPICAL CORTICOSTEROID MEDICATIONS
25B: TARGETED IMMUNOMODULATOR AGENTS
25C: ALLERGY IMMUNOTHERAPIES
25D: SKIN CANCER MEDICATIONS
25E: MALIGNANT HEMATOLOGY MEDICATIONS
25F: CONSTIPATION AND DIARRHEA MEDICATIONS
25G: BLADDER CONTROL MEDICATIONS
25H: HEREDITARY ANGIOEDEMA MEDICATIONS
25I: ANTI-ULCER MEDICATIONS
25J: NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)
FUTURE BUSINESS SUBJECT TO CHANGE.
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 26: ADJOURNMENT
The meeting was adjourned at 5:27pm.

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

Memorandum

Date: September 14, 2017

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 September 13, 2017

Recommendation 1: Medicaid Opioid Utilization Comparison

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Radicava™ (Edaravone)

MOTION CARRIED. Approval was not unanimous.

The College of Pharmacy recommends the prior authorization of Radicava™ (edaravone) with the following criteria:

Radicava™ (Edaravone) Approval Criteria:

1. An FDA approved diagnosis of amyotrophic lateral sclerosis (ALS); and
2. Member must have been evaluated by a physician specializing in the treatment of ALS within the last three months; and
3. Disease duration of two years or less (for initial approval); and
    a. A prior authorization request with patient-specific information may be submitted for consideration of edaravone for members with disease duration greater than two years, including but not limited to disease progression, specific symptoms related to the disease, activities of daily living currently affected by the disease, or prognosis; and

4. Approvals will be for the duration of six months. For each subsequent approval, the prescriber must document that the member is responding to the medication, as indicated by a slower progression in symptoms and/or slower decline in quality of life compared to the typical ALS disease progression.

Recommendation 3: Vote to Prior Authorize Eucrisa™ (Crisaborole 2% Ointment), Dupixent® (Dupilumab Injection), & Prudoxin™ and Zonalon® (Doxepin 5% Cream)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Eucrisa™ (crisaborole), Dupixent® (dupilumab), and Prudoxin™ and Zonalon® (doxepin cream) with the following criteria:

Eucrisa™ (Crisaborole Ointment) Approval Criteria:

1. An FDA approved indication for the treatment of mild-to-moderate atopic dermatitis (eczema); and
2. Member must be at least 2 years of age or older; and
3. Member must have documented trials within the last six months for a minimum of two weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. One Tier-1 topical corticosteroid; and
    b. One topical calcineurin inhibitor [e.g., Elidel® (pimecrolimus), Protopic® (tacrolimus)]; and
4. A quantity limit of one tube per 30 days will apply.
5. Initial approvals will be for the duration of one month. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Dupixent® (Dupilumab Injection) Approval Criteria:

1. An FDA approved diagnosis of moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies; and
2. Member must be 18 years of age or older; and
3. Member must have documented trials within the last six months for a minimum of two weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. One medium potency to very-high potency Tier-1 topical corticosteroid; and
    b. One topical calcineurin inhibitor [e.g., Elidel® (pimecrolimus), Protopic® (tacrolimus)]; and
4. Dupixent® must be prescribed by a dermatologist, allergist, or immunologist or the member must have been evaluated by a dermatologist, allergist, or immunologist within the last twelve months (or be an advanced care practitioner with a supervising physician who is a dermatologist, allergist, or immunologist); and
5. Requests for concurrent use of Dupixent® with other biologic medications will be reviewed on a case-by-case basis and will require patient-specific information to support the concurrent use. (Dupixent® has not been studied in combination with other biologic therapies.)

6. Initial approvals will be for the duration of 16 weeks. Reauthorization may be granted if the prescriber documents the member is responding well to treatment. Additionally, compliance will be evaluated for continued approval.

Prudoxin™ and Zonalon® (Doxepin Cream) Approval Criteria:

1. An FDA approved diagnosis for the short-term (up to eight days) management of moderate pruritus in patients with atopic dermatitis or lichen simplex chronicus; and
2. Requests for longer use than eight days will not generally be approved. Chronic use beyond eight days may result in higher systemic levels and should be avoided.

Recommendation 4: Vote to Prior Authorize Vimizim® (Elosulfase Alfa)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Vimizim® (elosulfase alfa) with the following criteria:

Vimizim® (Elosulfase Alfa) Approval Criteria:

1. An FDA approved diagnosis of Morquio A syndrome (mucopolysaccharidosis type IVA; MPS IVA) confirmed by:
   a. Enzyme assay demonstrating a deficiency of *N*-acetylgalactosamine-6-sulfatase (GALNS) enzyme activity; or
   b. Molecular genetic testing to confirm biallelic pathogenic variants in *GALNS*; and
2. Vimizim® must be administered by a healthcare professional prepared to manage anaphylaxis; and
3. Initial approvals will be for the duration of twelve months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.
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.

Recommendation 5: Vote to Prior Authorize Rayaldee® (Calcifediol), Parsabiv™ (Etelcalcetide), Zemplar® (Paricalcitol Capsules), and Hectorol® (Doxercalciferol Capsules)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Rayaldee® (calcifediol ER capsules), Parsabiv™ (etelcalcetide injection), Zemplar® (paricalcitol capsules), and Hectorol® (doxercalciferol capsules) with the following criteria:

Rayaldee® (Calcifediol ER Capsules) Approval Criteria:

1. An FDA approved indication for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease (CKD) stage 3 or 4; and
2. Member must not have CKD stage 5 or end-stage renal disease on dialysis; and
3. Member should have a serum total 25-hydroxyvitamin D level less than 30ng/mL before starting treatment; and

4. Member should have a serum calcium level below 9.8mg/dL before initiating treatment; and
5. Rayaldee® must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of SHPT; and
6. Member must have a documented failure or clinically-significant reason why the member cannot use available generic vitamin D analogs including calcitriol; and
7. Initial approval will be for 30mcg daily for three months; and
    a. After three months, approval for 60mcg daily for 12 months can be considered if intact parathyroid hormone (iPTH) is above the treatment goal and serum calcium is below 9.8mg/dL, phosphorus is below 5.5mg/dL, and 25-hydroxyvitamin D is below 100ng/mL.
    b. Additional approvals will not be granted if iPTH is persistently abnormally low, serum calcium is consistently above the normal range, or serum 25-hydroxyvitamin D is consistently above 100ng/mL; and
8. A quantity limit of 60 capsules per 30 days will apply.

Parsabiv™ (Etelcalcetide Injection) Approval Criteria:

1. An FDA approved indication for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with chronic kidney disease (CKD) on hemodialysis; and
2. Parsabiv™ will not be approved for parathyroid carcinoma, primary hyperparathyroidism, or in patients with CKD who are not on hemodialysis and is not recommended for use in these populations; and
3. Member's corrected serum calcium should be at or above the lower limit of normal (≥ 8.3mg/dL) prior to initiation, dose increase, or re-initiation of Parsabiv™; and
4. Parsabiv™ must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of SHPT; and
5. Member must have a documented failure or a clinically-significant reason why the member cannot use available generic vitamin D analogs including calcitriol; and
6. Member must have a documented failure or a clinically-significant reason why the member cannot use Sensipar® (cinacalcet); and
7. A quantity limit of 12 vials per month will apply.

Zemplar® (Paricalcitol Capsules) Approval Criteria:

1. Member must be 10 years of age or older; and
2. An FDA approved indication for the prevention and treatment of secondary hyperparathyroidism (SHPT) associated with one of the following:
    a. Chronic kidney disease (CKD) stage 3 or 4; or
    b. CKD stage 5 in patients on hemodialysis or peritoneal dialysis; and
        i. Members with CKD stage 5 should have a corrected total serum calcium equal to or less than 9.5mg/dL before initiating treatment; and
3. Zemplar® must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of SHPT; and
4. Member must have a documented failure or a clinically-significant reason why the member cannot use other generic vitamin D analogs available without prior authorization including calcitriol and Zemplar® injection; and
5. A quantity limit of 30 capsules per 30 days will apply.

Hectorol® (Doxercalciferol Capsules) Approval Criteria:

1. An FDA approved diagnosis; and
2. Member must have a documented failure or a clinically-significant reason why the member cannot use calcitriol.

Recommendation 6: Vote to Prior Authorize Marplan® (Isocarboxazid) and Desyrel® (Trazodone 300mg Tablets)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

1. The placement of Marplan® (isocarboxazid) into the Special Prior Authorization (PA) Tier of the Antidepressant Product Based Prior Authorization (PBPA) category based on wholesale acquisition cost (WAC). The following criteria will apply:
    a. **Marplan® (Isocarboxazid) Approval Criteria:**
        i. A patient-specific, clinically significant reason why the member cannot use any of the Tier-3 monoamine oxidase inhibitors (MAOIs) or other cost-effective, lower tiered alternatives in place of Marplan®. Tier structure rules still apply.
2. The placement of Desyrel® (trazodone) 300mg into the Special PA Tier of the Antidepressant PBPA category based on national average drug acquisition cost (NADAC) compared to other trazodone strengths. The following criteria will apply:
    a. **Desyrel® (Trazodone 300mg Tablets) Approval Criteria:**
        i. A patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 products including two trazodone 150mg tablets or three trazodone 100mg tablets to achieve a 300mg dose.
3. Move desvenlafaxine (generic Pristiq®) from Tier-3 to Tier-2 based on NADAC. Current Tier-2 criteria will apply.

Antidepressant Medications Tier-2 Approval Criteria:

1. Member must have a documented, recent (within six months) trial of two Tier-1 medications at least four weeks in duration each and titrated to recommended dosing, that did not provide an adequate response. Tier-1 selection must include at least one medication from the SSRI category and one trial with duloxetine; or
2. Prior stabilization on the Tier-2 medication documented within the last 100 days. A past history of success on the Tier-2 medication will also be considered with adequate documentation; or
3. A unique FDA-approved indication not covered by Tier-1 medications or other medications from a different therapeutic class; or
4. A petition may be submitted for consideration whenever a unique patient-specific situation exists.

Antidepressant Medications Tier-3 Approval Criteria:

1. Member must have a documented, recent (within six months) trial with two Tier-1 medications (one medication from the SSRI category and one trial with duloxetine) and a trial of a Tier-2 medication at least four weeks in duration each and titrated to recommended dosing, that did not provide an adequate response; or

2. Prior stabilization on the Tier-3 medication documented within the last 100 days. A past history of success on the Tier-3 medication will also be considered with adequate documentation; or
3. A unique FDA-approved indication not covered by a lowered tiered medication or other medications from a different therapeutic class; or
4. A petition may be submitted for consideration whenever a unique patient-specific situation exists.

Antidepressant Medications Special Prior Authorization (PA) Approval Criteria:

1. Use of any Special PA medication will require a patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 medications; or
2. A petition may be submitted for consideration whenever a unique patient-specific situation exists.
3. Tier structure rules still apply.
4. When Irenka™ (duloxetine 40mg) is being requested for non-depression related diagnoses, the criteria below will apply:
   a. An FDA approved diagnosis of diabetic peripheral neuropathy or chronic musculoskeletal pain; and
   b. A patient-specific, clinically significant reason why the member cannot use two duloxetine 20mg capsules in place of Irenka™ 40mg capsules; and
   c. A quantity limit of 30 capsules per 30 days will apply.
5. **Marplan® (Isocarboxazid) Approval Criteria:**
   a. A patient-specific, clinically significant reason why the member cannot use any of the Tier-3 monoamine oxidase inhibitors (MAOIs) or other cost-effective, lower tiered alternatives in place of Marplan®. Tier structure rules still apply.
6. **Desyrel® (Trazodone 300mg Tablets) Approval Criteria:**
   a. A patient-specific, clinically significant reason why the member cannot use other available generic Tier-1 products including two trazodone 150mg tablets or three trazodone 100mg tablets to achieve a 300mg dose.

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
citalopram (Celexa®)			fluoxetine 60mg tablets
escitalopram (Lexapro®)			fluoxetine DR (Prozac® Weekly™)
fluoxetine (Prozac®, Sarafem®)			fluvoxamine CR (Luvox CR®)
fluvoxamine (Luvox®)			paroxetine CR (Paxil CR®)
paroxetine (Paxil®)			paroxetine (Pexeva®)
sertraline (Zoloft®)			
Dual-Acting Antidepressants			
bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	**desvenlafaxine (Pristiq®)**	desvenlafaxine (Khedezla®)	bupropion ER (Aplenzin®)
duloxetine (Cymbalta®)	vilazodone (Viibryd®)	levomilnacipran (Fetzima®)	bupropion ER (Forfivo XL®)

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
mirtazapine (Remeron®, Remeron® SolTab™)		nefazodone (Serzone®)	duloxetine 40mg (Irenka™)
trazodone (Desyrel®)			**trazodone 300mg tablet (Desyrel®)**
venlafaxine (Effexor®, Effexor XR® capsules)			trazodone ER (Oleptro®)
			venlafaxine ER tablets (Effexor XR® tablets)
Monoamine Oxidase Inhibitors (MAOIs)			
		phenelzine (Nardil®)	**isocarboxazid (Marplan®)**
		selegiline (Emsam®)	
		tranylcypromine (Parnate®)	
Unique Mechanisms of Action			
		vortioxetine (Trintellix®)	

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
CR = Controlled-Release, DR = Delayed-Release, ER = Extended-Release

Recommendation 7: Vote to Prior Authorize Choline Fenofibrate Delayed-Release (Trilipix®) 135mg Capsules and Fenofibrate Micronized (Lofibra®) 200mg Capsules

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes to the fibric acid derivative medication Product Based Prior Authorization (PBPA) category:

1. Move fenofibric acid (Fibricor®) 35mg tablets into Tier-1 based on low net cost.
2. Move choline fenofibrate delayed-release (Trilipix®) 135mg capsules and fenofibrate micronized (Lofibra®) 200mg capsules into Tier-2 based on net cost. Current Tier-2 criteria will apply.

Fibric Acid Derivative Medications	
Tier-1	**Tier-2**
choline fenofibrate delayed-release (Trilipix® capsules) 48mg	**choline fenofibrate delayed-release (Trilipix® capsules) 135mg**
fenofibrate (Tricor® tablets)	fenofibrate (Fenoglide® tablets)
fenofibrate (Triglide® tablets)	fenofibrate (Lipofen® capsules)
fenofibrate micronized (Lofibra® capsules) 67mg, 134mg	fenofibrate micronized (Antara® capsules)
fenofibric acid (Fibricor® tablets) 35mg	**fenofibrate micronized (Lofibra® capsules) 200mg**
gemfibrozil (Lopid® tablets)	fenofibric acid (Fibricor® tablets) 105mg

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

Recommendation 8: Vote to Prior Authorize Arymo™ ER (Morphine Sulfate Extended-Release), Troxyca® ER (Oxycodone/Naltrexone Extended-Release), Vantrela™ ER (Hydrocodone Extended-Release), Oxaydo® (Oxycodone), and RoxyBond™ (Oxycodone)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

1. The implementation of an age restriction for all tramadol and codeine products for members younger than 12 years of age. Members younger than 12 years of age would require prior authorization approval for reimbursement of these products. This restriction would include both liquid and solid dosage forms. Authorization would require a patient-specific, clinically significant reason for use of these products despite the medication being contraindicated for the member's age.
2. The movement of Opana® ER [oxymorphone extended-release (ER)] from Tier-3 to the Special Prior Authorization (PA) Tier of the Opioid Analgesics Product Based Prior Authorization (PBPA) category based on FDA recommendations to remove the medication from the market. Authorization would require a patient-specific, clinically significant reason why the member could not use any other available extended-release opioid analgesics.
3. The placement of ConZip® (tramadol ER capsules) into the Special PA Tier of the Opioid Analgesics PBPA category based on net cost. Authorization would require a patient-specific, clinically significant reason why the member could not use the extended-release tablet formulation. Tier structure rules would apply.
4. The placement of Oxaydo® (oxycodone), RoxyBond™ (oxycodone), and Trezix® (dihydrocodeine/APAP/caffeine) into Tier-3 of the Opioid Analgesics PBPA category. Current short-acting Tier-3 criteria would apply.
5. The placement of Arymo™ ER (morphine sulfate ER), Troxyca® ER (morphine/naltrexone ER), and Vantrela™ ER (hydrocodone ER) into Tier-3 of the Opioid Analgesics PBPA category. Current long-acting Tier-3 criteria would apply.

Opioid Analgesics*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Long-Acting: oxycodone ER 10mg, 15mg, 20mg only (Oxycontin®)◊	**Long-Acting:** buprenorphine (Butrans®) fentanyl patches (Duragesic®) hydrocodone ER (Hysingla™ ER) morphine ER tabs (MS Contin®) oxycodone ER (Oxycontin®)◊	**Long-Acting:** buprenorphine ER buccal film (Belbuca™) **hydrocodone ER (Vantrela™ ER)** hydrocodone ER (Zohydro™ ER) hydromorphone ER (Exalgo®) methadone (Dolophine®) **morphine sulfate ER (Arymo™ ER)** morphine sulfate ER caps (Kadian®) morphine sulfate ER (MorphaBond™) morphine/naltrexone ER (Embeda®) **morphine/naltrexone ER (Troxyca® ER)** oxycodone ER (Xtampza™ ER) tapentadol ER (Nucynta® ER) tramadol ER tabs (Ultram ER®, Ryzolt®)	**Long-Acting:** **oxymorphone ER (Opana® ER)** oxycodone/APAP ER (Xartemis™ XR) **tramadol ER caps (ConZip®)**

Opioid Analgesics*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Short-Acting: ASA/butalbital/caff/cod (Fiorinal with Codeine®) codeine codeine/APAP dihydrocodone/ASA/caff (Synalgos-DC®) hydrocodone/APAP (Norco®) hydrocodone/IBU (Vicoprofen®, Ibudone®, Reprexain™) hydromorphone (Dilaudid®) morphine IR (MSIR®) oxycodone IR (Oxy IR®) oxycodone/APAP (Percocet®) oxycodone/ASA (Percodan®) oxycodone/IBU (Combunox™) tramadol/APAP (Ultracet®) tramadol (Ultram®)	**Short-Acting:** oxymorphone IR (Opana®) tapentadol IR (Nucynta®)	**Short-Acting:** **dihydrocodeine/APAP/caff (Trezix®)** hydrocodone/APAP (Xodol®, Zamicet®, Liquicet®) oxycodone (Oxecta®) **oxycodone (Oxaydo®)** **oxycodone (RoxyBond™)** oxycodone/APAP (Primlev™, Xolox®)	**Oncology Only:** fentanyl transmucosal lozenge (Actiq®) fentanyl buccal tabs (Fentora®) fentanyl buccal film (Onsolis®) fentanyl sublingual tabs (Abstral®) fentanyl nasal spray (Lazanda®) fentanyl SL spray (Subsys™)

APAP = Acetaminophen, ASA = Aspirin, IR = Immediate-Release, ER = Extended-Release, IBU = Ibuprofen, Cod = Codeine, Caff = Caffeine, Caps = capsules, Tabs = tablets, SL = sublingual

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

◊Brand name preferred.

Recommendation 9: Vote to Prior Authorize Brineura™ (Cerliponase Alfa)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Brineura™ (cerliponase alfa) with the following criteria:

Brineura™ (Cerliponase Alfa) Approval Criteria:

1. An FDA-approved diagnosis of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2) also known as tripeptidyl peptidase-1 (TPP-1) deficiency; and
2. Member must have confirmed TPP-1 enzymatic deficiency via enzyme assay, confirmed by molecular analysis; and
3. Member must be at least 3 years of age or older; and
4. Brineura™ must be prescribed by a specialist with expertise in treatment of CLN2 (or be an advanced care practitioner with a supervising physician who is a specialist with expertise in treating CLN2); and
5. Brineura™ must be administered in a healthcare facility by a prescriber who is knowledgeable in intraventricular administration; and
6. Member must not have ventriculoperitoneal shunts or acute intraventricular access device-related complications; and
7. Member must not have documented generalized status epilepticus within 4 weeks of initiating treatment; and

8. Prescriber must verify member's blood pressure and heart rate will be monitored prior to each infusion, during infusion, and post-infusion; and
9. Prescriber must be willing to perform regular 12-lead electrocardiogram (ECG) evaluation at baseline and at least every 6 months and verify that they are acceptable to the prescriber; and
10. A baseline assessment must be performed to assess the Motor plus Language CLN2 score; and
11. Initial authorizations will be for the duration of six months, at which time compliance will be required for continued approval. After 12 months of utilization, the prescriber must verify the member is responding to the medication as demonstrated by a two point or less decline in Motor plus Language CLN2 score from baseline; and
12. Approval quantity will be based on Brineura™ prescribing information and FDA approved dosing regimen.

Recommendation 10: Annual Review of Breast Cancer Medications and 30-Day Notice to Prior Authorize Kisqali® (Ribociclib), Kisqali® Femara® Co-Pack (Ribociclib/Letrozole), and Nerlynx™ (Neratinib)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Factor Replacement Products and 30-Day Notice to Prior Authorize Afstyla® [Antihemophilic Factor (Recombinant), Single Chain] and Rebinyn® [Coagulation Factor IX (Recombinant), GlycoPEGylated]

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Growth Hormone

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes to the growth hormone prior authorization criteria based on specialist(s) input and guideline recommendations:

1. Modify the growth velocity criteria from requiring a standard less than 5cm/year for most covered diagnoses to instead requiring less than 10% on a growth velocity curve for gender and age.
2. Authorize reimbursement of growth hormone therapy for members with secondary panhypopituitarism due to tumor, trauma, or surgery 12 months post trauma or surgery if no evidence of tumor recurrence and growth has not restarted. The member must still meet all the other criteria; authorization would not require height greater than 2.25 SD below the mean for age in these circumstances.
3. Allow for one-time testosterone prepubertal priming for boys prior to growth hormone stimulation testing.

Recommendation 13: Annual Review of Synagis® (Palivizumab)

NO ACTION REQUIRED.

Recommendation 14: 30-Day Notice to Prior Authorize Endari™ (L-Glutamine)

NO ACTION REQUIRED.

Recommendation 15: Annual Review of Insomnia Medications

MOTION CARRIED by unanimous approval.

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

1. Move ramelteon (Rozerem®) tablets into Tier-1 based on low net cost.
2. Add a previously failed trial of ramelteon (Rozerem®) and confirmation of Non-24-Hour Sleep-Wake Disorder (Non-24) diagnosis by a sleep specialist for authorization of Hetlioz® (tasimelteon).

The proposed changes can be seen in red in the following criteria and tier chart:

Hetlioz® (Tasimelteon) Approval Criteria:

1. An FDA approved diagnosis of Non-24-Hour Sleep-Wake Disorder (Non-24) confirmed by a sleep specialist; and
2. Member must be 18 years of age or older; and
3. Member must be totally blind; and
4. A failed trial of appropriately timed doses of melatonin; and
5. A failed trial of Rozerem® (ramelteon); and
6. Initial approvals will be for the duration of 12 weeks. For continuation, the prescriber must include information regarding improved response/effectiveness of this medication.
7. A quantity limit of 30 capsules for 30 days will apply.

Insomnia Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA***
estazolam (ProSom®)	zolpidem CR (Ambien® CR)	suvorexant (Belsomra®)	doxepin (Silenor®)
eszopiclone (Lunesta®)			tasimelteon (Hetlioz®)+
flurazepam (Dalmane®)			temazepam (Restoril®) 7.5mg and 22.5mg
ramelteon (Rozerem®)			zolpidem SL tablets (Edluar®)
temazepam (Restoril®) 15mg and 30mg			zolpidem SL tablets (Intermezzo®)
triazolam (Halcion®)			zolpidem oral spray (Zolpimist®)
zaleplon (Sonata®)			
zolpidem (Ambien®)			

CR = controlled release; SL = sublingual

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

*Unique dosage formulations require a special reason for use in place of Tier-1 formulations.

+Individual criteria specific to tasimelteon.

Recommendation 16: 30-Day Notice to Prior Authorize Fabrazyme® (Agalsidase Beta)

NO ACTION REQUIRED.

Recommendation 17: Annual Review of Antihyperlipidemics and 30-Day Notice to Prior Authorize Zypitamag™ (Pitavastatin Magnesium) and Nikita™ (Pitavastatin Sodium)

NO ACTION REQUIRED.

Recommendation 18: Annual Review of Alzheimer's Disease Medications and 30-Day Notice to Prior Authorize Namenda XR® (Memantine Extended-Release Capsules)

NO ACTION REQUIRED.

Recommendation 19: Annual Review of Anticoagulants and Platelet Aggregation Inhibitors

NO ACTION REQUIRED.

Recommendation 20: Industry News and Updates

NO ACTION REQUIRED.

Recommendation 21: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

NO ACTION REQUIRED.

Appendix B

2018 Drug Utilization Review Board Meeting Dates

Oklahoma Health Care Authority
October 2017

Meetings are held the second Wednesday of every month at 4:00 PM

January 10, 2018

February 14, 2018

March 14, 2018

April 11, 2018

May 9, 2018

June 13, 2018

July 11, 2018

August 8, 2018

September 12, 2018

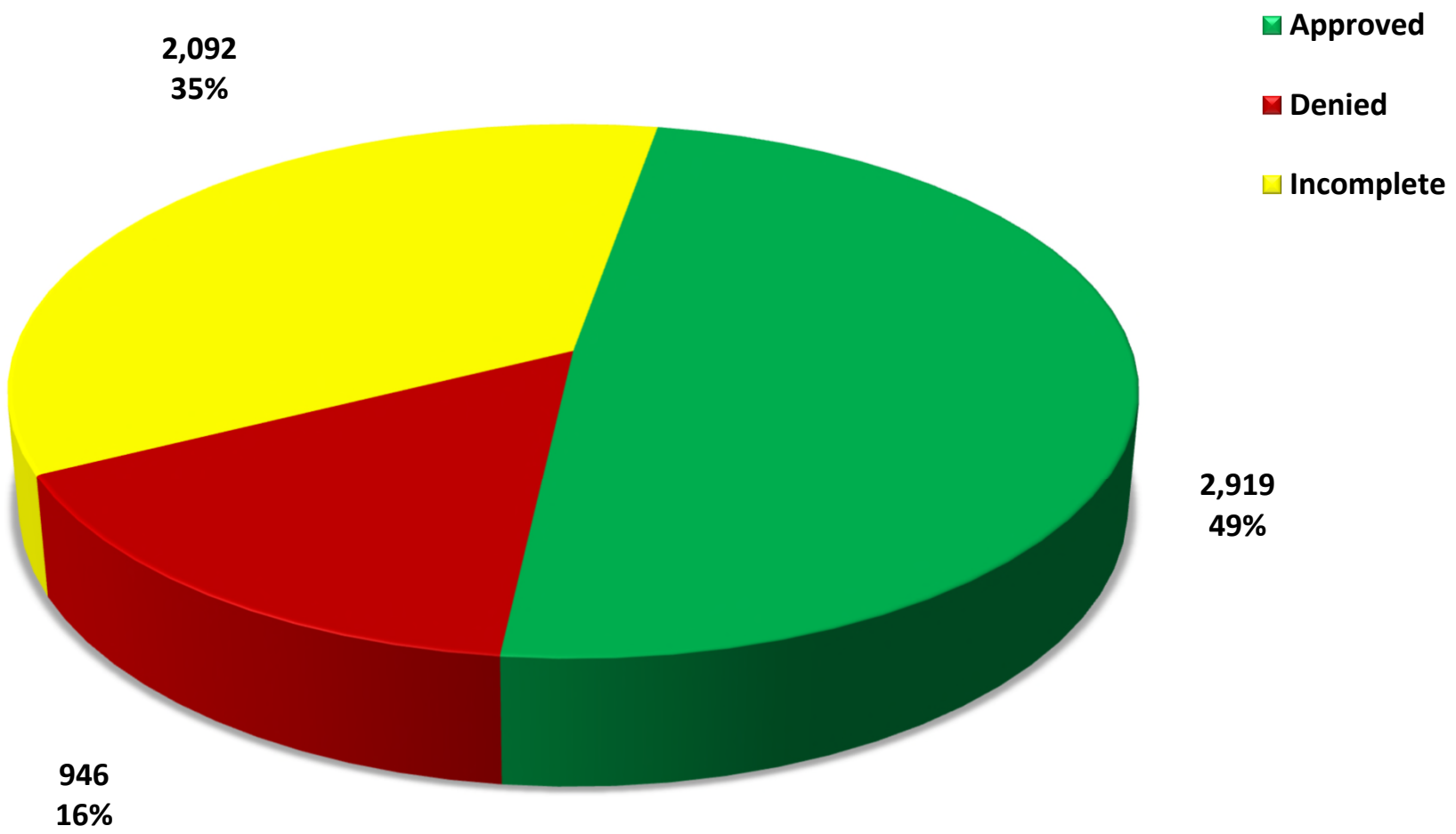
October 10, 2018

November 14, 2018

December 12, 2018

Appendix C

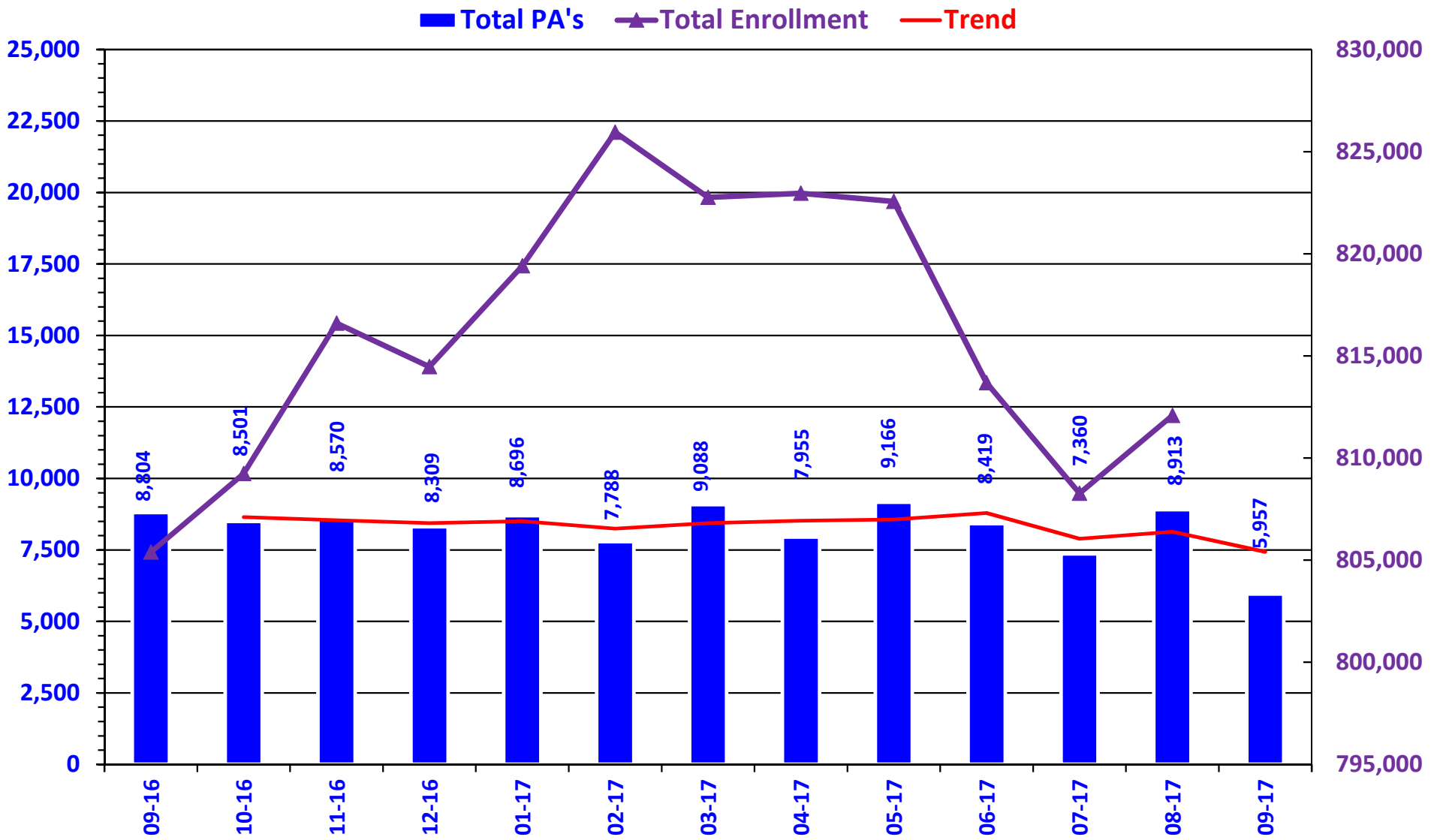
PRIOR AUTHORIZATION ACTIVITY REPORT: SEPTEMBER 2017



As of September 24, 2017. October numbers will be updated in the November DUR packet to reflect the full month.

PA totals include approved/denied/incomplete/overrides

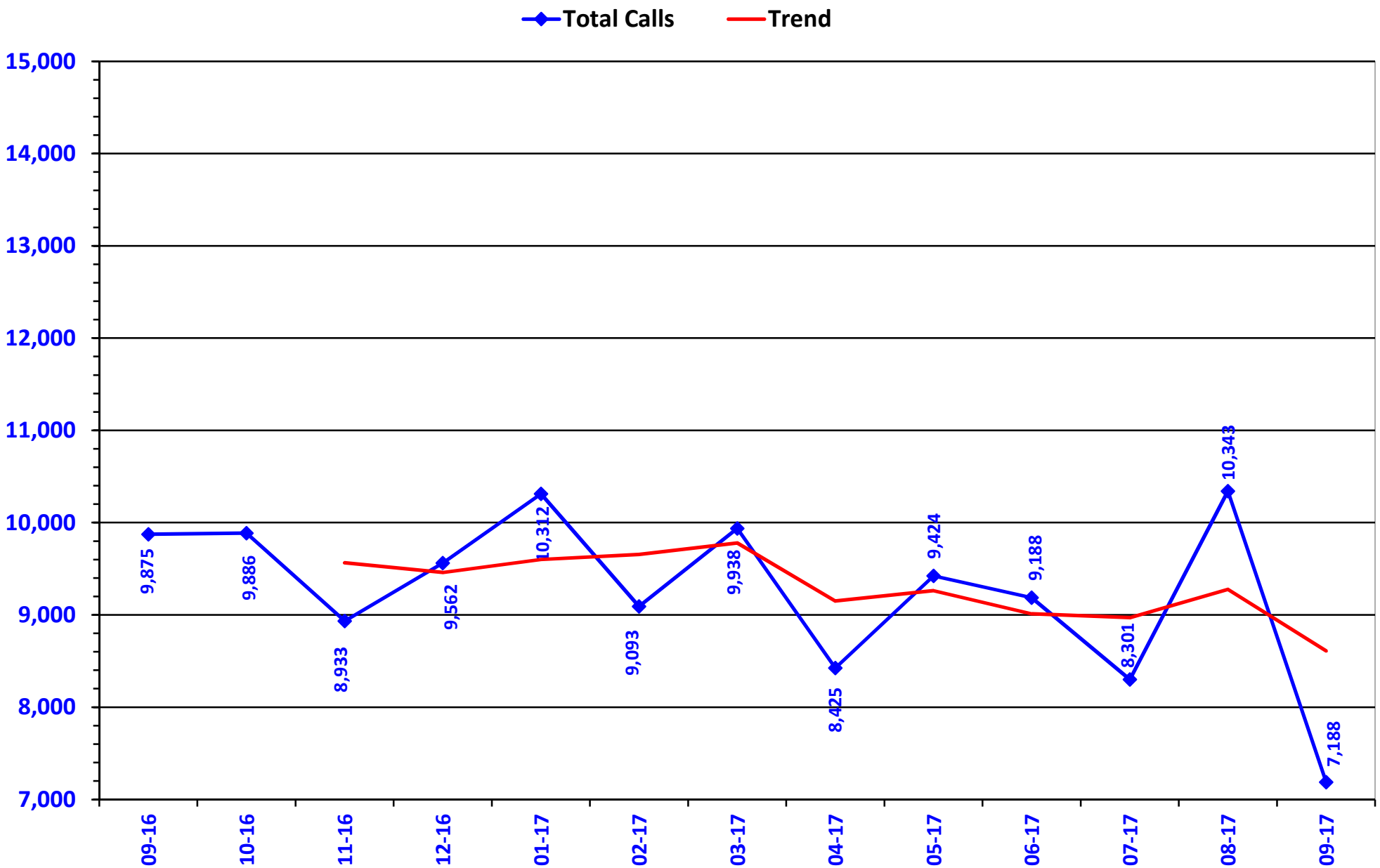
PRIOR AUTHORIZATION REPORT: SEPTEMBER 2016 – SEPTEMBER 2017



As of September 24, 2017. October numbers will be updated in the November DUR packet to reflect the full month.

PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
SEPTEMBER 2016 – SEPTEMBER 2017



As of September 24, 2017. October numbers will be updated in the November DUR packet to reflect the full month.

Prior Authorization Activity

9/1/2017 Through 9/24/2017

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	89	12	21	56	357
Analgesic - NonNarcotic	30	0	7	23	0
Analgesic - Narcotic	329	189	26	114	166
Antiasthma	28	11	1	16	357
Antibiotic	32	15	5	12	257
Anticonvulsant	92	43	10	39	322
Antidepressant	92	22	19	51	357
Antidiabetic	145	57	29	59	353
Antihistamine	154	110	17	27	148
Antimigraine	28	7	3	18	114
Antineoplastic	26	17	2	7	160
Antiulcers	119	21	40	58	120
Anxiolytic	49	29	3	17	278
Atypical Antipsychotics	187	102	29	56	338
Biologics	61	36	6	19	292
Bladder Control	23	2	7	14	358
Blood Thinners	184	122	9	53	329
Botox	28	16	8	4	340
Buprenorphine Medications	259	180	21	58	77
Cardiovascular	88	39	12	37	308
Chronic Obstructive Pulmonary Disease	120	22	33	65	342
Constipation/Diarrhea Medications	107	15	38	54	196
Contraceptive	16	7	3	6	358
Dermatological	98	21	42	35	171
Diabetic Supplies	349	204	11	134	202
Endocrine & Metabolic Drugs	87	54	5	28	140
Erythropoietin Stimulating Agents	16	10	4	2	116
Fibromyalgia	147	19	85	43	330
Fish Oils	15	2	3	10	360
Gastrointestinal Agents	76	15	16	45	157
Growth Hormones	75	53	5	17	148
Hepatitis C	178	118	19	41	8
HFA Rescue Inhalers	45	15	10	20	356
Insomnia	24	1	10	13	174
Insulin	56	20	10	26	344
Miscellaneous Antibiotics	10	5	0	5	10
Multiple Sclerosis	54	20	11	23	143
Muscle Relaxant	37	4	15	18	24
Nasal Allergy	51	2	16	33	223
Neurological Agents	40	21	7	12	335
Neuromuscular Agents	11	9	2	0	196
NSAIDs	138	12	47	79	223
Ocular Allergy	45	8	14	23	81
Osteoporosis	19	8	5	6	357
Other*	211	53	58	100	246
Otic Antibiotic	16	2	2	12	4
Statins	16	2	4	10	220
Stimulant	632	316	79	237	347
Testosterone	20	4	8	8	357
Topical Antifungal	17	2	8	7	39

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Topical Corticosteroids	87	3	33	51	154
Vitamin	44	13	19	12	232
Pharmacotherapy	39	36	0	3	247
Emergency PAs	0	0	0	0	
Total	**4,939**	**2,126**	**897**	**1,916**	
Overrides					
Brand	49	32	5	12	285
Cumulative Early Refill	2	2	0	0	97
Diabetic Supplies	1	1	0	0	10
Dosage Change	266	253	0	13	12
High Dose	2	2	0	0	359
Ingredient Duplication	18	14	0	4	6
Lost/Broken Rx	67	57	3	7	10
NDC vs Age	143	105	12	26	249
Nursing Home Issue	14	13	0	1	17
Opioid Quantity	13	11	1	1	175
Other*	26	22	0	4	10
Quantity vs. Days Supply	397	272	27	98	232
STBS/STBSM	13	7	0	6	38
Stolen	10	7	1	2	13
Third Brand Request	12	9	1	2	14
Wrong D.S. on Previous Rx	1	0	0	1	0
Overrides Total	**1,018**	**793**	**49**	**176**	
Total Regular PAs + Overrides	**5,957**	**2,919**	**946**	**2,092**	

Denial Reasons	
Unable to verify required trials.	1,597
Does not meet established criteria.	968

Other PA Activity	
Duplicate Requests	485
Letters	6,493
No Process	5
Changes to existing PAs	480
Helpdesk Initiated Prior Authorizations	462
PAs Missing Information	39

As of September 24, 2017. October numbers will be updated in the November DUR packet to reflect the full month.

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

Menopausal Hormone Therapy (MHT) for Vasomotor Symptoms Safety Mailing Update

Oklahoma Health Care Authority
October 2017

Introduction[1,2]

Menopause is defined as one year without menses and in the United States occurs on average around age 51. Vasomotor symptoms (VMS), including hot flashes and night sweats, are the hallmarks of menopause, although not all women experience these symptoms. The Endocrine Society Clinical Practice Guideline on the treatment of menopausal symptoms recommends menopausal hormone therapy (MHT) for women younger than 60 years of age or less than 10 years since menopause and experiencing bothersome VMS who do not have contraindications or excess cardiovascular or breast cancer risks. Data on treatment of women age 65 and older is limited; however, new-onset VMS in postmenopausal women 65 years of age and older may be associated with increased risk of major coronary heart disease and all-cause mortality. Potential risks associated with MHT include endometrial cancer, breast cancer, ovarian cancer, coronary heart disease, stroke, venous thromboembolic events, gallbladder disease, and incontinence.

MHT has been the most effective treatment for relief from menopause-associated VMS; however, studies show that MHT can have considerable risks in certain women and that the risks and benefits for each patient must be weighed prior to treatment.

Menopausal Hormone Therapy Prescriber Mailing Summary

In August 2016, the College of Pharmacy and Oklahoma Health Care Authority sent an educational letter to 24 prescribers of 37 unique patients who were 65 years of age or older and had at least 3 months of paid claims for MHT during the analysis time frame of January 2016 to July 2016.

Prescribers were notified of the current Endocrine Society Clinical Practice Guideline's standard recommendations including baseline assessment, specific cautions, and patient monitoring, and they were encouraged to discuss the risks associated with MHT with their patients.

Menopausal Hormone Therapy Mailing Results

The mailing was sent to 24 prescribers of 37 unique MHT users 65 years of age or older with at least 3 months of paid claims for MHT during the analysis time frame.

The post-analysis of the mailing reviewed claims from August 2016 to January 2017. During the post-mailing time frame there were 39 unique MHT users aged 65 years and older. Results found that of the 37 unique members identified in the pre-mailing time frame, only 12 of those members had continuation of MHT in the post-mailing time frame. There were 27 unique

members that had paid claims for MHT in the post-analysis period that did not have at least 3 months of MHT claims during the pre-mailing period.

Conclusions

Although analysis of the MHT mailing revealed the number of members 65 years of age or older receiving MHT increased from 37 to 39, of the original 37 members in the pre-mailing period only 12 members, a 68% reduction, continued on MHT in the post-mailing analysis period. The analysis also showed that of the 24 prescribers that were included in the mailing, only 13 of those prescribers, a 46% reduction, had prescribed MHT for members in the post-mailing analysis period. However, it cannot be explicitly stated that these reductions in members receiving MHT and providers prescribing these medications in the original pre-mailing time frame were based solely on the mailing. Treatment discontinuation could have been planned prior to the mailing based on meeting treatment goals. Furthermore, there were some members in the pre-mailing analysis that became eligible for Medicare during the post-analysis period.

[1] Stuenkel CA, Davis SR, Gompel A, Lumsden MA et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2015; 100(11): 3975-4011.

[2] Cobin RH, Futterweit W, Ginzburg SB, Goodman NF et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Diagnosis and Treatment of Menopause. *Endocr Pract*. 2006; 12(3): 315-37.

Appendix D

Vote to Prior Authorize Afstyla® [Antihemophilic Factor (Recombinant), Single Chain] and Rebinyn® [Coagulation Factor IX (Recombinant), GlycoPEGylated]

Oklahoma Health Care Authority
October 2017

Introduction[1,2]

Afstyla® [Antihemophilic Factor (Recombinant), Single Chain] was approved by the U.S. Food and Drug Adminstraion (FDA) in May 2016. It is a single-chain recombinant factor VIII with a truncated B domain which increases stability and affinity for von Willebrand Factor. Afsytla® is indicated in adults and children with hemophilia A (congenital factor VIII deficiency) for the following:

- On-demand treatment and control of bleeding episodes
- Routine prophylaxis to reduce the frequency of bleeding episodes
- Perioperative management of bleeding

The cost of 4 weeks of prophylaxis therapy using Afsytla® is $50,700[Ŧ] while 4 weeks of prophylaxis therapy using Advate® is $42,560[+].

[Ŧ]Afstyla® dosing based on 50 u/kg three times a week for a 50kg child.
[+]Advate® dosing based on 40 u/kg every other day for a 50kg child.

Rebinyn® [Coagulation Factor IX (Recombinant), GlycoPEGylated] was approved by the FDA in May 2017. Rebinyn® is a purified, recombinant, human factor IX (rFIX) with polyethylene-glycol (PEG) conjugated to the protein which slows down removal from the blood. Rebinyn® is indicated in adults and children with hemophilia B for the following:

- On-demand treatment and control of bleeding episodes
- Perioperative management of bleeding

There is no cost information currently available for Rebinyn®.

Recommendations

The Oklahoma Health Care Authority recommends the prior authorization of Afstyla® [antihemophilic factor (recombinant), single chain] and Rebinyn® [coagulation factor IX (recombinant), glycoPEGylated] with the following criteria:

Eloctate™, Adynovate®, Afstyla®, Alprolix®, Idelvion®, and Rebinyn® Approval Criteria:

1. An FDA approved indication; and
2. Requested medication must be prescribed by a hematologist specializing in hemophilia, or a mid-level practitioner with a supervising physician that is a hematologist specializing in hemophilia; and
3. A patient-specific, clinically significant reason why the member cannot use the following:
    a. Hemophilia A: Advate® or current factor VIII replacement product; or
    b. Hemophilia B: Benefix® or current factor IX replacement product; and

4. A half-life study must be performed to determine the appropriate dose and dosing interval; and
5. Initial approvals will be for the duration of the half-life study. If the half-life study shows significant benefit in prolonged half-life, subsequent approvals will be for the duration of one year.

[1] Afstyla® Prescribing information. CSL Behring. Availabe online at: http://labeling.cslbehring.com/PI/US/Afstyla/EN/Afstyla-Prescribing-Information.pdf. Last revised 04/2017. Last accessed 09/18/2017.

[2] Rebinyn® Prescribing Information. Novo Nordisk. Available online at: http://www.novo-pi.com/rebinyn.pdf. Last revised 05/17/2017. Last accessed 09/18/2017.

Appendix E

Vote to Prior Authorize Endari™ (L-Glutamine)

Oklahoma Health Care Authority
October 2017

Introduction[1,2]

Endari™ (L-glutamine oral powder) was approved by the U.S. Food and Drug Administration (FDA) in July 2017 for the treatment of patients 5 years of age and older with sickle cell disease (SCD) to reduce acute complications associated with the disease. This is the first new treatment for SCD approved by the FDA in nearly 20 years. The medication was granted orphan drug designation. The mechanism of action of the amino acid L-glutamine in treating SCD is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, NAD^+ and its reduced form NADH, play roles in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione. The efficacy of Endari™ in SCD was evaluated in a randomized, double-blind, placebo-controlled, multi-center clinical trial. The trial evaluated the efficacy and safety of Endari™ in 230 patients, ranging in age from 5 to 58 years, with sickle cell anemia or sickle beta thalassemia who had two or more painful crises within the 12 months prior to enrollment. Efficacy was demonstrated by a reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering among patients that received Endari™ compared to patients who received placebo. The recommended dose is 5 grams to 15 grams orally, twice daily based on body weight. The wholesale acquisition cost (WAC) of Endari™ is currently unavailable.

Recommendations

The College of Pharmacy recommends the prior authorization of Endari™ (L-glutamine) with the following criteria:

Endari™ (L-Glutamine) Approval Criteria:

1. An FDA approved diagnosis of sickle cell disease; and
2. Member must be at least 5 years of age or older; and
3. A trial of hydroxyurea or documentation why hydroxyurea is not appropriate for the member; and
4. Endari™ must be prescribed by, or in consultation with, a hematologist or a specialist with expertise in treatment of sickle cell disease (or in consultation with an advanced care practitioner with a supervising physician who is a hematologist or specialist with expertise in treating sickle cell disease); and
5. 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.

6. Initial approvals will be for a duration of six months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

[1] U.S. Food and Drug Administration. FDA Approves Endari, First New Sickle Cell Treatment in Two Decades. *P&T Community*. Available online at: https://www.ptcommunity.com/news/20170710/fda-approves-endari-first-new-sickle-cell-treatment-two-decades. Issued 07/07/2017. Last accessed 09/18/2017.

[2] Endari™ Prescribing Information. Emmaus Medical, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208587s000lbl.pdf. Last revised 07/2017. Last accessed 09/01/2017.

Appendix F

Vote to Prior Authorize Namenda XR® (Memantine Extended-Release Capsules) and Update Namzaric® (Memantine Extended-Release/Donepezil Capsules) Criteria

Oklahoma Health Care Authority
October 2017

Introduction[1,2]

- **Namenda XR® [memantine extended-release (ER) capsules]** is an N-methyl-D-aspartate (NMDA) receptor antagonist indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type.
- **Namzaric® [memantine extended-release (ER)/donepezil capsules]** is a combination of memantine hydrochloride, an NMDA receptor antagonist, and donepezil hydrochloride, an acetylcholinesterase inhibitor, indicated for the treatment of moderate-to-severe dementia of the Alzheimer's type in patients stabilized on 10mg of donepezil hydrochloride once daily.

Recommendations

The College of Pharmacy recommends the prior authorization of Namenda XR® (memantine ER capsules) with the following criteria:

Namenda XR® [Memantine Extended-Release (ER) Capsules] Approval Criteria:

1. An FDA approved diagnosis for the treatment of moderate-to-severe Alzheimer's type dementia; and
2. A patient-specific, clinically significant reason why the member cannot use memantine immediate-release tablets.

Additionally, the College of Pharmacy recommends the following changes noted in red to the Namzaric® (memantine ER/donepezil) prior authorization criteria:

Namzaric® [Memantine Extended-Release (ER)/Donepezil Capsules] Approval Criteria:

1. Member must have a patient-specific, clinically significant reason why the separate immediate-release products which do not require prior authorization cannot be used over this combination product; and
2. A quantity limit of 30 capsules per 30 days will apply.

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[1] Namenda XR® Prescribing Information. Licensed from Merz Pharmaceuticals & GmbH. Available online at: https://www.allergan.com/assets/pdf/namendaxr_pi. Last revised 09/2014. Last accessed 09/11/2017.
[2] Namzaric® Prescribing Information. Licensed from Merz Pharmaceuticals GmbH & Co. KGaA and Adamas Pharmaceuticals, Inc. Available online at: https://www.allergan.com/assets/pdf/namzaric_pi. Last revised 09/2016. Last accessed 09/14/2017.

Appendix G

Vote to Prior Authorize Zypitamag™ (Pitavastatin Magnesium) and Nikita™ (Pitavastatin Sodium)

Oklahoma Health Care Authority
October 2017

Introduction[1,2,3,4,5,6,7]

- **Vascepa® (icosapent ethyl) 0.5 gram capsules** were approved by the U.S. Food and Drug Administration (FDA) in February 2017 as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500mg/dL) hypertriglyceridemia. Vascepa® 1 gram capsules were first FDA approved in 2012 for the same indication. The recommended dose of Vascepa® is 4 grams per day, taken as four 0.5 gram capsules or two 1 gram capsules twice daily with food. The wholesale acquisition cost (WAC) of Vascepa® 0.5 gram is $1.25 per capsule ($300.00 per month), compared to the national average drug acquisition cost (NADAC) of Vascepa® 1 gram at $2.05 per capsule ($246.00 per month).
- **Zypitamag™ (pitavastatin magnesium)** was FDA approved in July 2017 for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated total cholesterol (TC), LDL-cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase HDL-cholesterol (HDL-C). The recommended dosing range is 1mg to 4mg once daily. Zypitamag™ tablets contain 1.026mg, 2.053mg, or 4.106mg of pitavastatin magnesium, which is equivalent to 1mg, 2mg, or 4mg, respectively, of free base. The anticipated release date and cost information for Zypitamag™ are not currently available.
- **Nikita™ (pitavastatin sodium)** was FDA approved in August 2017 for the treatment of patients with primary hyperlipidemia or mixed dyslipidemia as an adjunctive therapy to diet to reduce elevated TC, LDL-C, Apo B, TG, and to increase HDL-C. The recommended dosing range is 1mg to 4mg once daily. Nikita™ is available as 1mg, 2mg, and 4mg tablets. The anticipated release date and cost information for Nikita™ are not currently available.
- Compared to Zypitamag™ (pitavastatin magnesium) and Nikita™ (pitavastatin sodium), a different salt form, **Livalo® (pitavastatin calcium)**, was FDA approved in 2009 for the same indications and is available as 1mg, 2mg, and 4mg tablets. Livalo® is currently in the Special Prior Authorization (PA) Tier based on cost and LDL lowering capability. The NADAC of Livalo® 4mg is $8.28 per tablet ($248.40 per month), compared to the NADAC of atorvastatin 20mg at $0.10 per tablet ($3.00 per month), which is a Tier-1 product that has comparable LDL lowering capability to pitavastatin 4mg. Additionally, the first generic formulation of pitavastatin calcium was FDA approved in December 2016, followed by three others; however, the anticipated release date and cost information for the new generic products are not currently available.

Recommendations

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

1. Move rosuvastatin to Tier-1 based on low net cost and add a required trial with rosuvastatin to current Tier-2 criteria, in addition to an atorvastatin trial, based on LDL lowering capability and low net cost.
2. Place Zypitamag™ (pitavastatin magnesium) and Nikita™ (pitavastatin sodium) into the Special Prior Authorization (PA) Tier. Current Special PA criteria will apply.
3. Add criteria for Vascepa® 0.5 gram based on higher net cost compared to Vascepa® 1 gram. Use of Vascepa® 0.5 gram would require a patient-specific, clinically significant reason why the member cannot use Vascepa® 1 gram.

The proposed changes can be seen in red in the following criteria and tier chart:

Statin Medications and Ezetimibe Tier-2 Approval Criteria:

1. Member must have ~~a~~ documented trials with atorvastatin and rosuvastatin, consisting of at least 8 weeks of continuous therapy each, titrated to a dose of at least 40mg atorvastatin and 20mg rosuvastatin, which did not yield adequate LDL reduction. ~~The minimum starting dose of the Tier-2 medication may only be at the moderate-to-high LDL lowering doses (20mg rosuvastatin or higher)~~; or
2. A documented adverse effect or contraindication to all available lower tiered products; or
3. ~~A clinical exception will apply for Crestor® (rosuvastatin) 40mg for high-risk members hospitalized for recent acute myocardial infarction or acute coronary syndrome, or for pediatric members with homozygous familial hypercholesterolemia (HoFH); or~~
4. Clinical exceptions for ezetimibe include the following:
    a. Documented active liver disease; or
    b. Documented unexplained, persistent elevations of serum transaminases; or
    c. Documented statin-related myopathy.

Statin Medications and Ezetimibe Special Prior Authorization (PA) Approval Criteria:

1. Use of any Special PA medication will require a patient-specific, clinically significant reason why lower tiered medications with similar or higher LDL reduction cannot be used.

Statin Medications and Ezetimibe*		
Tier-1	**Tier-2**	**Special PA**
atorvastatin (Lipitor®)	ezetimibe (Zetia®)	fluvastatin (Lescol® & Lescol® XL)
lovastatin (Mevacor®)		lovastatin (Altoprev®)
pravastatin (Pravachol®)		pitavastatin **calcium** (Livalo®)
rosuvastatin (Crestor®)		**pitavastatin magnesium (Zypitamag™)**
simvastatin (Zocor®)		**pitavastatin sodium (Nikita™)**
		simvastatin/ezetimibe (Vytorin®)

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

~~*Crestor® 5mg and Crestor® 10mg require special reason for use.~~

Omega-3 Fatty Acids Approval Criteria:

1. Laboratory documentation of severe hypertriglyceridemia (fasting triglycerides ≥500mg/dL), and controlled diabetes (fasting glucose <150mg/dL at the time of triglycerides measurement and HgA1c <7.5%); and
2. Previous failure with both nicotinic acid and fibric acid medications; and
3. Use of Vascepa® or Epanova® requires a patient-specific, clinically significant reason why the member cannot use omega-3-acid ethyl esters (generic Lovaza®); and
4. Use of Vascepa® 0.5 gram requires a patient-specific, clinically significant reason why the member cannot use Vascepa® 1 gram.

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[1] U.S. Food and Drug Administration (FDA). ANDA Approval: Pitavastatin Calcium Tablets. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=078560. Issued 12/20/2016. Last accessed 09/11/2017.

[2] U.S. Food and Drug Administration (FDA). sNDA Approval: Vascepa® 0.5 gram Capsules. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Issued 02/16/2017. Last accessed 09/11/2017.

[3] U.S. Food and Drug Administration (FDA). NDA Approval: Zypitamag™ (Pitavastatin Magnesium) Tablets. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=208379. Issued 07/14/2017. Last accessed 09/11/2017.

[4] Han DH. Zypitamag Approved for Primary Hyperlipidemia, Mixed Dyslipidemia. *MPR.* Available online at: http://www.empr.com/news/mixed-dyslipidemia-zypitamag-hyperlipidemia/article/675839/. Issued 07/18/2017. Last accessed 09/11/2017.

[5] U.S. Food and Drug Administration (FDA). NDA Approval: Nikita™ (Pitavastatin Sodium) Tablets. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process. Issued 08/04/2017. Last accessed 09/11/2017.

[6] Lupin Press Release. Lupin Receives FDA Approval for Nikita™ (Pitavastatin) Tablets. Available online at: http://www.lupin.com/lupin-receives-fda-approval-for-nikitatm-pitavastatin-tablets.php. Issued 08/09/2017. Last accessed 09/11/2017.

[7] Livalo® (Pitavastatin Calcium) Package Insert. MedLibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/livalo-2/. Last revised 11/18/2016. Last accessed 09/11/2017.

Appendix H

Vote to Prior Authorize Fabrazyme® (Agalsidase Beta)

Oklahoma Health Care Authority
October 2017

Introduction[1,2,3]

Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway, caused by mutations in the galactosidase alpha (*GLA*) gene. The metabolic defect in Fabry disease is a deficiency of the lysosomal hydrolase, alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosyl-ceramide (GL-3). This results in accumulation of GL-3 within lysosomes throughout the body, particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system. This leads to variable manifestations of the disease. *GLA* gene mutations that result in an absence of alpha-Gal A activity lead to the classic, severe form of Fabry disease. Mutations that decrease but do not eliminate the enzyme's activity usually cause the milder, late-onset form of Fabry disease that affect only the heart or kidneys.

Fabry disease affects an estimated 1 in 40,000 to 60,000 males. This disorder also occurs in females, although the prevalence is unknown.

There is no cure for Fabry disease, and uniform recommendations for the use of enzyme replacement therapy (ERT) do not exist. Currently, Fabrazyme® (agalsidase beta) is the only U.S. Food and Drug Administration (FDA) approved ERT for Fabry disease. Fabrazyme® is supplied as 35mg or 5mg single-use vials of sterile, nonpyrogenic, lyophilized powder for reconstitution. The recommended dose is 1mg/kg of body weight given every two weeks as an intravenous (IV) infusion. Fabrazyme® is intended to provide an exogenous source alpha-Gal A in Fabry disease patients, and thus reduce GL-3 deposition in capillary endothelium of the kidney and certain other cell types. The relationship of GL-3 deposition reduction to specific clinical manifestations of Fabry disease has not been established.

Cost:

Medication	Cost Per Vial	Cost Per Treatment[Δ]	Cost Per Year
Fabrazyme® (agalsidase beta) 35mg vial	**$5,663.00**	**$12,135.00**	**$291,240.00**
Fabrazyme® (agalsidase beta) 5mg vial	**$809.00**	**$12,135.00**	**$291,240.00**

Costs based on National Average Drug Acquisition Cost (NADAC), State Maximum Allowable Cost (SMAC), or Wholesale Acquisition Cost (WAC) if NADAC unavailable.
Costs listed in the table above do not take into account federal or supplemental rebate participation; therefore, do not reflect net costs.
[Δ]Cost per treatment based on a 75kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Fabrazyme® (agalsidase beta) with the following criteria:

Fabrazyme® (Agalsidase Beta) Approval Criteria:

1. An FDA approved diagnosis of Fabry disease. Diagnosis must be confirmed by one of the following:
    a. Genetic testing confirming positive galactosidase alpha (*GLA*) gene mutation; or
    b. Decreased plasma levels of alpha-galactosidase A (less than 5% of normal); and
2. Fabrazyme® (agalsidase beta) will initially be approved for six months. After that time, compliance will be required for continued authorization; 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.

[1] Mauer M, Kopp JB. Clinical Features and Diagnosis of Fabry disease. *Up-To-Date®*. Available online at: http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-fabry-disease?source=search_result&search=fabry&selectedTitle=1%7E50. Last revised 10/21/2014. Last accessed 09/18/2017.
[2] Fabry disease. NIH U.S. National Library of Medicine. *Genetics Home Reference*. Available online at: https://ghr.nlm.nih.gov/condition/fabry-disease. Last revised 02/2012. Last accessed 09/18/2017.
[3] Fabrazyme® Prescribing Information. Genzyme Corporation. Available online at: https://www.fabrazyme.com/healthcare.aspx. Last revised 05/2010. Last accessed 09/18/2017.

Appendix I

Vote to Prior Authorize Kisqali® (Ribociclib), Kisqali® Femara® Co-Pack (Ribociclib/Letrozole), and Nerlynx™ (Neratinib)

Oklahoma Health Care Authority
October 2017

Introduction[1,2,3]

- **Kisqali® (ribociclib)** is a kinase Inhibitor indicated in combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor positive (HR+), Human Epidermal Receptor Type 2 (HER2)-negative advanced or metastatic breast cancer. Kisqali® is available as 200mg oral tablets dosed as 600mg (three 200mg tablets) orally once daily for 21 consecutive days followed by 7 days off treatment. The wholesale acquisition cost (WAC) of Kisqali® 600mg for 21 days (63 tablets) is $10,950.03.
- **Kisqali® Femara® Co-Pack (ribociclib/letrozole)** is a co-package of a kinase inhibitor and aromatase inhibitor indicated as initial endocrine-based therapy for the treatment of postmenopausal women with HR+, HER2-negative advanced or metastatic breast cancer. Kisqali® Femara® Co-Pack is available as a co-package containing Kisqali® 200mg oral tablets and Femara® 2.5mg oral tablets. The recommended dosing is Kisqali® 600mg (three 200mg tablets) orally once daily for 21 consecutive days followed by 7 days off treatment and Femara® 2.5mg (one tablet) orally once daily throughout the 28-day cycle. The WAC of 600mg Kisqali® for 21 days (63 tablets) plus Femara® 2.5mg for 28 days (28 tablets) is $10,950.03.
- **Nerlynx™ (neratinib)** is a kinase inhibitor indicated for the extended adjuvant treatment of adult patients with early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab-based therapy. Nerlynx™ is available as 40mg oral tablets dosed as 240mg (6 tablets) orally once daily with food, continuously for one year. The WAC of Nerlynx™ 240mg for 30 days (180 tablets) is $10,499.40.

Recommendations

The prior authorization of Kisqali® (ribociclib), Kisqali® Femara® Co-Pack (ribociclib/letrozole), and Nerlynx™ (neratinib) with the following criteria:

Kisqali® (Ribociclib) Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use the co-packaged formulation with letrozole; and
2. A diagnosis of advanced or metastatic breast cancer, initial therapy; and
3. Member must be Hormone Receptor (HR)-positive; and
4. Member must be Human Epidermal Receptor Type 2 (HER2)-negative; and
5. Ribociclib must be given in combination with an aromatase inhibitor; and
6. Ribociclib must be used in postmenopausal women only.

7. Authorizations will be for the duration of three months. Reauthorization may be granted if the patient does not show evidence of progressive disease while on ribociclib therapy.

Kisqali® Femara® Co-Pack (Ribociclib/Letrozole) Approval Criteria:

1. A diagnosis of advanced or metastatic breast cancer, initial therapy; and
2. Member must be Hormone Receptor (HR)-positive; and
3. Member must be Human Epidermal Receptor Type 2 (HER2)-negative; and
4. Ribociclib must be used in postmenopausal women only.
5. Authorizations will be for the duration of three months. Reauthorization may be granted if the patient does not show evidence of progressive disease while on ribociclib/letrozole therapy.

Nerlynx™ (Neratinib) Approval Criteria:

1. For adjuvant treatment in early stage breast cancer; and
2. Member must have Human Epidermal Receptor Type 2 (HER2)-overexpressed breast cancer; and
3. Neratinib must be used to follow adjuvant trastuzumab-based therapy.
4. Authorizations will be for the duration of three months. Reauthorization may be granted if the patient does not show evidence of progressive disease while on neratinib therapy.

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[1] Kisqali® Prescribing Information. Novartis Inc. Available online at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali.pdf. Last revised 03/2017. Last accessed 09/19/2017.

[2] Kisqali® Femara® Co-Pack Prescribing Information. Novartis Inc. Available online at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/kisqali_copack.pdf. Last revised 05/2017. Last accessed 09/19/2017.

[3] Nerlynx™ Prescribing Information. Puma Biotechnology, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208051s000lbl.pdf. Last revised 07/2017. Issued 09/19/2017.

Appendix J

Fiscal Year 2017 Annual Review of Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) Medications and 30-Day Notice to Prior Authorize Blincyto® (Blinatumomab), Besponsa® (Inotuzumab Ozogamicin), Bosulif® (Bosutinib), Gleevec® (Imatinib), Iclusig® (Ponatinib), Kymriah™ (Tisagenlecleucel), Synribo® (Omacetaxine), Sprycel® (Dasatinib), and Tasigna® (Nilotinib)

Oklahoma Health Care Authority
October 2017

Introduction[1,2,3,4]

Leukemia is an abnormal and autonomous proliferation of one or more blood-forming elements with infiltrations of the bone marrow and other organs. Leukemia is a heterogeneous group of neoplasms arising from the malignant transformation of hematopoietic cells that eventually replaces the normal marrow, leading to the signs and symptoms of leukemia. Approximately 62,130 new cases of leukemia are expected to be diagnosed in 2017 and approximately 24,500 deaths from leukemia are expected.

Chronic myeloid leukemia (CML) is a slowly progressive blood and bone marrow disease that usually occurs during or after middle age and rarely occurs in children. CML occurs due to a genetic mutation called the Philadelphia chromosome (Ph) resulting in the bone marrow making an enzyme called tyrosine kinase that causes too many stem cells to become white blood cells (blasts). A piece of chromosome 9 and a piece of chromosome 22 break off and trade places forming the BCR-ABL gene. CML treatment changed dramatically with the approval of imatinib in 2001, a targeted therapy that inhibits the BCR-ABL tyrosine kinase. Currently there are several tyrosine kinase inhibitors approved to treat CML including imatinib, nilotinib, dastanib, and ponatinib; these are the mainstays of treatment for CML.

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, but can also be seen in adults. In 2014, there were an estimated 81,837 people with ALL; it is estimated that there will be 5,970 new cases in 2017 and 1,440 estimated deaths. The majority of patients with ALL are between 15 to 39 years of age. Adult and young adolescent (AYA) patients are treated similar to pediatric patients receiving aggressive chemotherapy including induction, consolidation, and maintenance for 1 to 3 years. Adults can be treated similar to AYA patients or with multi-agent chemotherapy. Some patients, typically adults, have Philadelphia chromosome positive (Ph+) disease and can be treated with BCR-ABL tyrosine kinase inhibitors in addition to chemotherapy.

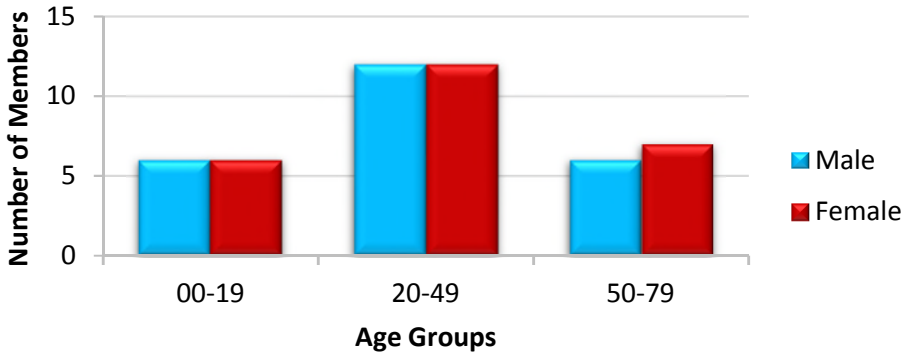
Utilization of ALL/CML Medications: Fiscal Year 2017

Comparison of Fiscal Years

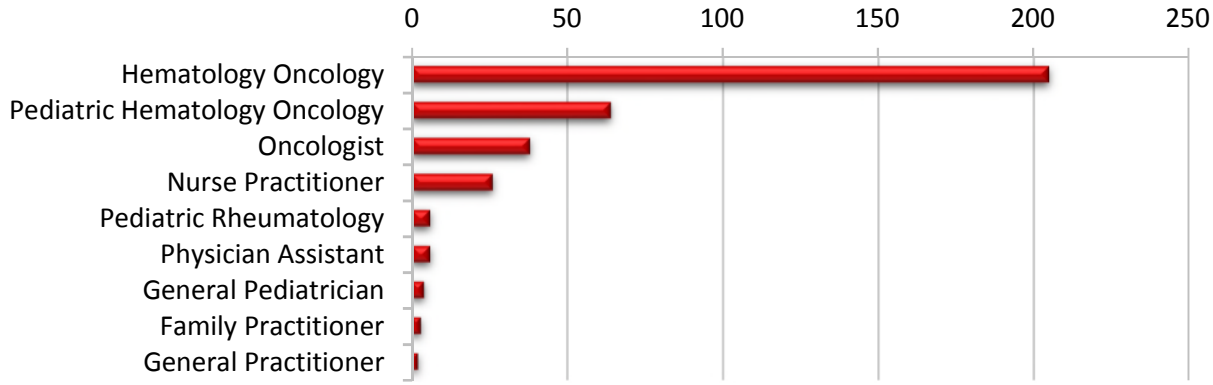
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	45	310	$3,277,072.55	$10,571.20	$357.37	17,317	9,170
2017	49	354	$3,626,596.07	$10,244.62	$342.49	39,056	10,589
% Change	**8.90%**	**14.20%**	**10.70%**	**-3.10%**	**-4.20%**	**125.50%**	**15.50%**
Change	**4**	**44**	**$349,523.52**	**-$326.58**	**-$14.88**	**21,739**	**1,419**

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

Demographics of Members Utilizing ALL/CML Medications: Pharmacy Claims



Top Prescriber Specialties of ALL/CML Medications By Number of Claims



Market News and Updates[5,6,7,8,9,10]

Generic Availability:

- Gleevec® (imatinib) generic approved August 2016

Anticipated Patent Expiration(s):

- Sprycel® (dasatinib): June 2020
- Tasigna® (nilotinib): July 2023

- Bosulif® (bosutinib): April 2024
- Synribo® (omacetaxine): October 2026
- Iclusig® (ponatinib): December 2026

New U.S. Food and Drug Administration (FDA) Approval(s):
- Besponsa® (inotuzumab ozogamicin): August 2017
- Kymriah™ (tisagenlecleucel): August 2017

Pipeline:
- ABL001:
  - Asciminib (BCR-ABL inhibitor) for 3rd line CML
  - Currently in Phase 1, planned filing dates 2020
- CMLVAX100: vaccine in combination with imatinib for CML
- Programmed death 1 (PD-1) inhibitors and ruxolitinib being studied in CML

Product Summaries[11,12,13,14,15,16,17,18,19,20]

Blincyto® (Blinatumomab):
- **Therapeutic Class:** Anti-CD19/CD3 monoclonal antibody (bispecific T-cell engager, BiTE®)
- **Indication(s):** Treatment of relapsed or refractory B-cell precursor ALL
- **How Supplied:** 35mcg vials for intravenous (IV) solution
- **Dose:**
  - Patients ≥45kg (fixed dose):
    - Cycle 1: 9mcg daily administered as a continuous infusion on days 1 to 7, followed by 28mcg daily as a continuous infusion on days 8 to 28 of a 6-week treatment cycle
    - Cycles 2 through 5: 28mcg daily administered as a continuous infusion on days 1 to 28 of a 6-week treatment cycle
    - Cycles 6 through 9: 28mcg daily administered as a continuous infusion on days 1 to 28 of a 12-week treatment cycle
  - Patients <45kg (dose based on body surface area [BSA]):
    - Cycle 1: 5mcg/m^2/day (maximum: 9mcg/day) administered as a continuous infusion on days 1 to 7, followed by 15mcg/m^2/day (maximum: 28mcg/day) as a continuous infusion on days 8 to 28 of a 6-week treatment cycle
    - Cycles 2 through 5: 15mcg/m^2/day (maximum: 28mcg/day) administered as a continuous infusion on days 1 to 28 of a 6-week treatment cycle
    - Cycles 6 through 9: 15mcg/m^2/day (maximum: 28mcg/day) administered as a continuous infusion on days 1 to 28 of a 12-week treatment cycle
- **Cost:** $4,319.43 per 35mcg vial

Besponsa® (Inotuzumab Ozogamicin):
- **Therapeutic Class:** Anti-CD22 monoclonal antibody
- **Indication(s):** Treatment of relapsed or refractory B-cell precursor ALL in adults
- **How Supplied:** 0.9mg vial for IV solution

- **Dose:**
  - Cycle 1: 0.8mg/m^2 on day 1 and 0.5mg/m^2 on days 8 and 15 of a 21-day treatment cycle (total dose/cycle 1: 1.8mg/m^2); treatment cycle may be extended to 4 weeks if complete remission (CR) is achieved, or CR with incomplete hematologic recovery (CRi), and/or to allow for recovery from toxicity
  - Subsequent Cycles:
    - *Patients who achieve CR or CRi:* 0.5mg/m^2 on days 1, 8, and 15 of a 28-day treatment cycle (total dose/cycle: 1.5mg/m^2)
    - *Patients who do NOT achieve CR or CRi:* 0.8mg/m^2 on day 1 and 0.5mg/m^2 on days 8 and 15 of a 28-day treatment cycle (total dose/cycle: 1.8mg/m^2); if CR or CRi is not achieved within 3 cycles, treatment should be discontinued
- **Cost:** $18,700 per 0.9mg vial

Bosulif® (Bosutinib):
- **Therapeutic Class:** BCR-ABL Tyrosine Kinase Inhibitor (TKI)
- **Indication(s):** Chronic, accelerated, or blast phase CML
- **How Supplied:** 100mg and 500mg oral tablets
- **Dose:** 500mg once daily, may increase to 600mg daily
- **Cost:** $13,539 for a 1-month supply of 500mg tablets

Gleevec® (Imatinib):
- **Therapeutic Class:** BCR-ABL TKI
- **Indication(s):**
  - Ph+ ALL (pediatric and adult)
  - Aggressive, systemic mastocytosis
  - Chronic, accelerated, or blast phase CML
  - Dermatofibrosarcoma protuberans
  - Gastrointestinal (GI) stromal tumors
  - Hypereosinophilic syndrome and/or chronic eosinophilic leukemia
  - Myelodysplastic/myeloproliferative diseases
- **How Supplied:** 100mg and 400mg oral tablets
- **Dose:** 400mg daily
  - Chronic Phase: 400mg once daily; may be increased to 600mg daily, if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6 to 12 months, or loss of previous hematologic or cytogenetic response; an increase to 800mg daily has been used
  - Accelerated Phase or Blast Crisis: 600mg once daily; may be increased to 800mg daily (400mg twice daily), if tolerated, for disease progression, lack of hematologic response after 3 months, lack of cytogenetic response after 6 to 12 months, or loss of previous hematologic or cytogenetic response
- **Cost:** $10,122.30 for a 1-month supply of 400mg tablets

Iclusig® (Ponatinib):

- **Therapeutic Class:** BCR-ABL TKI
- **Indication(s):**
  - Ph+ ALL in patients for whom no other TKI therapy is indicated
  - Chronic phase, accelerated phase, or blast phase CML for whom no other TKI therapy is indicated
  - T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL
- **How Supplied:** 15mg and 45mg oral tablets
- **Dose:** 45mg once daily
- **Cost:** $16,560.90 for a 1-month supply of 45mg tablets

Kymriah™ (Tisagenlecleucel):

- **Therapeutic Class:** CD19-directed genetically modified autologous T cell immunotherapy
- **Indication(s):** Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse
- **How Supplied:** Patient-specific infusion bag
- **Dose:**
  - Dosing is based on the number of chimeric antigen receptor (CAR)-positive viable T cells
  - ≤50kg: 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight IV
  - >50kg: 0.1 to 2.5 x 108 total CAR-positive viable T cells (non-weight based) IV
- **Cost:** $475,000 per one-time treatment

Synribo® (Omacetaxine):

- **Therapeutic Class:** Cephalotaxine, protein synthesis inhibitor
- **Indication(s):** Chronic or accelerated phase CML
- **How Supplied:** 3.5mg vial for subcutaneous (SQ) solution
- **Dose:**
  - Induction: 1.25mg/m^2 twice daily for 14 consecutive days of a 28-day treatment cycle; treatment should be continued until hematologic response is achieved
  - Maintenance: 1.25mg/m^2 twice daily for 7 consecutive days of a 28-day treatment cycle; treatment should be continued until the patient is no longer achieving a clinical treatment benefit
- **Cost:** $957.00 per 3.5mg vial

Sprycel® (Dasatinib):

- **Therapeutic Class:** BCR-ABL TKI
- **Indication(s):**
  - Ph+ ALL
  - Chronic, accelerated, or blast phase CML
- **How Supplied:** 20mg, 50mg, 70mg, 80mg, 100mg, and 140mg oral tablets
- **Dose:**

- Chronic Phase CML: 100mg daily, may increase to 140mg if not achieving hematologic or cytogenetic response
- Accelerated or Blast Phase CML: 140mg once daily
- Ph+ ALL: 140mg once daily

- **Cost:** $11,616.00 for a 1-month supply of 100mg tablets

Tasigna® (Nilotinib):

- **Therapeutic Class:** BCR-ABL TKI
- **Indication(s):** Chronic or accelerated phase CML
- **How Supplied:** 150mg and 200mg oral tablets
- **Dose:**
  - Chronic Phase CML: 300mg twice daily
  - Resistant, Chronic Phase or Accelerated Phase CML: 400mg twice daily
- **Cost:** $12,415.20 for a 1-month supply of 150mg tablets

Recommendations

Blincyto® (Blinatumomab) Approval Criteria:

1. Blincyto® should be used as a single-agent only; and
2. For **one** of the following diseases:
   a. Relapsed/refractory Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL); or
   b. Relapsed/refractory Philadelphia chromosome positive (Ph+) ALL after failure of two Tyrosine Kinase Inhibitors (TKIs); or
   c. Ph- ALL as consolidation in adult/young adolescent or patients <65 years without substantial comorbidity with persistent or late clearance minimal residual disease positive (MRD+) following a complete response to induction.

Besponsa® (Inotuzumab Ozogamicin) Approval Criteria:

1. Besponsa® must be used as a single-agent only; and
2. Member must have **one** of the following:
   a. Relapsed/refractory Philadelphia chromosome negative (Ph-) acute lymphoblastic leukemia (ALL); or
   b. Relapsed/refractory Philadelphia chromosome positive (Ph+) ALL who are intolerant/refractory to Tyrosine Kinase Inhibitors (TKIs).

Bosulif® (Bosutinib) Approval Criteria [Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Diagnosis]:

1. Bosulif® may be authorized for relapsed/refractory ALL either as:
   a. Single-agent; or
   b. In combination with an induction regimen not previously given; and
2. Bosulif® must be used in patients with E255K/V, F317L/VI/C, F359V/C/I, T315A, or Y253H mutations.

Bosulif® (Bosutinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Patients with chronic, accelerated, or blast phase CML with resistance or intolerance after primary treatment with either: dasatinib, imatinib, or nilotinib with the following BCR-ABL1 transcript levels:
    a. 0.01% to 1% at >12 months; or
    b. >1% to 10% at ≥12 months; or
    c. >10% at any milestone.

Gleevec® (Imatinib) Approval Criteria [Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Diagnosis]:

1. Gleevec® may be approved for one of the following indications:
    a. Upfront therapy (including induction and consolidation) in combination with multi-agent chemotherapy or as a single-agent; or
    b. Maintenance therapy including:
        i. In combination with vincristine and prednisone, with or without methotrexate and mercaptopurine; or
        ii. Post-hematopoietic stem cell transplant; or
    c. In relapsed/refractory ALL and as a single-agent or in combination with multi-agent chemotherapy.

Gleevec® (Imatinib) Approval Criteria [Bone Cancer – Chordoma Diagnosis]:

1. Single-agent therapy or in combination with cisplatin or sirolimus for the treatment of recurrent disease.

Gleevec® (Imatinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Member must have **<u>one</u>** of the following:
    a. Newly diagnosed chronic, accelerated, or blast phase CML; or
    b. Post-hematopoietic stem cell transplant.

Gleevec® (Imatinib) Approval Criteria [Melanoma Diagnosis]:

1. Member must meet **<u>all</u>** of the following criteria:
    a. Gleevec® must be used as a single-agent; and
    b. Second-line or subsequent therapy for disease progression or after maximum clinical benefit from BRAF targeted therapy; and
    c. Metastatic or unresectable tumors; and
    d. Activating mutations of C-KIT; and
    e. Member must have an ECOG performance status of 0 to 2.

Gleevec® (Imatinib) Approval Criteria [Myelodysplastic Syndrome (MDS) Diagnosis]:

1. Chronic myelomonocytic leukemia (CMML) for 5q31-33 translocations and/or PDGFRβ gene rearrangements.

Gleevec® (Imatinib) Approval Criteria [Non-Melanoma Skin Cancers – Dermatofibrosarcoma Protuberans (DFSP) Diagnosis]:

1. Tumors with t(17;22) translocation; and
2. Member must have **<u>one</u>** of the following:

a. Adjuvant therapy for positive surgical margins following excision; or
b. Recurrent disease if disease is unresectable or if additional resection would lead to unacceptable functional or cosmetic outcomes; or
c. For metastatic disease.

Gleevec® (Imatinib) Approval Criteria [Soft Tissue Sarcoma – Desmoid Tumors (Aggressive Fibromatosis) Diagnosis]:

1. Primary, recurrent, or progressive disease with **one** of the following:
   a. Initial treatment for resectable disease; or
   b. Adjuvant treatment for gross residual disease; or
   c. Initial treatment for unresectable disease or for disease for which surgery would be unacceptably morbid.

Gleevec® (Imatinib) Approval Criteria [Soft Tissue Sarcoma – Gastrointestinal Stromal Tumors (GIST) Diagnosis]:

1. Primary/preoperative treatment for patients with documented GIST with **one** of the following:
   a. Resectable with risk of significant morbidity; or
   b. Unresectable; or
   c. Recurrent; or
   d. Metastatic; or
2. Postoperative treatment with **one** of the following:
   a. Complete resection of primary GIST; or
   b. Persistent gross residual disease; or
3. Continued treatment for **one** of the following:
   a. Limited progression; or
   b. Generalized progression.

Gleevec® (Imatinib) Approval Criteria [Soft Tissue Sarcoma – Pigmented Villonodular Synovitis/Tenosynovial Giant Cell Tumor Diagnosis]:

1. Gleevec® must be used as a single-agent only.

Iclusig® (Ponatinib) Approval Criteria [Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Diagnosis]:

1. Member must have **one** of the following:
   a. Induction/consolidation with HyperCVAD; or
   b. Maintenance therapy in combination with vincristine and prednisone, with or without methotrexate and mercaptopurine; or
   c. Maintenance therapy post-hematopoietic stem cell transplant; or
   d. Relapsed/refractory disease either as a single-agent, in combination with chemotherapy not previously given, or in patients with T315I mutations.

Iclusig® (Ponatinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Member must have **one** of the following:
   a. In patients with a T315I mutation; or

b. Intolerant or resistant to all other Tyrosine Kinase Inhibitors (TKIs); or
c. Post-hematopoietic stem cell transplantation in patients with prior accelerated or blast phase prior to transplant or who have relapsed.

Kymriah™ (Tisagenlecleucel) Approval Criteria:

1. **All** of the following must be met for approval:
    a. B-Cell prescursor acute lymphoblastic leukemia (ALL); and
    b. Member must be 25 years of age or younger; and
    c. Refractory or in second or later relapse:
        i. Philadelphia chromosome negative (Ph-): ALL must be refractory or with ≥2 relapses; or
        ii. Philadelphia chromosome positive (Ph+): ALL must have failed ≥2 tyrosine kinase inhibitors (TKIs); and
    d. Therapies to consider prior to tisagenlecleucel if appropriate: clinical trial, multi-agent chemotherapy with or without hematopoietic cell transplantation (HCT), blinatumomab (category 1 recommendation), and inotuzumab (category 1 recommendation); and
    e. Tisagenlecleucel should be given inpatient to allow for appropriate monitoring of cytokine release syndrome and other adverse effects.

Synribo® (Omacetaxine) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Synribo® must be used as a single-agent only; and
2. Member must have **one** of the following:
    a. Primary treatment of advanced phase CML with disease progression to accelerated phase; or
    b. Post-hematopoietic stem cell transplant in patients who have relapsed; or
    c. Patients with T315I mutation; or
    d. Patients who are intolerant or resistant to two or more Tyrosine Kinase Inhibitors (TKIs).

Sprycel® (Dasatinib) Approval Criteria [Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Diagnosis]:

1. Member must have **one** of the following:
    a. Upfront therapy (including induction and consolidation) in combination with multi-agent chemotherapy or as a single-agent; or
    b. Maintenance therapy including:
        i. In combination with vincristine and prednisone, with or without methotrexate and mercaptopurine; or
        ii. Post-hematopoietic stem cell transplant; or
    c. Relapsed/refractory as a single-agent or in combination with multi-agent chemotherapy.

Sprycel® (Dasatinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Member must have **one** of the following:
    a. Newly diagnosed chronic, accelerated, or blast phase CML; or

b. Post-hematopoietic stem cell transplant.

Sprycel® (Dasatinib) Approval Criteria [Soft Tissue Sarcoma – Gastrointestinal Stromal Tumors (GIST) Diagnosis]:

1. Member must have all of the following:
    a. Progressive disease and failed imatinib, sunitinib, or regorafenib; and
    b. PDGFRA D842V mutation.

Tasigna® (Nilotinib) Approval Criteria [Philadelphia Chromosome Positive (Ph+) Acute Lymphoblastic Leukemia (ALL) Diagnosis]:

1. Member must have **one** of the following:
    a. Upfront therapy (including induction and consolidation) in combination with multi-agent chemotherapy or as a single-agent; or
    b. Maintenance therapy including:
        i. In combination with vincristine and prednisone, with or without methotrexate and mercaptopurine; or
        ii. Post-hematopoietic stem cell transplant; or
    c. Relapsed/refractory as a single-agent or in combination with multi-agent chemotherapy.

Tasigna® (Nilotinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Member must have **one** of the following:
    a. Newly diagnosed chronic, accelerated, or blast phase CML; or
    b. Post-hematopoietic stem cell transplant.

Tasigna® (Nilotinib) Approval Criteria [Soft Tissue Sarcoma – Gastrointestinal Stromal Tumors (GIST) Diagnosis]:

1. Member must have progressive disease and failed imatinib, sunitinib, or regorafenib.

Utilization Details of ALL/CML Medications: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
BLINATUMOMAB PRODUCTS					
BLINCYTO INJ 35MCG	15	4	$396,286.52	3.75	$26,419.10
SUBTOTAL	**15**	**4**	**$396,286.52**	**3.75**	**$26,419.10**
DASATINIB PRODUCTS					
SPRYCEL TAB 100MG	95	14	$1,190,129.73	6.79	$12,527.68
SPRYCEL TAB 50MG	32	7	$263,933.69	4.57	$8,247.93
SPRYCEL TAB 140MG	23	3	$275,832.22	7.67	$11,992.71
SPRYCEL TAB 70MG	10	2	$106,613.48	5.00	$10,661.35
SPRYCEL TAB 80MG	1	1	$12,085.19	1.00	$12,085.19
SUBTOTAL	**161**	**27**	**$1,848,594.31**	**5.96**	**$11,481.95**
IMATINIB PRODUCTS					
IMATINIB MES TAB 400MG	96	13	$701,558.21	7.38	$7,307.90
IMATINIB MES TAB 100MG	39	9	$237,518.62	4.33	$6,090.22
SUBTOTAL	**135**	**22**	**$939,076.83**	**6.14**	**$6,956.12**
NILOTINIB PRODUCTS					
TASIGNA CAP 150MG	23	4	$159,486.49	5.75	$6,934.20
TASIGNA CAP 200MG	8	2	$84,042.55	4.00	$10,505.32
SUBTOTAL	**31**	**6**	**$243,529.04**	**5.17**	**$7,855.78**
PONATINIB PRODUCTS					
ICLUSIG TAB 15MG	12	1	$199,109.37	12.00	$16,592.45
SUBTOTAL	**12**	**1**	**$199,109.37**	**12.00**	**$16,592.45**
TOTAL	**354**	**49***	**$3,626,596.07**	**7.22**	**$10,244.62**

*Total number of unduplicated members.

Costs do not reflect rebated prices or net costs.

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Appendix K

Fiscal Year 2017 Annual Review of Skin Cancer Medications and 30-Day Notice to Prior Authorize Bavencio® (Avelumab)

Oklahoma Health Care Authority
October 2017

Introduction[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Skin cancers are commonly divided into two different types: nonmelanoma skin cancer (NMSC) and melanoma skin cancer. In general, NMSC are far more common than melanomas but result in lower mortality. Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common forms of NMSC. BCC is the most common cancer diagnosed in the United States, occurring in over 2 million people annually and the incidence of BCC continues to be on the incline. More people are diagnosed with BCC than all other cancers combined. The incidence of SCC is approximately half of BCC. Because NMSC rarely metastasizes, treatment is largely focused on localized therapies including different surgical approaches and topical agents. Systemic therapy is reserved for the select number of advanced and metastatic cases. Up until 2012, there were no specific agents indicated to treat advanced cases of NMSC. Within the past 4 years, two new agents classified as Hedgehog pathway inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of advanced BCC. Due to their novel mechanism of action, it is anticipated that the usage of these drugs will expand into other diagnoses in coming years.

According to the National Cancer Institute, in 2017 an estimated 87,110 new cases of melanoma skin cancer will be diagnosed in the United States. The average lifetime risk of developing melanoma in the United States is 1 in 34 for women and 1 in 53 for men. While the incidence of melanoma is far lower than NMSC, melanomas behave much more aggressively and have high rates of metastases leading to poor survival outcomes in advanced cases. Survival rates vary based on the clinical stage of the disease at diagnosis, with 5-year survival ranging from 15% to 60% in patients with distant and local metastases, respectively. Traditional cytotoxic chemotherapy has failed to provide successful treatment outcomes in this patient population and has very little role in treating patients with melanoma. Surgery, immunotherapy, molecularly targeted agents, and radiation are the cornerstones to the treatment of melanoma. Over the past 10 years, drug developers have focused on agents that target various immune checkpoints, specifically cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death 1/programmed death ligand 1 (PD-1/PD-L1) pathway, which result in a tumor-specific immune response in a subset of patients. Additionally, the development of molecularly targeted therapy began after it was found that activating BRAF mutations occur in half of all melanomas. BRAF mutations lead to activation of the mitogen-activated protein kinase (MAPK) pathway and promote tumor development. Research in these areas has led to FDA approval for the following agents in the last 5 years: ipilimumab, vemurafenib, pembrolizumab, dabrafenib, trametinib, cobimetinib, and nivolumab. The National Comprehensive Cancer Network (NCCN) guidelines for melanoma treatment

recommend all of these agents, some as monotherapy and others in combination, as first-line therapy. Increased use and FDA approval of these agents in the adjuvant setting is also expected. The development of these new drugs has produced an increase in response rates and modest improvements in survival in some melanoma cases. The cost associated with treating skin cancer, approximately $8.1 billion, increased 5 times faster than treatments for any other cancer between 2002 and 2011.

Previously Voted Prior Authorization Criteria

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

1. Diagnosis of locally advanced BCC that has either:
    a. Recurred following surgery or radiation therapy; or
    b. Surgery or radiation is contraindicated; or
2. Diagnosis of metastatic BCC.

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

1. Diagnosis of locally advanced BCC that has either:
    a. Recurred following surgery or radiation therapy; or
    b. Surgery or radiation is contraindicated; or
2. Diagnosis of metastatic BCC.

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

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

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

1. Diagnosis of relapsed or refractory classical Hodgkin lymphoma; and
    a. Exception: lymphocyte-predominant Hodgkin lymphoma
2. Pembrolizumab must be used as a single-agent; and
3. 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. Diagnosis of metastatic NSCLC; and
2. Tumors express PD-L1 detected by an FDA approved test; and
3. Patient meets one of the following:
    a. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin); or

b. Patients with EGFR-mutation-positive disease should have disease progression on an FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
    i. Examples of drugs for EGFR-mutation-positive tumors: osimertinib, erlotinib, afatinib, or gefitinib
c. 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
    i. Examples of drugs for ALK-mutation-positive tumors: crizotinib, ceritinib, or alectinib

4. ECOG performance status of 0 to 2; and
5. The patient has not previously failed other PD-1 inhibitors [i.e., Opdivo® (nivolumab)].

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

1. Diagnosis of recurrent or metastatic disease; and
2. Squamous cell histology; and
3. Patient has received a prior platinum containing regimen (cisplatin or carboplatin); and
4. ECOG performance status of 0 to 1; and
5. Dose does not exceed 200mg every three weeks.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. Nivolumab must be used as a single-agent or in combination with ipilimumab:
    a. As first-line therapy for untreated melanoma; or
    b. As second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy:
        i. If the patient has not previously failed other PD-1 inhibitors [i.e., Keytruda® (pembrolizumab)]; and
        ii. Patient has an ECOG performance status of 0 to 2; and
3. Dose as follows:
    a. Single-agent: 240mg every two weeks; or
    b. 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. Diagnosis of metastatic NSCLC; and
2. Tumor histology is one of the following:
    a. Adenocarcinoma; or
    b. Squamous cell; or
    c. Large Cell; and
3. Nivolumab must be used as a single-agent; and
4. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin); and
5. ECOG performance status of 0 to 2; and

6. The patient has not previously failed other PD-1 inhibitors [i.e., Keytruda® (pembrolizumab)]; and
7. Dose as follows:
    a. Single-agent: 240mg every two weeks.

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

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

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

1. Diagnosis of relapsed or refractory classical Hodgkin lymphoma; and
    a. Exception: lymphocyte-predominant Hodgkin lymphoma
2. Nivolumab must be used as a single-agent; and
3. The patient has not previously failed other PD-1 inhibitors [i.e., Keytruda® (pembrolizumab)].

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

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

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

1. Ipilimumab is used in combination with nivolumab as:
    a. First-line therapy; or
    b. Second-line or subsequent therapy for disease progression if nivolumab was not previously used; or
2. Ipilimumab is used as a single-agent for one of the following:
    a. First-line therapy as a single course of four treatments; or
    b. Second-line or subsequent lines of therapy as a single course of four treatments; or
    c. 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
3. ECOG performance status of 0 to 2; and
4. Maximum dose of 3mg/kg will apply.

Yervoy® (Ipilimumab) Approval Criteria [Adjuvant Treatment of Melanoma]:
1. Patient has complete resection of melanoma with lymphadenectomy; and
2. Patient has Stage III disease with regional nodes of greater than 1mm and no in-transit metastasis; and
3. Ipilimumab must be used as a single-agent; and
4. Maximum doses of 10mg/kg will apply.

Yervoy® (Ipilimumab) Approval Criteria [Small Cell Lung Cancer Diagnosis]:
1. One of the following criteria is met:
   a. Disease relapsed within six months of initial chemotherapy; or
   b. Disease is progressive on initial chemotherapy; and
2. Used in combination with nivolumab; and
3. ECOG performance status of 0 to 2.

Tafinlar® (Dabrafenib) Approval Criteria [Melanoma Diagnosis]:
1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation detected by an FDA-approved test; and
   a. Not indicated for wild-type BRAF melanoma
3. Dabrafenib must be used as a single-agent or in combination with trametinib (Mekinist®); and
4. One of the following is met:
   a. Used as first-line therapy; or
   b. 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. BRAF V600E or V600K mutation detected by an FDA-approved test; and
   a. Not indicated for wild-type BRAF NSCLC
2. Dabrafenib must be used as a single-agent or in combination with trametinib (Mekinist®).

Zelboraf® (Vemurafenib) Approval Criteria [Melanoma Diagnosis]:
1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation detected by an FDA-approved test; and
   a. Not indicated for wild-type BRAF melanoma
3. Vemurafenib must be used as a single-agent or in combination with cobimetinib; and
4. One of the following is met:
   a. Used as first-line therapy; or
   b. 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. BRAF V600E or V600K mutation detected by an FDA-approved test; and
    a. Vemurafenib is not indicated for wild-type BRAF NSCLC
2. Vemurafenib must be used as a single-agent.

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

1. Vemurafenib must be used as a single-agent; and
2. 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. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation detected by an FDA-approved test; and
    a. Cobimetinib is not indicated for wild-type BRAF melanoma
3. One of the following is met:
    a. Used as first-line therapy in combination with vemurafenib; or
    b. 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. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation detected by an FDA-approved test; and
    a. Trametinib is not indicated for wild-type BRAF melanoma
3. One of the following is met:
    a. Used as first-line therapy in combination with dabrafenib; or
    b. Used as second-line therapy or subsequent therapy with dabrafenib and patient has an ECOG performance status of 0 to 2; or
    c. Used as second-line therapy or subsequent therapy as a single-agent if:
        i. Patient was intolerant to prior BRAF inhibitor therapy (i.e., dabrafenib, vemurafenib); and
        ii. No evidence of disease progression on prior BRAF inhibitor therapy (i.e., dabrafenib, vemurafenib); and
        iii. ECOG performance status of 0 to 2.

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

1. BRAF V600E or V600K mutation detected by an FDA-approved test; and
    a. Trametinib is not indicated for wild-type BRAF NSCLC
2. Trametinib must be used in combination with dabrafenib.

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

1. Patient has unresectable cutaneous, subcutaneous, or nodal lesions that are recurrent after initial surgery; and
    a. Talimogene laherparepvec is not indicated with visceral metastases
2. The patient is not immunocompromised or pregnant.

Utilization of Skin Cancer Medications: Fiscal Year 2017

Comparison of Fiscal Years: Skin Cancer Medications (Pharmacy Claims)

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	10	74	$728,918.89	$9,850.26	$335.60	7,382	2,172
2017	11	55	$514,455.38	$9,353.73	$319.93	6,042	1,608
% Change	**10.00%**	**-25.70%**	**-29.40%**	**-5.00%**	**-4.70%**	**-18.20%**	**-26.00%**
Change	**1**	**-19**	**-$214,463.51**	**-$496.53**	**-$15.67**	**-1,340**	**-564**

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

Fiscal Year 2017 Utilization of Skin Cancer Medications: Medical Claims

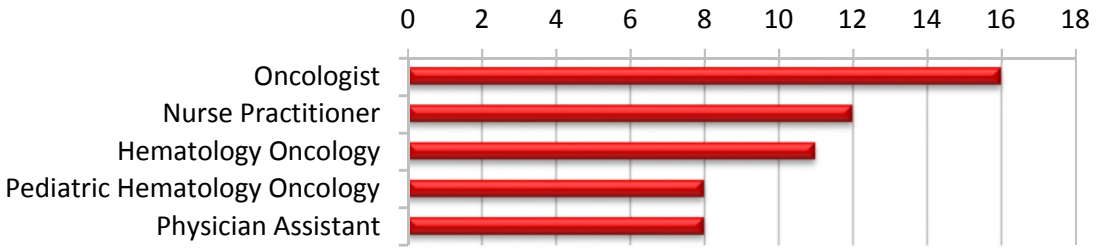
*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
77	385	$2,730,238.57	$7,091.53	92,243

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

Demographics of Members Utilizing Skin Cancer Medications: Pharmacy Claims

- Due to the small number of members utilizing skin cancer medications, detailed demographic information could not be provided.

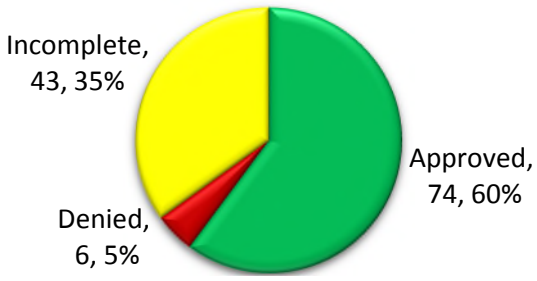
Top Prescriber Specialties of Skin Cancer Medications By Number of Claims: Pharmacy Claims



Prior Authorization of Skin Cancer Medications

There were 123 prior authorization requests submitted for 64 unique members for skin cancer medications during fiscal year 2017. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[15,16,17,18,19,20,21,22,23,24,25,26,27,28]

New Drug Approval(s):

- **March 2017:** The FDA approved Bavencio® (avelumab) for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC), including those who have not received prior chemotherapy. This is the first FDA-approved treatment for metastatic MCC, a rare, aggressive form of skin cancer.

New Indication(s):

- **September 2016:** The FDA modified the dosage regimen for Opdivo® (nivolumab) for renal cell carcinoma, metastatic melanoma, and non-small cell lung cancer (NSCLC). The approval replaces the single-dose regimen of nivolumab (3mg/kg intravenously [IV] every two weeks) with the new recommended regimen of 240mg IV every two weeks until disease progression or intolerable toxicity for renal cell carcinoma, metastatic melanoma, and NSCLC.
- **October 2016:** The FDA approved Keytruda® (pembrolizumab) for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥ 50%) as determined by an FDA-approved test. This is the first FDA approval of a checkpoint inhibitor for first-line treatment of lung cancer. This approval also expands the indication in second-line treatment of lung cancer to include all patients with PD-L1-expressing NSCLC.
- **November 2016:** The FDA approved Opdivo® (nivolumab) for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after a platinum-based therapy.
- **February 2017:** The FDA granted accelerated approval to Opdivo® (nivolumab) for treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy.
- **March 2017:** The FDA approved Keytruda® (pembrolizumab) for the treatment of adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or those who have relapsed after three or more prior lines of therapy.
- **May 2017:** The FDA approved Keytruda® (pembrolizumab) for two new indications:
  - Locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy; and
  - The treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- **May 2017:** The FDA approved Keytruda® (pembrolizumab) for use in combination with pemetrexed (brand name Alimta®) and carboplatin (pem/carbo) for the first-line treatment of metastatic nonsquamous NSCLC, irrespective of PD-L1 expression.
- **May 2017:** The FDA approved Keytruda® (pembrolizumab) for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors

that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs (i.e., fluoropyrimidine, oxaliplatin, and irinotecan).

- **May 2017:** The FDA granted accelerated approval to Bavencio® (avelumab) for patients with locally advanced or metastatic urothelial carcinoma whose disease progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.
- **June 2017:** The FDA granted regular approvals to Tafinlar® (dabrafenib) and Mekinist® (trametinib) administered in combination for patients with metastatic NSCLC with BRAF V600E mutation as detected by an FDA-approved test. These are the first FDA approvals specifically for treatment of patients with BRAF V600E mutation-positive metastatic NSCLC.
- **July 2017:** The FDA granted accelerated approval to Opdivo® (nivolumab) for the treatment of patients 12 years and older with dMMR and MSI-H metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- **September 2017:** The FDA approved Opdivo® (nivolumab) for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Accelerated approval for this indication was granted based on tumor response rate and durability of response.

Pipeline:

- **September 2017:** The FDA granted fast track designation to LN-144, an investigational drug that uses tumor-infiltrating lymphocyte (TIL) technology to bolster the body's immune system to attack cancer cells, for the treatment of metastatic melanoma.

Bavencio® (Avelumab) Product Summary[29]

Bavencio® (Avelumab):

- **Therapeutic Class:** PD-L1 blocking antibody
- **Indication(s):** Adults and pediatric patients 12 years and older with metastatic MCC, or patients with locally advanced or metastatic urothelial carcinoma who:
    - Have disease progression during or following platinum-containing chemotherapy; or
    - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- **How Supplied:** 200mg/10mL single-dose vial
- **Dose:** 10mg/kg as an IV infusion over 60 minutes every 2 weeks
- **Cost:** Wholesale Acquisition Cost (WAC) of $150.40 per mL or $1,504.00 per 10mL vial

Recommendations

- Update the prior authorization criteria to reflect new FDA approved indications and guideline recommendations. Changes can be seen in the following criteria listed in red (only criteria with updates listed).
- The prior authorization of Bavencio® (avelumab) with the following criteria listed in red.

Bavencio® (Avelumab) Approval Criteria [Merkel Cell Carcinoma (MCC) Diagnosis]:

1. Diagnosis of metastatic MCC; and
2. Member must be 12 years of age or older.

Bavencio® (Avelumab) Approval Criteria [Urothelial Carcinoma Diagnosis]:

1. Diagnosis of locally advanced or metastatic urothelial carcinoma; and
2. Disease has progressed during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

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

1. A diagnosis of metastatic NSCLC; and
2. The member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
3. Tumor proportion scores for PD-L1 expression as follows:
    a. Single-agent, first-line: ≥50%; or
    b. First-line in combination with carboplatin and pemetrexed: no expression required; or
    c. Single-agent, second-line: ≥1%; and
4. Member meets one of the following:
    a. Previously untreated metastatic non-squamous NSCLC in combination with pemetrexed and carboplatin; or
    b. New diagnosis as first-line therapy (patient has not received chemotherapy to treat disease) if:
        i. Tumor does not express sensitizing Epidermal Growth Factor Receptor (EGFR) mutations or Anaplastic Lymphoma Kinase (ALK) translocations; and
        ii. Member has an ECOG performance status of 0 to 1; or
    c. Single-agent for disease progression on or after platinum-containing chemotherapy (e.g., cisplatin or carboplatin):
        i. Patients with EGFR-mutation-positive disease should have disease progression on an FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
            1. *Examples of drugs for EGFR-mutation-positive tumors: osimertinib, erlotinib, afatinib, or gefitinib*
        ii. Patients with ALK genomic tumor aberrations should have disease progression on an FDA-approved therapy for these aberrations prior to

receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and

1. *Examples of drugs for ALK-mutation-positive tumors: crizotinib, ceritinib, or alectinib*

iii. Member has an ECOG performance status of 0 to 2.

Keytruda® (Pembrolizumab) Approval Criteria [Urothelial Carcinoma Diagnosis]:

1. Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy; or
2. Within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; or
3. Frontline pembrolizumab for patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
    a. Cisplatin ineligibility is defined as:
        i. Baseline creatinine clearance of <60mL/min, or an ECOG performance status of 2, or Class III heart failure, or grade 2 or greater peripheral neuropathy, or grade 2 or greater hearing loss.

Keytruda® (Pembrolizumab) Approval Criteria [Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumor (Tissue/Site-Agnostic) or Metastatic Colorectal Cancer Diagnosis]:

1. MSI-H or dMMR solid tumors that have progressed following prior treatment with no satisfactory alternative treatment options; or
2. MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Opdivo® (Nivolumab) Approval Criteria [Urothelial Bladder Cancer Diagnosis]:

1. Diagnosis of metastatic or unresectable locally advanced cancer; and
2. Used as second-line or greater therapy; and
3. Patient has failed a platinum containing regimen; and
4. Member has ECOG performance status of 0 to 1.

Opdivo® (Nivolumab) Approval Criteria [Hepatocellular Carcinoma (HCC) Diagnosis]:

1. Relapsed or progressive disease; and
2. Member must have been previously treated with sorafenib.

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

1. Diagnosis of relapsed or surgically unresectable stage IV disease; and
~~2. Tumor histology: predominantly clear cell; and~~
3. Failed prior therapy with one of the following medications:
    a. Sunitinib; or
    b. Sorafenib; or
    c. Pazopanib; or
    d. Axitinib; and
4. Nivolumab must be used as a single-agent; and

5. ECOG performance status of 0 to 2; and
6. The patient has not previously failed other PD-1 inhibitors [i.e., Keytruda® (pembrolizumab)]; and
7. Dose as follows:
    a. Single-agent: 240mg every two weeks.

Utilization Details of Skin Cancer Medications: Fiscal Year 2017

Pharmacy Claims: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
VEMURAFENIB PRODUCTS					
ZELBORAF TAB 240MG	21	3	$193,878.14	7	$9,232.29
SUBTOTAL	**21**	**3**	**$193,878.14**	**7**	**$9,232.29**
TRAMETINIB PRODUCTS					
MEKINIST TAB 2MG	14	5	$148,270.36	2.8	$10,590.74
MEKINIST TAB 0.5MG	5	2	$23,388.72	2.5	$4,677.74
SUBTOTAL	**19**	**7**	**$171,659.08**	**2.71**	**$9,034.69**
DABRAFENIB PRODUCTS					
TAFINLAR CAP 75MG	8	2	$78,214.36	4	$9,776.80
SUBTOTAL	**8**	**2**	**$78,214.36**	**4**	**$9,776.80**
VISMODEGIB PRODUCTS					
ERIVEDGE CAP 150MG	6	2	$64,146.55	3	$10,691.09
SUBTOTAL	**6**	**2**	**$64,146.55**	**3**	**$10,691.09**
COBIMETINIB PRODUCTS					
COTELLIC TAB 20MG	1	1	$6,557.25	1	$6,557.25
SUBTOTAL	**1**	**1**	**$6,557.25**	**1**	**$6,557.25**
TOTAL	**55**	**11***	**$514,455.38**	**5**	**$9,353.73**

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

Medical Claims: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM
J9271 PEMBROLIZUMAB INJECTION	84	20	$757,873.80	$9,022.31
J9299 NIVOLUMAB INJECTION	301	59	$1,972,364.77	$6,552.71
TOTAL	**385+**	**77***	**$2,730,238.57**	**$7,091.53**

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

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Appendix L

Fiscal Year 2017 Annual Review of Hereditary Angioedema Medications and 30-Day Notice to Prior Authorize Haegarda® [C1 Esterase Inhibitor (Human)]

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Cinryze® (C1 Esterase Inhibitor) Approval Criteria:

1. An FDA approved diagnosis of hereditary angioedema (HAE); and
2. Cinryze® must be used for *prophylaxis* of HAE; and
3. History of at least one or more abdominal or respiratory HAE attacks per month, or history of laryngeal attacks, or three or more emergency medical treatments per year; and
4. Member must not be currently taking an angiotensin converting enzyme (ACE) inhibitor or estrogen replacement therapy; and
5. Member meets the following:
    a. Documented intolerance, insufficient response, or contraindication to attenuated androgens (e.g., danazol, stanozolol, oxandrolone, methyltestosterone); and
    b. Documented intolerance, insufficient response, or contraindication to antifibrinolytic agents (e.g., ε – aminocaproic acid, tranexamic acid); or
    c. Recent hospitalization for severe episode of angioedema; and
6. Dosing:
    a. The recommended dose of Cinryze® is 1,000 units intravenously (IV) every three to four days, approximately two times per week, to be infused at a rate of 1mL/min.
    b. Initial doses should be administered in an outpatient setting by a healthcare provider. Patients can be taught by their healthcare provider to self-administer Cinryze® intravenously.
    c. A quantity limit of 8,000 units per month will apply (i.e., two treatments per week or eight treatments per month).

Berinert® (C1 Esterase Inhibitor), Kalbitor® (Ecallantide), and Firazyr® (Icatibant) Approval Criteria:

1. An FDA approved diagnosis of hereditary angioedema (HAE); and
2. Berinert®, Kalbitor®, or Firazyr® must be used for the *treatment* of acute attacks of hereditary angioedema.

Ruconest® (C1 Esterase Inhibitor) Approval Criteria:

1. An FDA approved diagnosis of hereditary angioedema (HAE); and
2. Ruconest® must be used for *treatment* of acute attacks of hereditary angioedema; and
3. A patient-specific, clinically significant reason why the member cannot use Berinert® (C1 esterase inhibitor).

Utilization of Hereditary Angioedema (HAE) Medications: Fiscal Year 2017

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	2	14	$1,003,742.26	$71,695.88	$2,586.96	370	388
2017	2	37	$1,238,526.45	$33,473.69	$2,497.03	451	496
% Change	**0.00%**	**164.30%**	**23.40%**	**-53.30%**	**-3.50%**	**21.90%**	**27.80%**
Change	**0**	**23**	**$234,784.19**	**-$38,222.19**	**-$89.93**	**81**	**108**

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

Demographics of Members Utilizing HAE Medications

- Due to the small number of members utilizing HAE medications, detailed demographic information could not be provided.

Top Prescriber Specialties of HAE Medications by Number of Claims

- The only prescriber specialties listed on paid HAE medication claims during fiscal year 2017 were internist and allergist.

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

New FDA Approval(s):

- **June 2017:** The U.S. Food and Drug Administration (FDA) approved Haegarda®, a plasma-derived concentrate of C1 esterase inhibitor (human) (C1-INH), for routine prophylaxis to prevent HAE attacks in adolescent and adult patients. This is the first subcutaneous (SC) formulation available for prevention of HAE.

Pipeline Update(s):

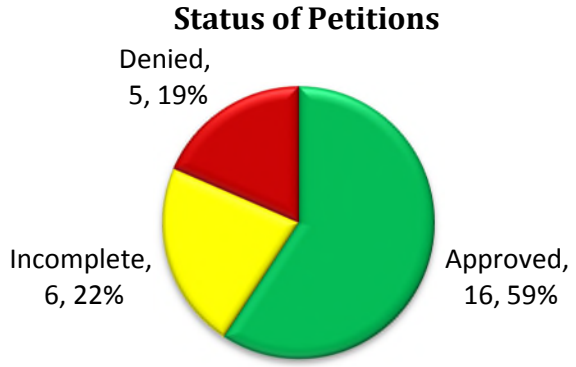
- **BCX7353:** Biocryst Pharmaceuticals, Inc. announced final results from its Phase 2, 3-part, dose ranging trial to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of BCX7353. BCX7353 is a novel, once daily, oral, liquid inhibitor of plasma kallikrein, for the treatment of acute attacks in patients with HAE. The 125mg dose showed a 79% decrease in peripheral attacks ($p<0.001$), a 63% decrease in abdominal attacks ($p=0.048$), and a 73% decrease in all attacks ($p<0.001$). Biocryst intends to meet with the FDA during the 4th quarter of 2017 to finalize Phase 3 program requirements.
- **Cinryze® SC (SHP616):** Shire announced topline Phase 3 results for a SC formulation of Cinryze® for HAE prophylaxis in patients 12 years of age and older. The fixed 2,000 international unit (IU) dose, administered every three to four days as a single 4mL SC injection, led to a statistically significant and clinically meaningful reduction of 2.32 attacks/month in the mean HAE attack rate (95% CI: 1.74-2.89; $p<0.0001$). SHP616 yielded a median HAE attack rate reduction of 79% from Day 0 (entire treatment period)

or 85% from Day 14 (after reaching steady state), compared to placebo. A total of 78% of patients experienced a 50% or greater reduction in HAE attack rate compared to placebo. Additionally, 38% of patients were attack-free during the treatment period, compared to 9% during the placebo period.

- **Lanadelumab (SHP643):** Lanadelumab is a fully human monoclonal antibody that specifically binds and inhibits plasma kallikrein and is in development for prevention of HAE attacks. A global, multi-center, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial was done over a 26-week period in 125 patients age 12 years or older with HAE. Patients were randomized into one of four arms (lanadelumab 300mg SC every two weeks, lanadelumab 300mg SC every four weeks, lanadelumab 150mg SC every four weeks, or placebo). Results showed the 300mg dose of lanadelumab administered once every two weeks resulted in a statistically significant reduction in mean HAE attack frequency of 87% compared to placebo ($p<0.001$), and results were consistent regardless of baseline attack rate. Shire plans to submit the Biologics License Application (BLA) to the FDA by late 2017 or early 2018. Lanadelumab has received both Orphan Drug Designation and Breakthrough Therapy Designation by the FDA.

Prior Authorization of HAE Medications

There were 27 prior authorization requests submitted for HAE medications during fiscal year 2017. The following chart shows the status of the submitted petitions.



Haegarda® [C1 Esterase Inhibitor (Human)] Product Summary[5,6]

Indications: Haegarda® is a plasma-derived concentrate of C1-INH indicated for routine prophylaxis to prevent HAE attacks in adolescent and adult patients.

Dosing:

- Haegarda® is supplied as a kit with a white lyophilized powder in single-use vials containing 2,000 or 3,000 IU of C1-INH with sterile water for injection and one Mix2Vial® filter transfer set.
    - Haegarda® should be reconstituted with sterile water for injection prior to administration. Once reconstituted, Haegarda® should be administered within 8 hours.

- The recommended dose is 60 IU per kg body weight by SC injection twice weekly (every 3 or 4 days).

Mechanism of Action: C1-INH is a normal constituent of human plasma and belongs to a group of serine protease inhibitors that have an important inhibiting potential on several of the major human cascade systems, including the complement, fibrinolytic, and coagulation systems. C1-INH, which is usually activated during the inflammatory process, inhibits C1r and C1s subcomponents of the complement component 1 (C1), coagulation factor XIIa, and plasma kallikrein. C1-INH is also the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade. HAE patients have absence or low levels of endogenous or functional C1-INH. Suppression of contact system activation by C1-INH through inactivation of plasma kallikrein and factor XIIa is thought to modulate vascular permeability by preventing the generation of bradykinin.

Contraindication(s):

- Patients with known hypersensitivity to any C1-INH preparations or any of its excipients.

Warnings and Precautions:

- Hypersensitivity: Severe hypersensitivity reactions may occur including hives, tightness of the chest, difficulty breathing, wheezing, hypotension, and/or anaphylaxis during or after injection. Epinephrine should be immediately available for treatment of severe hypersensitivity reactions.
- Thromboembolic Events: At the recommended dose, a causal relationship between thromboembolic events and the use of Haegarda® has not been established. Thrombosis has occurred in treatment attempts with high doses of intravenous (IV) C1-INH for prevention or therapy of capillary leak syndrome before, during, or after cardiac surgery (non-FDA approved indication and dose).
- Transmissible Infectious Agents: Since Haegarda® is made from human blood, it may carry a risk of transmitting infectious agents. The risk has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current viruses, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing. Despite these measures, the risk of transmission of infectious agents cannot be totally eliminated.

Adverse Reactions: The most common adverse reactions to Haegarda® (incidence greater than or equal to 4%) were injection site reactions, hypersensitivity, nasopharyngitis, and dizziness.

Use in Specific Populations:

- Pregnancy: There are no available data on the use of Haegarda® in pregnant women. In an observational registry, data were collected on 11 pregnancies in 10 subjects (age 16 to 40 years) receiving up to 3,000 IU C1-INH (IV administration) to treat or prevent HAE attacks. No adverse events were associated with C1-INH treatment.
- Lactation: There is no information available regarding the excretion of Haegarda® in human milk, the effect on the breastfed infant, or the effects on milk production. In a retrospective case collection study, breastfeeding was documented for neonates from 21 of 35 births with a median duration of 4.8 months. Mothers were treated

postpartum with C1-INH doses up to 1,000 IU via IV administration for the treatment of acute HAE attacks. No adverse events to the mothers were associated with C1-INH treatment after pregnancy, but no information regarding the effect on the breastfed infant was reported.

- Pediatric Use: The safety and effectiveness of Haegarda® were evaluated in a subgroup of six patients 12 to 17 years of age in the randomized routine prophylaxis trial. Results of the subgroup were consistent with overall study results.
- Geriatric Use: The safety and effectiveness of Haegarda® were evaluated in a subgroup of eight patients 65 to 72 years of age in the randomized routine prophylaxis trial. Results of the subgroup were consistent with overall study results.

Efficacy: The efficacy of Haegarda® was demonstrated in a multicenter, randomized, double-blind, placebo-controlled, crossover study of 90 adult and adolescent subjects with HAE type I or II. Subjects were randomized to receive either 60 IU/kg or 40 IU/kg in one 16-week treatment period and placebo in the other 16-week placebo period. Subjects self-administered Haegarda® or placebo SC two times per week. Efficacy was evaluated for the last 14 weeks of each treatment period.

- The time-normalized number of HAE attacks (the rate of attacks) in subjects dosed with 60 IU/kg was 0.52 attacks per month compared to 4.03 attacks per month while receiving placebo ($p<0.001$). The time-normalized number of HAE attacks in subjects dosed with 40 IU/kg was 1.19 attacks per month compared to 3.61 attacks per month while receiving placebo ($p<0.001$).
- The median percentage reduction in the time-normalized number of HAE attacks relative to placebo was 95% on Haegarda® 60 IU/kg and 89% on 40 IU/kg.
- The percentage of responders with a 50% or greater reduction in the time-normalized number of HAE attacks on Haegarda® relative to placebo was 83%. Of the subjects on Haegarda® 60 IU/kg, 90% responded to treatment and 76% of subjects on Haegarda® 40 IU/kg responded to treatment.
- The percentage of subjects with 70% or greater and 90% or greater reductions in the time-normalized number of HAE attacks on Haegarda® relative to placebo were 83% and 58%, respectively, for subjects on 60 IU/kg and 67% and 43%, respectively, for subjects on 40 IU/kg. A total of 40% of subjects on 60 IU/kg and 38% of subjects on 40 IU/kg were attack-free, and median rate of HAE attacks per month was 0.3 on both doses.
- Haegarda® resulted in a significant difference in the time-normalized number of uses of rescue medication (the rate of rescue medication use) relative to placebo. A dose of 60 IU/kg resulted in a mean rate of rescue medication of 0.3 uses per month, compared to 3.9 uses per month with placebo. A dose of 40 IU/kg resulted in a mean rate of rescue medication use of 1.1 uses per month, compared to 5.6 per month with placebo.

Cost Comparison:

Medication	Cost Per Vial	Cost for 28 Days of Therapy*
Haegarda® (C1 esterase inhibitor [human])	**$1,880.00 – $2,820.00**	**$37,600.00◊**
Cinryze® (C1 esterase inhibitor [human])	$2,758.79	$44,140.64

Costs do not include rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Cost (SMAC) if NADAC unavailable.
*28 days of therapy based on recommended dosing.
◊Weight-based dosing based on 70kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Haegarda® (C1 esterase inhibitor [human]) similar to the other prior authorized hereditary angioedema (HAE) prophylaxis medications with the following criteria:

Cinryze® (C1 Esterase Inhibitor) and Haegarda® (C1 Esterase Inhibitor) Approval Criteria:

1. An FDA diagnosis of hereditary angioedema (HAE); and
2. Must be used for *prophylaxis* of HAE; and
3. History of at least one or more abdominal or respiratory HAE attacks per month, or history of laryngeal attacks, or three or more emergency medical treatments per year; and
4. Not currently taking an angiotensin converting enzyme (ACE) inhibitor or estrogen replacement therapy; and
5. Member meets the following:
    a. Documented intolerance, insufficient response, or contraindication to attenuated androgens (e.g., danazol, stanozolol, oxandrolone, methyltestosterone); and
    b. Documented intolerance, insufficient response, or contraindication to antifibrinolytic agents (e.g., ε – aminocaproic acid, tranexamic acid); or
    c. Recent hospitalization for severe episode of angioedema; and
6. Cinryze® Dosing:
    a. The recommended dose of Cinryze® is 1,000 units IV every 3 to 4 days, approximately two times per week, to be infused at a rate of 1mL/min.
    b. Initial doses should be administered in an outpatient setting by a healthcare provider. Patients can be taught by their healthcare provider to self-administer Cinryze® intravenously.
    c. A quantity limit of 8,000 units per month will apply (i.e., two treatments per week or eight treatments per month).
7. Haegarda® Dosing:
    a. 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.
    b. A quantity limit of two treatments per week or eight treatments per month will apply.

Utilization Details of Hereditary Angioedema Medications: Fiscal Year 2017

Product Utilized	Total Claims	Total Members	Total Cost	Claims/ Client	Cost/ Claim
CINRYZE SOL 500 UNIT	26	2	$928,316.30	13	$35,704.47
BERINERT INJ 500 UNIT	6	2	$162,249.35	3	$27,041.56
FIRAZYR INJ 30MG/3ML	5	1	$147,960.80	5	$29,592.16
Total	**37**	**2***	**$1,238,526.45**	**18.5**	**$33,473.69**

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

[1] CSL Behring. FDA Approves Haegarda® (C1 Esterase Inhibitor Subcutaneous [Human]), First and Only Subcutaneous Preventive Treatment of Hereditary Angioedema. Available online at: http://www.cslbehring-us.com/newsroom/fda-approves-HAEGARDA-for-hereditary-angiodema. Issued 06/23/2017. Last accessed 07/13/2017.

[2] BioCryst Pharmaceuticals, Inc. BioCryst Announces Positive Results from its APeX-1 Phase 2 Trial in HAE. Available online at: http://investor.shareholder.com/biocryst/releasedetail.cfm?ReleaseID=1039048. Issued 09/05/2017. Last accessed 09/19/2017.

[3] Shire. Shire's Investigational Subcutaneous C1 esterase inhibitor (C1 INH [Human]) Liquid for Injection (SHP616) Significantly Reduces Hereditary Angioedema Monthly Attack Rate Versus Placebo in a Phase 3 Pivotal Trial. Available online at: https://www.shire.com/en/newsroom/2017/september/cwabkg. Issued 09/11/2017. Last accessed 09/19/2017.

[4] Shire. Shire's Investigational Treatment Lanadelumab Reduces Hereditary Angioedema Monthly Attack Rate by 87% Versus Placebo in Phase 3 26-Week Pivotal Trial. Available online at: https://www.shire.com/en/newsroom/2017/may/uftdvu. Issued 05/18/2017. Last accessed 09/19/2017.

[5] Haegarda® Prescribing Information. CSL Behring. Available online at: https://www.haegarda.com/. Last revised 06/2017. Last accessed 07/13/2017.

[6] U.S. Food and Drug Administration (FDA). FDA approves first subcutaneous C1 Esterase Inhibitor to treat rare genetic disease. Available online at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm564332.htm. Issued 06/22/2017. Last accessed 08/30/2017.

Appendix M

Fiscal Year 2017 Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Kevzara® (Sarilumab), Siliq™ (Brodalumab), Tremfya™ (Guselkumab), Cyltezo™ (Adalimumab-adbm), and Renflexis™ (Infliximab-abda)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

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®)Ω
		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), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) 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
+May be rebated to Tier-2 status only
¥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).
ΩFor Cosentyx™ (secukinumab) only a trial of Humira® from the available Tier-2 medications will be required (based on supplemental rebate participation).

- Current tier trial requirements can be found in the recommendations section at the end of this report.

Utilization of Targeted Immunomodulator Agents: Fiscal Year 2017

Comparison of Fiscal Years: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	751	4,587	$20,946,818.64	$4,566.56	$158.20	37,556	132,409
2017	828	5,189	$26,888,694.63	$5,181.86	$177.76	74,181	151,264
% Change	**10.30%**	**13.10%**	**28.40%**	**13.50%**	**12.40%**	**97.50%**	**14.20%**
Change	**77**	**602**	**$5,941,875.99**	**$615.30**	**$19.56**	**36,625**	**18,855**

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

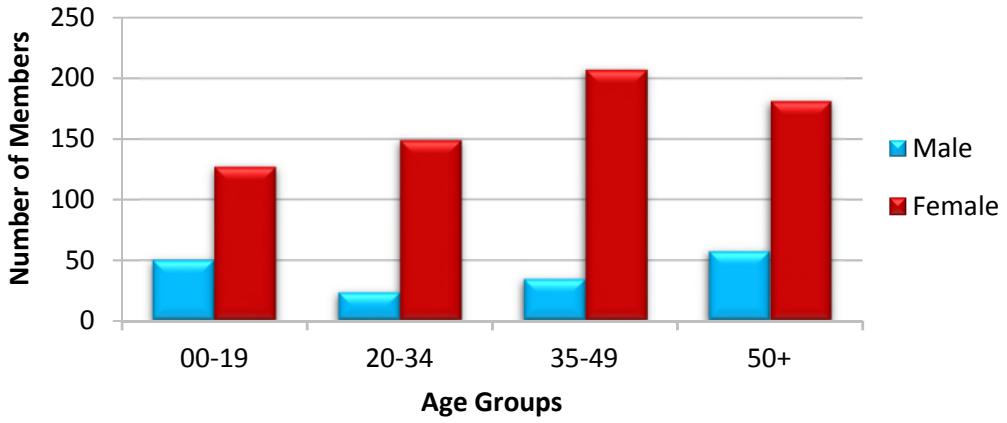
- There was a significant increase in cost while utilization remained relatively flat. It is important to note that several of these products are in their waning patent stages and will soon face biosimilar competition; typically when a product is close to the end of its patent life the manufacturer will raise the price. The consumer price index (CPI) penalty of the federal rebate is designed to keep Medicaid net cost relatively flat despite price increases. The cost increase in the table does not reflect the net cost increase. Additionally, the majority of utilization was seen in Tier-2 medications which are supplementally rebated medications. The supplementally rebated prices are also not reflected in the fiscal year comparison table.

Fiscal Year 2017 Utilization of Targeted Immunomodulator Agents: Medical Claims

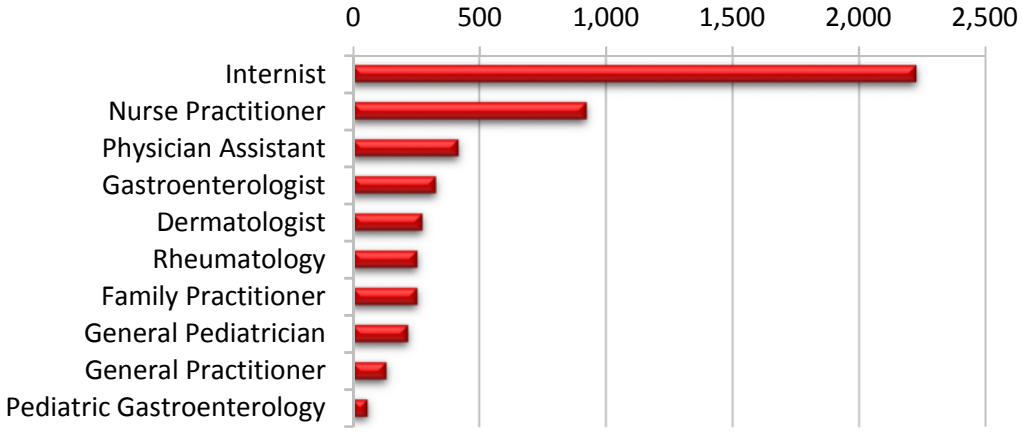
*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
165	563	$2,616,196.42	$4,646.89	32,859

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

Demographics of Members Utilizing Targeted Immunomodulator Agents: Pharmacy Claims



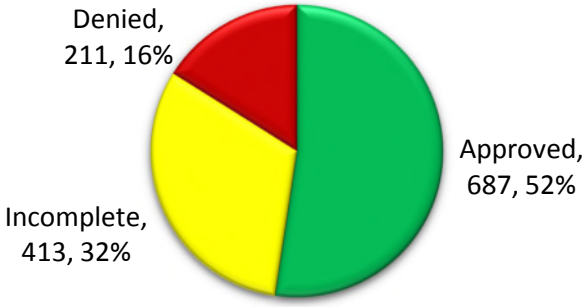
Top Prescriber Specialties of Targeted Immunomodulator Agents by Number of Claims: Pharmacy Claims



Prior Authorization of Targeted Immunomodulator Agents

There were 1,311 prior authorization requests submitted for targeted immunomodulator agents during fiscal year 2017. The following chart shows the status of the submitted petitions during fiscal year 2017.

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]

New U.S. Food and Drug Administration (FDA) Approval(s):

- **February 2017:** Siliq™ (brodalumab)
- **April 2017:** Renflexis™ (infliximab-abda)
- **May 2017:** Kevzara® (sarilumab)
- **July 2017:** Tremfya™ (guselkumab)
- **August 2017:** Cyltezo™ (adalimumab-adbm)

New Indication(s):

- **November 2016:** The FDA approved Enbrel® (etanercept) to treat moderate-to-severe plaque psoriasis (PsO) in children 4 years of age and older. Etanercept was previously approved for moderate-to-severe rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and moderate-to-severe PsO in adults.

- **May 2017:** The FDA approved subcutaneous (SC) Actemra® (tocilizumab) for the treatment of adults with giant cell arteritis (GCA). SC tocilizumab was previously approved for moderate-to-severe RA. Intravenous (IV) tocilizumab is approved for moderate-to-severe RA, systemic juvenile idiopathic arthritis (SJIA), and polyarticular JIA. IV tocilizumab is not approved in patients with GCA.
- **June 2017:** The FDA expanded the use of Orencia® (abatacept) for polyarticular JIA to include patients 2 years of age and older. Abatacept was previously approved for polyarticular JIA in patients 6 years of age and older.

News:

- **November 2016:** The National Psoriasis Foundation (NPF) updated the recommendations for psoriasis patients and established treatment targets. The recommendations included the following:
  - PsO target is down to 1% of body surface area (BSA) <3 months after starting a new treatment. Once achieved, follow-ups should occur every 6 months.
    - Acceptable response also considered PsO ≤3% of BSA or 75% improvement
  - If target after 3 months not achieved, options include to monitor for an additional 3 months or switch to an alternative treatment option.
- **January 2017:** The FDA released its final guidance for "Nonproprietary Naming of Biological Products." The guidance recommends that previously approved, originator drugs also have distinguishable suffixes devoid of meaning and composed of four lowercase letters to minimize substitution of products that have not yet been determined to be interchangeable. The FDA is still evaluating the suffix format for interchangeable products.
- **March 2017:** The Institute for Clinical and Economic Review (ICER) released its report on the value of targeted immunomodulators (TIMs) for RA. ICER determined that none of the available TIMs were within accepted thresholds for cost effectiveness ($50,000 to $150,000 per quality-adjusted life year [QALY] gained). The report stated that TIMs "provide substantial clinical benefit" in comparison to conventional disease modifying antirheumatic drugs (DMARDs) alone. However, "their additional costs translate into cost effectiveness estimates that exceed commonly cited thresholds, in that they range from approximately $170,000 to $270,000 per QALY gained."
- **August 2017:** Otezla® (apremilast) was added to the FDA watch list of drugs with possible safety issues for increased risk of diarrhea, nausea, and vomiting.

Pipeline Update(s):

- **Xeljanz® (tofacitinib):** Pfizer announced that the FDA Arthritis Advisory Committee (AAC) voted to recommend approval of tofacitinib for the treatment of adult patients with PsA. The FDA decision is anticipated by December 2017.
- **M923:** M923, a Humira® (adalimumab) biosimilar candidate, met its primary endpoint in a PsO Phase 3 study. Momenta Pharmaceuticals plans to submit a Biologic License Application (BLA) to the FDA for M923 in 2017.
- **M834:** M834, an Orencia® (abatacept) biosimilar candidate, is currently in Phase 1 trials.
- **Sirukumab:** Sirukumab, an anti-interleukin (IL)-6 monoclonal antibody under investigation for the treatment of RA, was not recommended for approval by the FDA AAC in August 2017 based on uncertainty regarding the safety profile.

- **Baricitinib:** Eli Lilly announced that a resubmission to the FDA of the New Drug Application (NDA) for baricitinib, a once-daily, oral medication for the treatment of RA, will be delayed beyond 2017.
- **Tildrakizumab:** Tildrakizumab, an investigational anti-IL-23 monoclonal antibody for PsO, was found superior to placebo and etanercept in June 2017.
- **Upadacitinib:** Upadacitinib, an investigational Janus Kinase-1 (JAK-1) inhibitor, is currently in Phase 3 trials for RA and PsA.

Kevzara® (Sarilumab) Product Summary[19]

Indications: Kevzara® (sarilumab) is an IL-6 receptor antagonist indicated for the treatment of adult patients with moderate-to-severe, active RA who have had an inadequate response or intolerance to one or more DMARDs.

Dosing:

- Kevzara® is supplied as 150mg/1.14mL or 200mg/1.14mL single-dose, pre-filled syringes. The syringes must be refrigerated and removed from refrigeration 30 minutes prior to injection. Syringes must be used within 14 days of being removed from refrigeration.
- The recommended dose of sarilumab is 200mg via SC injection once every two weeks.
- A patient may self-inject sarilumab after proper training.
- Injections may be given in the upper arm, abdomen, or front of the thigh. Injection sites should be rotated with each injection.
- Sarilumab should be avoided with biological DMARDs because of the possibility of increased immunosuppression and increased risk of infection.
- Sarilumab initiation is not recommended in patients with an absolute neutrophil count (ANC) <2,000 per mm^3, platelet count <150,000 per mm^3, or who have alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 times the upper limit of normal (ULN).
- The dose should be reduced to 150mg every two weeks in cases of neutropenia, thrombocytopenia, and elevated liver enzymes. Please see prescribing information for a complete list of dosage modifications.

Boxed Warning: Risk of Serious Infections

- Serious infections leading to hospitalization or death, including bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving sarilumab. Most patients who developed infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. Use of sarilumab should be avoided in patients with an active infection.

Mechanism of Action: Sarilumab binds to both soluble and membrane-bound IL-6 receptors, and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pro-inflammatory cytokine produced by a variety of cell types including synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as RA.

Contraindication(s): Sarilumab is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients.

Warnings and Precautions:

- Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including sarilumab for RA. The most frequently observed serious infections with sarilumab included pneumonia and cellulitis.
- Laboratory Abnormalities: Treatment with sarilumab was associated with decreases in ANC, including neutropenia, reductions in platelet counts, transaminase elevations, and increases in lipid parameters (e.g., LDL, HDL, triglycerides).
- Gastrointestinal (GI) Perforations: GI perforations have been reported, primarily as complications of diverticulitis. GI perforation risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids.
- Immunosuppression: Treatment with immunosuppressants may result in an increased risk of malignancies. The impact of treatment with sarilumab on the development of malignancies is not known.
- Hypersensitivity Reactions: Hypersensitivity reactions have been reported in association with sarilumab. Hypersensitivity reactions that required treatment discontinuation were reported in 0.3% of patients in controlled RA trials. Injection site rash and urticaria were the most frequently reported hypersensitivity reactions.
- Active Hepatic Disease and Hepatic Impairment: Treatment with sarilumab is not recommended in patients with active hepatic disease or hepatic impairment, as treatment with sarilumab was associated with transaminase elevations.
- Immunizations: Concurrent use of live vaccines should be avoided during treatment with sarilumab due to increased risk of infections; the safety of live vaccines during sarilumab treatment has not been established.

Efficacy: The efficacy and safety of sarilumab were assessed in two randomized, double-blind, placebo-controlled multicenter studies (Study 1 and Study 2) in adult patients with moderate-to-severe RA diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. In Studies 1 and 2, the primary endpoint was the proportion of patients who achieved an ACR20 response (RA symptoms have improved by 20%) at Week 24.

- Study 1 evaluated 1,197 patients with RA who had inadequate response to methotrexate (MTX). Patients received SC sarilumab 200mg, sarilumab 150mg, or placebo every two weeks with concomitant MTX.
- Study 2 evaluated 546 patients with RA who had an inadequate response or were intolerant to one or more tumor necrosis factor (TNF)-alpha antagonists. Patients received SC sarilumab 200mg, sarilumab 150mg, or placebo every two weeks with concomitant conventional DMARDs (e.g., MTX, sulfasalazine, leflunomide, hydroxychloroquine).
- Results of Study 1 and Study 2 can be found in the following table:

Percentage of Patients						
	Study 1 [+ MTX]			Study 2 [+ DMARD(s)]		
Week 24	Placebo (N=398)	Sarilumab 150mg (N=400)	Sarilumab 200mg (N=399)	Placebo (N=181)	Sarilumab 150mg (N=181)	Sarilumab 200mg (N=184)
ACR20	33.4%	58.0%	66.4%	33.7%	55.8%	60.9%
Difference from placebo*	NA	24.6% (18.0%, 31.3%)	33.0% (26.5%, 39.5%)	NA	22.1% (12.6%, 31.6%)	27.4% (17.7%, 37.0%)

*95% Confidence Interval (CI)
+ = plus, MTX = methotrexate, DMARD(s) = disease-modifying antirheumatic drugs, N = number, ACR = American College of Rheumatology, NA = not applicable

Cost Comparison:

Medication	Cost Per Syringe or Pen	Cost for 6 Months of Therapy
Kevzara® (sarilumab) 200mg/1.14mL syringe	**$1,500.00**	**$18,000.00**
Enbrel® (etanercept) 50mg/mL SureClick® autoinjector	$1,099.06	$26,377.44
Humira® (adalimumab) 40mg/0.8mL pen	$2,144.44	$25,733.28

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) if NADAC unavailable.
Dosing based on treatment of RA in a 70kg patient.
Cost for 6 months of therapy based on maintenance treatment dosing after initial dosing is complete.

Siliq™ (Brodalumab) Product Summary[20]

Indications: Siliq™ (brodalumab) is a human interleukin-17 receptor A (IL-17RA) antagonist indicated for the treatment of moderate-to-severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

Dosing:

- Siliq™ is supplied as 210mg/1.5mL single-dose, pre-filled syringes. The syringes must be refrigerated and removed from refrigeration 30 minutes prior to injection. Syringes must be used within 14 days of being removed from refrigeration.
- The recommended dose of brodalumab is 210mg via SC injection at weeks 0, 1, and 2 followed by 210mg once every two weeks.
- If an adequate response has not been achieved after 12 to 16 weeks of treatment with brodalumab, consideration should be given to discontinuing therapy. Continued treatment beyond 16 weeks in patients who have not achieved an adequate response is not likely to result in greater success.
- A patient may self-inject brodalumab after proper training.
- Injections may be given in the upper arm, abdomen, or thigh. Injection sites should be rotated with each injection. Patients should not inject brodalumab into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by PsO.

Boxed Warning: Suicidal Ideation and Behavior

- Suicidal ideation and behavior, including completed suicides, have occurred in patients treated with brodalumab. Prior to prescribing brodalumab, prescribers should weigh the potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior. Because of the observed suicidal behavior in

subjects treated with brodalumab, brodalumab is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Siliq™ REMS Program.

Mechanism of Action: Brodalumab is a human monoclonal immunoglobulin (Ig) G2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokine IL-17A. IL-17RA is a protein expressed on the cell surface and is a required component of receptor complexes utilized by multiple IL-17 family cytokines. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines.

Contraindication(s): Brodalumab is contraindicated in patients with Crohn's disease as it may cause worsening of disease.

Warnings and Precautions:

- Suicidal Ideation and Behavior: Suicidal ideation and behavior, including four completed suicides, occurred in subjects treated with brodalumab in the PsO clinical trials. Brodalumab users with a history of suicidality or depression had an increased incidence of suicidal ideation and behavior as compared to users without such a history. Prescribers should weigh the potential risks and benefits before using brodalumab in patients with a history of depression or suicidality. Because of the observed suicidal ideation and behavior in subjects treated with brodalumab, if an adequate response to brodalumab has not been achieved within 12 to 16 weeks, consideration should be given to discontinuing therapy.
- Siliq™ REMS Program: Brodalumab is available only through the Siliq™ REMS Program because of the observed suicidal ideation and behavior in subjects treated with brodalumab. Requirements of the Siliq™ REMS Program include the following:
  - Prescribers must be certified with the program.
  - Patients must sign a Patient-Prescriber Agreement Form.
  - Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive brodalumab.
- Infections: Brodalumab may increase the risk of infections. In clinical trials, subjects treated with brodalumab had a higher rate of serious infections than subjects treated with placebo (0.5% versus 0.2%) and higher rates of fungal infections (2.4% versus 0.9%).
- Risk for Latent Tuberculosis (TB) Reactivation: Patients should be evaluated for TB infection prior to initiating treatment with brodalumab, and brodalumab should not be administered to patients with an active TB infection.
- Crohn's Disease (CD): In PsO trials, which excluded subjects with active CD, CD occurred in one subject during treatment with brodalumab and led to discontinuation of therapy. In other trials, exacerbation of CD was observed with brodalumab use. Brodalumab is contraindicated in patients with CD and should be discontinued if the patient develops CD while taking brodalumab.
- Immunizations: Use of live vaccines should be avoided in patients treated with brodalumab. No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with brodalumab.

Efficacy: Three randomized, double-blind, controlled trials (Trials 1, 2, and 3) enrolled a total of 4,373 adult subjects with moderate-to-severe PsO. Subjects were randomized to treatment with placebo or brodalumab 210mg every 2 weeks for 12 weeks. In the two active comparator trials (Trials 2 and 3), subjects could also be randomized to ustekinumab. All trials assessed the change from baseline to week 12 compared to placebo in the two co-primary endpoints: 1) Psoriasis Area and Severity Index (PASI) 75, the proportion of subjects who achieved at least a 75% reduction in the PASI composite score (score takes into consideration both the percentage of BSA affected and the nature and severity of psoriatic changes), and 2) the proportion of subjects with an static Physician's Global Assessment (sPGA) of 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline. In Trials 2 and 3, comparisons were also made to ustekinumab for the primary endpoint of the proportion of subjects who achieved a reduction in PASI score of 100% (PASI 100) from baseline at week 12. Approximately 30% of subjects had previously received a biologic therapy and 12% of subjects had failed previous biologic therapy. The results of Trials 1, 2, and 3 are presented in the following table:

Endpoint	Trial 1*		Trial 2*			Trial 3*		
	Brod N=222	Plac N=220	Brod N=612	Ust N=300	Plac N=309	Brod N=624	Ust N=313	Plac N=315
PASI 75	185 (83)	6 (3)	528 (86)	210 (70)	25 (8)	531 (85)	217 (69)	19 (6)
PASI 100	93 (42)	1 (<1)	272 (44)	65 (22)	2 (1)	229 (37)	58 (19)	1 (<1)
sPGA 0 or 1	168 (76)	3 (1)	481 (79)	183 (61)	12 (4)	497 (80)	179 (57)	13 (4)
sPGA 0	93 (42)	1 (<1)	274 (45)	65 (21)	2 (1)	229 (37)	58 (19)	1 (<1)

*n (%)

Brod = brodalumab, Plac = placebo, Ust = ustekinumab, N = number, PASI = Psoriasis Area and Severity Index, sPGA = static Physician's Global Assessment

Cost Comparison:

Medication	Cost Per Syringe or Pen	Cost for 6 Months of Therapy
Siliq™ (brodalumab) 210mg/1.5mL syringe	**$1,750.01**	**$21,000.06**
Enbrel® (etanercept) 50mg/mL SureClick® autoinjector	$1,099.06	$26,377.44
Humira® (adalimumab) 40mg/0.8mL pen	$2,144.44	$25,733.28

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) if NADAC unavailable.
Dosing based on treatment of PsO in a 70kg patient.
Cost for 6 months of therapy based on maintenance treatment dosing after initial dosing is complete.

Tremfya™ (Guselkumab) Product Summary[21]

Indication(s): Tremfya™ (guselkumab) is an interleukin-23 (IL-23) blocker indicated for the treatment of adult patients with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy.

Dosing:

- Tremfya™ is supplied as 100mg/mL single-dose, pre-filled syringes. The syringes must be refrigerated and removed from refrigeration 30 minutes prior to injection.
- The recommended dose of guselkumab is 100mg via SC injection at weeks 0, 4, and every 8 weeks thereafter.

- A patient may self-inject guselkumab after proper training.
- Injections may be given in the upper arm, abdomen, or thigh. Patients should not inject guselkumab into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by PsO.

Mechanism of Action: Guselkumab is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of IL-23 and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

Contraindication(s): None.

Warnings and Precautions:

- Infections: Guselkumab may increase the risk of infection. In clinical trials, infections occurred in 23% of subjects in the guselkumab group versus 21% of subjects in the placebo group through 16 weeks of treatment. Treatment with guselkumab should not be initiated in patients with any clinically important active infection until the infection resolves or is adequately treated.
- Pre-Treatment Evaluation for TB: Patients should be evaluated for TB infection prior to initiating treatment with guselkumab. Latent TB should be treated prior to administering guselkumab, and guselkumab should not be administered to patients with active TB infection.
- Immunizations: Prior to initiating therapy with guselkumab, consideration should be given to completing all age appropriate immunizations according to current immunization guidelines. Use of live vaccines should be avoided in patients treated with guselkumab. No data are available on the response to live or inactive vaccines.

Efficacy: Two randomized, double-blind trials (VOYAGE 1 and VOYAGE 2) enrolled 1,443 adult subjects with moderate-to-severe PsO. Both trials assessed the responses at week 16 compared to placebo for the two co-primary endpoints: the proportion of subjects who achieved an Investigator's Global Assessment (IGA) score of 0 ("cleared") or 1 ("minimal"), and the proportion of subjects who achieved at least a 90% reduction from baseline in the PASI composite score (PASI 90). Comparisons between guselkumab and adalimumab were secondary endpoints. The results of VOYAGE 1 and VOYAGE 2 at week 16 in comparison to adalimumab are presented in the following table:

	VOYAGE 1*		VOYAGE 2*	
Endpoint	**Guselkumab N=115**	**Adalimumab N=115**	**Guselkumab N=160**	**Adalimumab N=81**
IGA Response of 0/1	97 (84)	70 (61)	119 (74)	50 (62)
PASI 75	105 (91)	80 (70)	132 (83)	51 (63)
PASI 90	84 (73)	47 (41)	102 (64)	34 (42)

*n (%)

N = number, PASI = Psoriasis Area and Severity Index, IGA = Investigator's Global Assessment

Cost Comparison:

Medication	Cost Per Syringe or Pen	Cost for 6 Months of Therapy
Tremfya™ (guselkumab) 100mg/mL syringe	**$9,684.00**	**$29,052.00**
Enbrel® (etanercept) 50mg/mL SureClick® autoinjector	$1,099.06	$26,377.44
Humira® (adalimumab) 40mg/0.8mL pen	$2,144.44	$25,733.28

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) if NADAC unavailable.
Dosing based on treatment of PsO in a 70kg patient.
Cost for 6 months of therapy based on maintenance treatment dosing after initial dosing is complete.

Biosimilar Product Summaries[22,23,24,25]

Cyltezo™ (Adalimumab-adbm):

- **Reference Product:** Humira® (adalimumab)
- **Indication(s):** RA, JIA, PsA, AS, adult CD, ulcerative colitis (UC), PsO; Cyltezo™ is indicated for all Humira® indications except ages 2 to 4 years in JIA, pediatric CD, hidradenitis suppurativa (HS), and uveitis (UV)
- **Mechanism of Action:** TNF blocker
- **Dosing:** Varies by disease state; maintenance dosing ranges from 40mg every other week to 40mg every week
- **How Supplied:** 40mg/0.8mL single-use, prefilled syringes intended for SC use
- **Cost:** Cost information for Cyltezo™ is not yet available

Renflexis™ (Infliximab-abda):

- **Reference Product:** Remicade® (infliximab)
- **Indication(s):** CD, pediatric CD, UC, RA in combination with methotrexate, AS, PsA, PsO; Renflexis™ is indicated for all Remicade® indications except pediatric UC
- **Mechanism of Action:** TNF blocker
- **Dosing:** Varies by disease state; maintenance dosing ranges from 3mg/kg to 10mg/kg every 4 to 8 weeks
- **How Supplied:** 100mg/10mL vial intended for IV administration
- **Cost:**

Medication	Cost Per Vial	Cost for 6 Months of Therapy
Renflexis™ (infliximab-abda) 100mg/10mL vial	**$753.39**	**$9,040.68**
Remicade® (infliximab) 100mg/20mL vial	$1,130.59	$13,567.08

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) if NADAC unavailable.
Cost for 6 months of therapy based on maintenance treatment dosing after initial dosing is complete in a 70kg patient receiving 5mg/kg every 8 weeks.

Giant Cell Arteritis (GCA) Summary [7,26,27,28,29,30,31]

Giant cell arteritis (GCA), also known as temporal arteritis, is a chronic, systemic, inflammatory vasculitis of medium and large vessels, particularly the superficial temporal arteries. The etiology of GCA is unknown, however the greatest risk factor for developing GCA is aging. GCA almost never occurs before age 50 years, with over 80% of patients with GCA being older than

70 years of age. The incidence of GCA is estimated to be 0.5 to 27 cases per 100,000 people age 50 years and older.

Common symptoms of GCA include headache, visual disturbances, jaw claudication, neck pain, scalp tenderness, fever, fatigue, and weight-loss. Permanent vision loss, which may occur in up to 20% of GCA patients, is one of the most significant complications of GCA. Vision loss can be sudden and bilateral. Suspected cases of GCA should be immediately treated with corticosteroid therapy to prevent potential vision loss. GCA may also lead to increased risk of death by myocardial infarction (MI), stroke, and peripheral vascular disease (PVD). An estimated 50% of patients with GCA have underlying polymyalgia rheumatica (PMR) which is characterized by aching and morning stiffness.

The diagnosis of GCA should be considered in patients 50 years of age and older with new-onset headache and who have an elevated erythrocyte sedimentation rate (ESR). The laboratory hallmarks of GCA are an elevation in ESR (>30mm/hr) and C-reactive protein (CRP) (≥1mg/dL). Temporal artery biopsy remains the gold standard for GCA diagnosis.

Corticosteroids are the mainstay of GCA treatment. GCA typically progressively improves with corticosteroid treatment, and treatment often results in complete resolution. The average duration of corticosteroid treatment is 2 years, but some patients may require treatment for 5 years or more. The majority of patients respond to steroids and can be tapered within the first 4 to 6 weeks with eventual discontinuation. Cyclosporine, azathioprine, or methotrexate have been used in corticosteroid-resistant cases.

In May 2017, the FDA approved Actemra® (tocilizumab) for the treatment of adults with GCA based on a randomized, double-blind study in patients with active GCA. A total of 251 patients with new-onset or relapsing GCA were randomized to tocilizumab 162mg every week, tocilizumab 162mg every other week, or placebo. The diagnosis of GCA was based on results of a temporal artery biopsy or large vessel vasculitis on angiography. All patients received background prednisone therapy. Each of the tocilizumab-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen with the aim to reach 0mg by 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen with the aim to reach 0mg by 52 weeks. The primary efficacy endpoint was the proportion of patients achieving sustained remission from week 12 through week 52. Sustained remission was defined by a patient attaining a sustained absence of GCA signs and symptoms, normalization of ESR (to <30mm/hr, without an elevation to ≥30mm/hr), normalization of CRP (to <1mg/dL, with an absence of successive elevations to ≥1mg/dL), and successful adherence to the prednisone taper defined by not more than 100mg of excess prednisone. Both tocilizumab groups showed superiority in achieving sustained remission from week 12 through week 52 compared with placebo. Results can be seen in the following table:

Parameter	PBO + 26 wk taper (N=50)	PBO + 52 wk taper (N=51)	TCZ QW + 26 wk taper (N=100)	TCZ Q2W + 26 wk taper (N=49)
Responders, n (%)	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Difference in proportions vs PBO + 26 wk taper*	N/A	N/A	42.0% (18.0, 66.0)	39.1% (12.5, 65.7)
Difference in proportions vs PBO + 52 wk taper*	N/A	N/A	38.4% (14.4, 62.3)	35.4% (8.6, 62.2)

PBO = placebo, wk = week, N = number, TCZ = tocilizumab, QW = every week dosing, Q2W = every other week dosing, N/A = not applicable
*99.5% Confidence interval

Recommendations

The College of Pharmacy recommends the addition of Kevzara® (sarilumab), Siliq™ (brodalumab), Tremfya™ (guselkumab), Cyltezo™ (adalimumab-adbm), and Renflexis™ (infliximab-abda) 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 Cyltezo™ (adalimumab-adbm) and Renflexis™ (infliximab-abda) is determined to be greater than the net cost of the reference product formulations of Cyltezo™ and Renflexis™, authorization would also require a patient-specific, clinically significant reason why the member could not use the reference product formulations of Cyltezo™ and Renflexis™.
- The following criteria will also apply for authorization of Siliq™ (brodalumab):
  - Initial authorizations of Siliq™ (brodalumab) will be for the duration of 12 weeks at which time the prescriber must verify the member is responding to treatment. If an adequate response has not been achieved after 12 to 16 weeks of treatment with brodalumab, consideration should be given to discontinuing therapy.
  - Members must also be enrolled in the Siliq™ REMS Program for approval.
  - Members with a concomitant diagnosis of Crohn's disease will not be approved.

Additionally, the College of Pharmacy recommends the following criteria for Actemra® (Tocilizumab) for a diagnosis of giant cell arteritis:

Actemra® (Tocilizumab) Approval Criteria [Giant Cell Arteritis Diagnosis]:

1. An FDA approved diagnosis of giant cell arteritis (GCA); and
2. Member must be 50 years of age or older; and
3. A history of erythrocyte sedimentation rate (ESR) of ≥30mm/hr or a history of C-reactive protein (CRP) ≥1mg/dL; and
4. Member should have a trial of glucocorticoids for a minimum of four weeks or a reason why this is no appropriate; and
5. Actemra® will be taken in combination with tapering course of a glucocorticoid upon initiation; and
6. Member must have baseline liver enzymes, absolute neutrophil count (ANC), lipid panel, and platelet count and verification that they are acceptable to prescriber; and
7. Member must not have severe hepatic impairment; and

8. Actemra® should not be initiated in patients with active or chronic infection including hepatitis B, hepatitis C, human immunodeficiency virus, or tuberculosis; and
9. Approval quantity will be based on Actemra® prescribing information and FDA approved dosing regimen.

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

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC) or State Maximum Allowable Costs (SMAC) 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

±Biosimilars or reference products preferred based on lowest net cost product. Authorization of higher net cost biosimilars or reference products requires a patient-specific, clinically significant reason why the member could not use the preferred formulation.

+May be rebated to Tier-2 status only.

¥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).

ΩFor Cosentyx™ (secukinumab) only a trial of Humira® from the available Tier-2 medications will be required (based on supplemental rebate participation).

πUnique criteria applies for a diagnosis of giant cell arteritis.

Targeted Immunomodulator 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.

Targeted Immunomodulator 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) Approval Criteria [Hidradenitis Suppurativa Diagnosis]:

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 three 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.

Humira® (Adalimumab) Approval Criteria [Noninfectious Intermediate and Posterior Uveitis or Panuveitis Diagnosis]:

1. A diagnosis of noninfectious intermediate uveitis, posterior uveitis, or panuveitis in adults; and
2. A failed trial with a corticosteroid injection or systemic steroid 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.

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

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.

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, 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; or
        ii. Body weight 15kg to 40kg: 2mg/kg. If inadequate response, may be increased to 3mg/kg; and
5. Approvals will be for the duration of one year.

Utilization Details of Targeted Immunomodulator Agents: Fiscal Year 2017

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TIER-2 PRODUCTS					
ADALIMUMAB PRODUCTS					
HUMIRA PEN INJ 40MG/0.8ML	1,969	368	$10,176,342.59	5.35	$5,168.28
HUMIRA KIT 40MG/0.8ML	381	80	$2,059,527.35	4.76	$5,405.58
HUMIRA KIT 20MG/0.4ML	46	6	$152,405.00	7.67	$3,313.15
HUMIRA PEN INJ CROHNS 40MG/0.8ML	44	44	$567,651.47	1	$12,901.17
HUMIRA PEN INJ PSORIASIS 40MG/0.8ML	40	38	$344,616.10	1.05	$8,615.40
HUMIRA INJ 10MG/0.2ML	10	1	$43,787.72	10	$4,378.77
SUBTOTAL	**2,490**	**440**	**$13,344,330.23**	**5.66**	**$5,359.17**
ETANERCEPT PRODUCTS					
ENBREL SRCLK INJ 50MG/ML	1,009	189	$4,451,998.54	5.34	$4,412.29
ENBREL INJ 50MG/ML	324	59	$1,467,596.36	5.49	$4,529.62
ENBREL INJ 25/0.5ML	89	20	$236,845.60	4.45	$2,661.19
ENBREL INJ 25MG	86	16	$196,840.67	5.38	$2,288.85
SUBTOTAL	**1,508**	**267**	**$6,353,281.17**	**5.65**	**$4,213.05**
TIER-2 SUBTOTAL	**3,998**	**654**	**$19,697,611.40**	**6.11**	**$4,926.87**
TIER-3 PRODUCTS					
INFLIXIMAB PRODUCTS					
REMICADE INJ 100MG	211	39	$1,231,500.38	5.41	$5,836.49
SUBTOTAL	**211**	**39**	**$1,231,500.38**	**5.41**	**$5,836.49**
ABATACEPT PRODUCTS					
ORENCIA INJ 125MG/ML	146	24	$511,354.37	6.08	$3,502.43
ORENCIA CLCK INJ 125MG/ML	9	3	$31,965.99	3	$3,551.78
SUBTOTAL	**155**	**25**	**$543,320.36**	**6.2**	**$3,505.29**
CERTOLIZUMAB PRODUCTS					
CIMZIA PREFL KIT 200MG/ML	110	24	$411,675.66	4.58	$3,742.51
CIMZIA KIT STARTER	15	15	$154,486.92	1	$10,299.13
SUBTOTAL	**125**	**29**	**$566,162.58**	**4.31**	**$4,529.30**
GOLIMUMAB PRODUCTS					
SIMPONI INJ 50MG/0.5ML	99	15	$395,258.20	6.6	$3,992.51
SIMPONI INJ 50MG/0.5ML	3	1	$12,116.86	3	$4,038.95
SUBTOTAL	**102**	**15**	**$407,375.06**	**6.8**	**$3,993.87**
CANAKINUMAB PRODUCTS					
ILARIS INJ 180MG	75	16	$1,673,788.88	4.69	$22,317.19
ILARIS INJ 150MG/ML	22	14	$388,742.45	1.57	$17,670.11
SUBTOTAL	**97**	**17**	**$2,062,531.33**	**5.71**	**$21,263.21**
TOCILIZUMAB PRODUCTS					
ACTEMRA INJ 80MG/4ML	56	6	$30,069.58	9.33	$536.96
ACTEMRA INJ 200/10ML	47	5	$60,043.59	9.4	$1,277.52
ACTEMRA INJ 162/0.9ML	47	7	$134,297.82	6.71	$2,857.40
ACTEMRA INJ 400/20ML	45	5	$101,306.91	9	$2,251.26
SUBTOTAL	**195**	**15**	**$325,717.90**	**13**	**$1,670.35**
TOFACITINIB PRODUCTS					
XELJANZ TAB 5MG	52	17	$190,181.34	3.06	$3,657.33
XELJANZ XR TAB 11MG	30	7	$109,689.36	4.29	$3,656.31

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBTOTAL	**82**	**23**	**$299,870.70**	**3.57**	**$3,656.96**
APREMILAST PRODUCTS					
OTEZLA TAB 30MG	46	13	$115,420.00	3.54	$2,509.13
OTEZLA TAB STARTER 10/20/30	9	9	$24,851.47	1	$2,761.27
SUBTOTAL	**55**	**17**	**$140,271.47**	**3.24**	**$2,550.39**
SECUKINUMAB PRODUCTS					
COSENTYX PEN INJ 300MG DOSE	36	7	$243,036.07	5.14	$6,751.00
COSENTYX PEN INJ 150MG/ML	13	4	$110,633.37	3.25	$8,510.26
COSENTYX INJ 300MG DOSE	6	2	$33,983.61	3	$5,663.94
COSENTYX INJ 150MG/ML	1	1	$17,240.31	1	$17,240.31
SUBTOTAL	**56**	**14**	**$404,893.36**	**4**	**$7,230.24**
USTEKINUMAB PRODUCTS					
STELARA INJ 90MG/ML	34	10	$644,101.69	3.4	$18,944.17
STELARA INJ 45MG/0.5ML	28	8	$255,914.46	3.5	$9,139.80
SUBTOTAL	**62**	**18**	**$900,016.15**	**3.44**	**$14,516.39**
IXEKIZUMAB PRODUCTS					
TALTZ INJ 80MG/ML	19	5	$168,903.85	3.8	$8,889.68
SUBTOTAL	**19**	**5**	**$168,903.85**	**3.8**	**$8,889.68**
VEDOLIZUMAB PRODUCTS					
ENTYVIO INJ 300MG	12	3	$58,369.93	4	$4,864.16
SUBTOTAL	**12**	**3**	**$58,369.93**	**4**	**$4,864.16**
ANAKINRA PRODUCTS					
KINERET INJ 100MG/0.67ML	11	1	$41,486.39	11	$3,771.49
SUBTOTAL	**11**	**1**	**$41,486.39**	**11**	**$3,771.49**
RITUXIMAB PRODUCTS					
RITUXAN INJ 500MG	5	3	$32,504.69	1.67	$6,500.94
RITUXAN INJ 100MG	4	2	$8,159.08	2	$2,039.77
SUBTOTAL	**9**	**4**	**$40,663.77**	**2.25**	**$4,518.20**
TIER-3 SUBTOTAL	**1,191**	**207**	**$7,191,083.23**	**5.75**	**$6,037.85**
TOTAL	**5,189**	**828***	**$26,888,694.63**	**6.27**	**$5,181.86**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Table includes targeted immunomodulator agents in Tier-2 and Tier-3 and does not include Tier-1 DMARDs as they are indicated for multiple diagnoses.

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	UNITS	COST/ CLAIM
REMICADE INJ J1745	237	49	$683,460.83	10,758	$2,883.80
RITUXAN INJ J9310	228	90	$1,494,587.14	1,891	$6,555.21
ORENCIA INJ J0129	36	7	$147,349.50	3,275	$4,093.04
SIMPONI ARIA INJ J1602	24	10	$115,278.85	5,365	$4,803.29
CIMZIA INJ J0717	21	4	$48,744.00	6,800	$2,321.14
ENTYVIO INJ J3380	14	5	$80,382.00	4,500	$5,741.57
STELARA INJ J3357	3	1	$46,394.10	270	$15,464.70
TOTAL	**563+**	**165***	**$2,616,196.42**	**32,859**	**$4,646.89**

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

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Appendix N

Fiscal Year 2017 Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Trulance™ (Plecanatide), Xermelo™ (Telotristat Ethyl), Symproic® (Naldemedine), and Motofen® (Difenoxin/Atropine)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Relistor® (Methylnaltrexone) Injection Approval Criteria [Terminal Disease Diagnosis Receiving Palliative Care]:

1. An FDA approved diagnosis of opioid-induced constipation (OIC) in patients with severe terminal disease who are receiving only palliative care (life expectancy less than six months); and
2. Current use of opioid medications; and
3. Documented treatment attempts with a minimum of three alternate products, excluding bulk forming laxatives; 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
4. Mechanical gastrointestinal obstruction has been ruled out.
5. 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.
6. A quantity limit of 30 units per month will apply.
7. Approvals will be for the duration of 16 weeks of therapy. Use of Relistor® beyond four months has not been studied in patients with severe terminal disease.

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, non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation; 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 older 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.

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, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation; 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 older 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.

Linzess® (Linaclotide) Approval Criteria:

1. An FDA approved diagnosis of chronic idiopathic constipation (CIC) or irritable bowel syndrome with constipation (IBS-C) in members 18 years of age or older; and

2. Documentation that constipation-causing therapies for other disease states have been discontinued (excluding opioid pain medications for cancer patients); and
3. Documented and updated colon screening for members older than 50 years of age; and
4. 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
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
6. A quantity limit of 30 capsules for a 30 day supply will apply.

Amitiza® (Lubiprostone) Approval Criteria [Chronic Idiopathic Constipation or Irritable Bowel Syndrome with Constipation Diagnosis]:

1. An FDA approved diagnosis of chronic idiopathic constipation (CIC) in members 18 years of age or older, or irritable bowel syndrome with constipation (IBS-C) in female members 18 years of age or older; and
2. Documentation that constipation-causing therapies for other disease states have been discontinued (excluding opioid pain medications for cancer patients); and
3. Documented and updated colon screening for members older than 50 years of age; and
4. 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
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
6. A quantity limit of 60 capsules for a 30 day supply will apply.

Amitiza® (Lubiprostone) Approval Criteria [Opioid-Induced Constipation Diagnosis]:

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, except methadone, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation; and
2. Documentation of the underlying cause of chronic pain, or reason why member is on chronic opioid therapy; and
3. Documented and updated colon screening for members older than 50 years of age; and
4. 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
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
6. A quantity limit of 60 capsules for a 30 day supply will apply.

Movantik® (Naloxegol) 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, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation; 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 older 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. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
7. Movantik® must be discontinued if treatment with the opioid pain medication is also discontinued.
8. A quantity limit of 30 tablets for a 30 day supply will apply.

Viberzi® (Eluxadoline) Approval Criteria:

1. An FDA approved diagnosis of irritable bowel syndrome with diarrhea (IBS-D); and
2. Member must be 18 years of age or older; and
3. Documentation of trials of two of the following three medications that failed to relieve diarrhea: loperamide, dicyclomine, or diphenoxylate/atropine (each trial should be for at least 10 to 14 consecutive days at the recommended dosing). Trials must be within the past 90 days. Documentation should be provided including dates, dosing, and reason for trial failure.
4. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
5. A quantity limit of 60 tablets for a 30 day supply will apply.

Xifaxan® (Rifaximin) 200mg Approval Criteria:

1. An FDA approved diagnosis of traveler's diarrhea (TD); and

2. Member must be 12 years of age or older; and
3. TD must be due to noninvasive strains of *Escherichia coli*; and
4. A patient-specific, clinically significant reason why the member cannot use a fluoroquinolone antibiotic (e.g., ciprofloxacin, levofloxacin) must be provided.
5. A quantity limit of 9 tablets for a 3 day supply will apply.

Xifaxan® (Rifaximin) 550mg Approval Criteria:

1. An FDA approved indication for the reduction in risk of overt hepatic encephalopathy (HE) recurrence; or
2. An FDA approved diagnosis of irritable bowel syndrome with diarrhea (IBS-D); and
   a. For the diagnosis of IBS-D: Documentation of trials of two of the following three medications that failed to relieve diarrhea: loperamide, dicyclomine, or diphenoxylate/atropine (each trial should be for at least 10 to 14 consecutive days at the recommended dosing). Trials must be within the past 90 days. Documentation should be provided including dates, dosing, and reason for trial failure; and
   b. For the diagnosis of IBS-D: Member must be 18 years of age or older.
3. A quantity limit of 60 tablets for a 30 day supply will apply. Members with the diagnosis of IBS-D needing 42 tablets for a 14-day treatment regimen (550mg three times daily for 14 days) will be approved for a quantity limit override upon meeting Xifaxan® approval criteria. Members with IBS-D who experience a recurrence of symptoms can be retreated up to two times with the same dosage regimen (550mg three times daily for 14 days).

Utilization of Constipation and Diarrhea Medications: Fiscal Year 2017

Comparison of Fiscal Years: Constipation and Diarrhea Medications

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	134	528	$185,294.43	$350.94	$11.64	21,430	15,922
2017	177	822	$300,790.27	$365.92	$12.13	31,758	24,792
% Change	**32.10%**	**55.70%**	**62.30%**	**4.30%**	**4.20%**	**48.20%**	**55.70%**
Change	**43**	**294**	**$115,495.84**	**$14.98**	**$0.49**	**10,328**	**8,870**

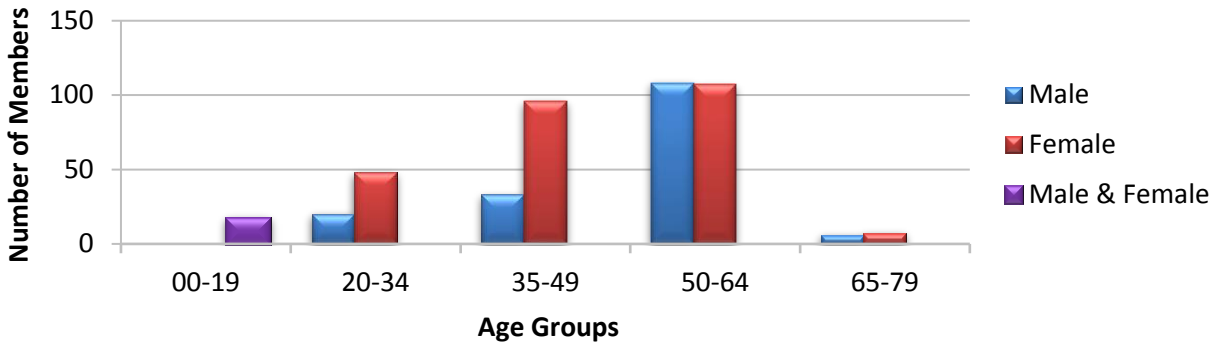
*Total number of unduplicated members. Costs do not reflect rebated prices or net costs. Please note, the above data does not include Xifaxan® (rifaximin).

Comparison of Fiscal Years: Xifaxan® (Rifaximin)

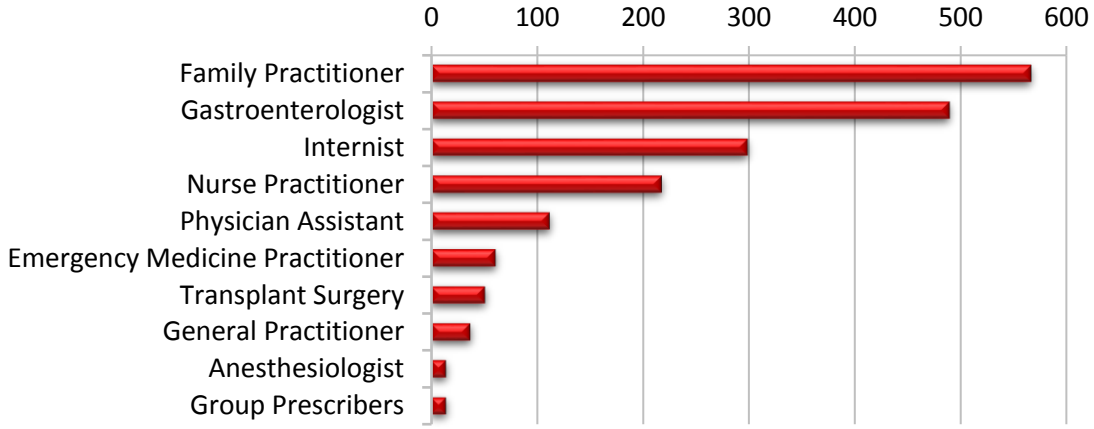
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	284	1,163	$1,935,906.11	$1,664.58	$60.49	63,823	32,004
2017	266	1,113	$1,979,951.68	$1,778.93	$62.83	62,573	31,515
% Change	**-6.30%**	**-4.30%**	**2.30%**	**6.90%**	**3.90%**	**-2.00%**	**-1.50%**
Change	**-18**	**-50**	**$44,045.57**	**$114.35**	**$2.34**	**-1,250**	**-489**

*Total number of unduplicated members. Costs do not reflect rebated prices or net costs. Xifaxan® was first FDA approved in 2004 and has a significant federal rebate. Please note, the majority of utilization of rifaximin was for the 550mg strength for the reduction in risk of overt hepatic encephalopathy (HE) recurrence.

Demographics of Members Utilizing Constipation and Diarrhea Medications



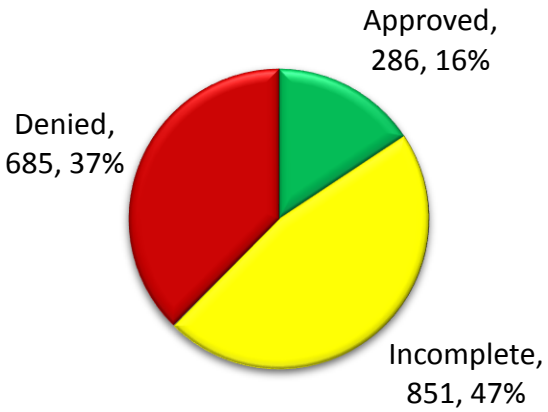
Top Prescriber Specialties of Constipation and Diarrhea Medications by Number of Claims



Prior Authorization of Constipation and Diarrhea Medications

There were 1,822 prior authorization requests submitted for constipation and diarrhea medications during fiscal year 2017. 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]

Anticipated Patent Expiration(s):

- Amitiza® (lubiprostone): October 2027
- Xifaxan® (rifaximin): March 2030
- Relistor® (methylnaltrexone): March 2031
- Movantik® (naloxegol): April 2032
- Viberzi® (eluxadoline): March 2033
- Linzess® (linaclotide): August 2033

New FDA Approval(s):

- **January 2017:** The U.S. Food and Drug Administration (FDA) approved a supplemental New Drug Application (sNDA) for a new dosage regimen of Linzess® (linaclotide), 72mcg once daily, for the treatment of adults with chronic idiopathic constipation (CIC). Linzess® was first FDA approved in 2012 for two strengths: 145mcg for the treatment of CIC and 290mcg for the treatment of irritable bowel syndrome with constipation (IBS-C). The recommended dosage of Linzess® for the treatment of CIC is 145mcg once daily; however, the new dosage regimen, 72mcg once daily, may be used based on individual presentation or tolerability.
- **January 2017:** The FDA approved a New Drug Application (NDA) for Trulance™ (plecanatide) for the treatment of CIC in adult patients. Trulance™, taken orally once daily, works locally in the upper gastrointestinal (GI) tract to stimulate secretion of intestinal fluid and support regular bowel function.
- **February 2017:** The FDA approved Xermelo™ (telotristat ethyl) as an orphan drug for use in combination with somatostatin analog (SSA) therapy [e.g., Somatuline® (lanreotide), Sandostatin® (octreotide)] for the treatment of adults with carcinoid syndrome diarrhea that SSA therapy alone has inadequately controlled. Xermelo™, in a regimen with SSA therapy, is approved in tablet form to be taken orally three times daily with food. When cancer occurs in the neuroendocrine system, it is called a neuroendocrine tumor (NET). A carcinoid tumor is a specific type of NET and most often develops in the GI tract or lungs. When carcinoid tumors become large or spread to other parts of the body, they can release extra serotonin into the body, which can cause carcinoid syndrome. Carcinoid syndrome commonly causes diarrhea, abdominal pain, and facial flushing, and can also damage the heart valves and lead to carcinoid heart disease. Xermelo™ targets the overproduction of serotonin by NETs and reduces the frequency of carcinoid syndrome diarrhea. In clinical trials, other symptoms of carcinoid syndrome (abdominal pain or facial flushing) did not show improvement in the comparison of Xermelo™ to placebo.
- **March 2017:** The FDA approved an NDA for Symproic® (naldemedine) as a once-daily, oral, peripherally-acting mu-opioid receptor antagonist (PAMORA) medication for the treatment of opioid-induced constipation (OIC) in adult patients with chronic, non-cancer pain. Symproic® is currently a Schedule II controlled substance because it is structurally related to naltrexone; however, the manufacturer of Symproic® has submitted a petition for removal of the controlled substance classification to the U.S. Drug Enforcement Administration (DEA), which is currently under evaluation.

- **March 2017:** The FDA approved an sNDA for Motofen® (difenoxin 1mg/atropine 0.025mg oral tablets) to transfer the ownership to Sebela Pharmaceuticals, and it is anticipated to be available on the market soon. First FDA approved in 1978, Motofen® is an antiperistaltic anti-diarrheal medication indicated as adjunctive therapy in the management of acute nonspecific diarrhea and acute exacerbations of chronic functional diarrhea. Motofen® is contraindicated in patients with diarrhea associated with organisms that penetrate the intestinal mucosa (e.g., toxigenic *E. coli*, *Salmonella* species, *Shigella*) and pseudomembranous colitis associated with broad spectrum antibiotics. The recommended dosing for patients age 12 years and older is an initial dose of two tablets orally, followed by one tablet orally after each loose stool or every 3 to 4 hours as needed, with a maximum of eight tablets per 24 hours. If clinical improvement is not observed in 48 hours, continued administration of this type of medication is not recommended. For acute diarrhea and acute exacerbations of functional diarrhea, treatment beyond 48 hours is usually not necessary. Safety and effectiveness of Motofen® in children younger than 12 years of age have not been established, and Motofen® is contraindicated in children younger than 2 years of age. The current wholesale acquisition cost (WAC) of Motofen® is $6.88 per tablet, resulting in a cost of $55.04 per day at maximum dosing (eight tablets/day). The national average drug acquisition cost (NADAC) of diphenoxylate/atropine (generic Lomotil®) is $0.42 per tablet, resulting in a cost of $3.36 per day at maximum dosing (eight tablets/day). Lomotil® is indicated in children ages 2 years and older and is also available as an oral solution ($8.80 per day at maximum dosing).
- **August 2017:** The FDA approved an sNDA for Amitiza® (lubiprostone), Movantik® (naloxegol), Relistor® (methylnaltrexone), and Symproic® (naldemedine) to provide clarification of the OIC indication in the prescribing information for each medication. Specifically, the labeling now states that these medications are indicated for the treatment of OIC in adult patients with chronic non-cancer pain, *including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.* The current prior authorization (PA) criteria for Amitiza®, Movantik®, and Relistor® have been updated to include this clarification (shown in red in the *Current Prior Authorization Criteria* section at the beginning of this report); recommended PA criteria for Symproic® is found at the end of this report in the *Recommendations* section.

News:

- **July 2016:** The FDA issued a Drug Safety Communication to update the warnings for oral and injectable fluoroquinolone antibiotics due to disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. The FDA revised fluoroquinolones' Boxed Warning to address these serious safety concerns and also added new warnings and updated other parts of the drug label. The FDA determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side

effects generally outweighs the benefits in these patients. For some serious bacterial infections, the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

- The current approval criteria for Xifaxan® (rifaximin) 200mg for the diagnosis of traveler's diarrhea requires a reason why the member cannot use a fluoroquinolone antibiotic, which is recommended in The American Academy of Family Physicians treatment guidelines as the antibiotic of choice for traveler's diarrhea in most parts of the world because of their efficacy against most enteropathogens. Rifaximin is FDA approved for the treatment of traveler's diarrhea due to noninvasive strains of *Escherichia coli (E. coli)* and is recommended as an option in places where noninvasive *E. coli* is the predominant pathogen (e.g., Mexico). Azithromycin is recommended as the antibiotic of choice for children and pregnant women, as well as in places where quinolone-resistant *Campylobacter* is present (e.g., Thailand). Treatment guidelines for traveler's diarrhea have not been updated since the FDA updated the warnings for fluoroquinolones. The Centers for Disease Control and Prevention (CDC) provides similar guidelines for the treatment of traveler's diarrhea, including fluoroquinolones as first-line antibiotics. However, the CDC addresses the FDA Drug Safety Communication regarding the potential serious side effects of fluoroquinolones and concludes that due to the short duration of therapy for traveler's diarrhea, the side effects are not believed to be a significant risk.

- **March 2017:** The FDA issued a Drug Safety Communication to warn about an increased risk of serious pancreatitis with Viberzi® (eluxadoline) in patients without a gallbladder. An FDA review found that these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death, and the FDA concluded that healthcare professionals should not prescribe Viberzi® to patients who do not have a gallbladder and should consider alternative treatment options in these patients. Viberzi® is indicated for the treatment of irritable bowel syndrome with diarrhea (IBS-D), and the package labeling for Viberzi® has been updated to include patients without a gallbladder as a contraindication.

Pipeline:

- **July 2016:** A systematic review and meta-analysis of published randomized, controlled trials demonstrated that prucalopride, a highly selective serotonin (5-HT_4) agonist with strong enterokinetic activity, is an effective pharmacotherapy in the management of chronic constipation with acceptable, transient, and negligible side effects. Prucalopride is highly selective and has greater than 150-fold higher affinity for 5-HT_4 receptors than for other receptors. This differs from other 5-HT_4 agonists such as tegaserod and cisapride, which at therapeutic concentrations also interact with other receptors and this may account for the adverse cardiovascular events that have resulted in the restricted availability of these medications (tegaserod was withdrawn from the market; cisapride is only available through an investigational limited access program). Clinical trials evaluating the effect of prucalopride on QT interval and related adverse events have not demonstrated significant differences compared with placebo. Prucalopride is

currently approved for the treatment of chronic constipation in Europe, Canada, and Israel, but has not yet been approved in the United States. The anticipated date of submission of an NDA to the FDA for prucalopride is currently unknown.

- **June 2017:** Synergy Pharmaceuticals submitted an sNDA to the FDA to add IBS-C as an indication for Trulance™ (plecanatide), which was FDA approved in January 2017 for the treatment of CIC in adult patients. The sNDA has a Prescription Drug User Fee Act (PDUFA) date of January 24, 2018.

Trulance™ (Plecanatide) Product Summary[20,21]

Indication(s): Trulance™ (plecanatide) is indicated for the treatment of CIC in adults.

Dosing:

- Trulance™ is available as oral tablets containing 3mg of plecanatide.
- The recommended dosage of plecanatide is 3mg orally once daily.
- During clinical studies, plecanatide 6mg once daily did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions than plecanatide 3mg once daily. Therefore, plecanatide 6mg once daily is not recommended.
- Plecanatide tablets should be swallowed whole and may be taken with or without food.
- For adult patients with swallowing difficulties, plecanatide tablets can be crushed and administered orally either in applesauce or with water, or administered with water via a nasogastric or gastric feeding tube.

Boxed Warning: Risk of Serious Dehydration in Pediatric Patients

- Plecanatide is contraindicated in patients younger than 6 years of age; in nonclinical studies in young juvenile mice, administration of a single oral dose of plecanatide caused deaths due to dehydration.
- Use of plecanatide should be avoided in patients 6 years to younger than 18 years of age.
- The safety and effectiveness of plecanatide have not been established in patients younger than 18 years of age.

Mechanism of Action: Plecanatide is structurally related to human uroguanylin, and similar to uroguanylin, plecanatide functions as a guanylate cyclase-C (GC-C) agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel, resulting in increased intestinal fluid and accelerated transit.

Contraindication(s):

- Patients younger than 6 years of age due to the risk of serious dehydration
- Patients with known or suspected mechanical GI obstruction

Warnings and Precautions:

- Risk of Serious Dehydration in Pediatric Patients: Plecanatide is contraindicated in patients younger than 6 years of age. The safety and effectiveness of plecanatide in patients younger than 18 years of age have not been established. In young juvenile mice (human age equivalent of approximately 1 month to less than 2 years), plecanatide increased fluid secretion into the intestines as a consequence of stimulation of GC-C, resulting in mortality in some mice within the first 24 hours, apparently due to dehydration. Due to increased intestinal expression of GC-C, patients younger than 6 years of age may be more likely than patients 6 years of age and older to develop severe diarrhea and its potentially serious consequences. Use of plecanatide should also be avoided in patients 6 years to younger than 18 years of age. Although there were no deaths in older juvenile mice, given the deaths in younger mice and the lack of clinical safety and efficacy data in pediatric patients, the use of plecanatide should be avoided in patients 6 years to younger than 18 years of age.
- Diarrhea: Diarrhea was the most common adverse reaction in the two placebo-controlled clinical trials. Severe diarrhea was reported in 0.6% of patients and was reported to occur within the first 3 days of treatment. If severe diarrhea occurs, dosing should be suspended and the patient should be rehydrated.

Adverse Reactions: In clinical trials, the most common adverse reaction(s) reported in at least 2% of the CIC patients in the plecanatide-treated group and at an incidence that was greater than in the placebo group was diarrhea. The majority of reported cases of diarrhea occurred within 4 weeks of treatment initiation. Discontinuation due to diarrhea occurred in 2% of plecanatide-treated patients.

Use in Specific Populations:

- Pregnancy: Plecanatide and its active metabolite are negligibly absorbed systemically following oral administration and maternal use is not expected to result in fetal exposure of the drug. However, the available data on plecanatide use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage.
- Lactation: There is no information regarding the presence of plecanatide in human milk, or its effects on milk production or the breastfed infant. It is unknown whether the negligible systemic absorption of plecanatide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for serious adverse effects.
- Pediatric Use: Plecanatide is contraindicated in patients younger than 6 years of age and should also be avoided in patients 6 years to younger than 18 years of age. The safety and efficacy of plecanatide in pediatric patients younger than 18 years of age have not been established.
- Geriatric Use: Clinical studies of plecanatide did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients. Of the 2,601 patients in clinical trials of plecanatide, 10% were 65 years of age and older, and 2% were 75 years of age and older.

Efficacy: The efficacy of plecanatide for the management of symptoms of CIC was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients (Study 1 and Study 2).

- In the Intention-to-Treat (ITT) population, a total of 905 patients (Study 1) and 870 patients (Study 2) were randomized 1:1 to either placebo or plecanatide 3mg, once daily.
- The efficacy of plecanatide was assessed using a responder analysis and change-from-baseline in complete spontaneous bowel movement (CSBM) and spontaneous bowel movement (SBM) endpoints. A SBM is a bowel movement occurring in the absence of laxative use; a CSBM is a SBM that is associated with a sense of complete evacuation.
- Efficacy was assessed using information provided by patients on a daily basis in an electronic diary.
- A responder was defined as a patient who had at least three CSBMs in a given week and an increase of at least one CSBM from baseline in the same week for at least 9 weeks out of the 12-week treatment period and at least 3 of the last 4 weeks of the study (*see responder rates in the following table*).
- In both studies, improvement in the frequency of CSBMs/week were seen as early as week 1 with improvement maintained through week 12. The difference between the plecanatide group and the placebo group in the mean change of CSBMs/week frequency from baseline to week 12 was approximately 1.1 CSBMs/week.

Efficacy Responder Rates			
Study 1			
	Plecanatide 3mg N=453	**Placebo N=452**	**Treatment Difference* [95% CI]**
Responder	21%	10%	11% [6.1%, 15.4%]
Study 2			
	Plecanatide 3mg N=430	**Placebo N=440**	**Treatment Difference* [95% CI]**
Responder	21%	13%	8% [2.6%, 12.4%]

*p-value <0.005
CI = confidence interval

Cost: The NADAC of Trulance™ is $11.26 per tablet, resulting in a monthly cost of $337.80.

Xermelo™ (Telotristat Ethyl) Product Summary[22,23]

Indication(s): Xermelo™ (telotristat ethyl) is indicated for the treatment of carcinoid syndrome diarrhea in combination with SSA therapy in adults inadequately controlled by SSA therapy.

Dosing:

- Xermelo™ is available as oral tablets containing 250mg of telotristat ethyl.
- The recommended dosage of telotristat ethyl is 250mg orally three times daily for patients whose diarrhea is inadequately controlled by SSA therapy.
- During clinical studies, telotristat ethyl 500mg three times daily did not demonstrate additional treatment benefit and had a greater incidence of adverse reactions than

telotristat ethyl 250mg three times daily. Therefore, telotristat ethyl 500mg three times daily is not recommended.
- Telotristat ethyl should be taken with food and should be discontinued if severe constipation develops.
- When short-acting octreotide is used in combination with telotristat ethyl, it should be administered at least 30 minutes after administering telotristat ethyl.

Mechanism of Action: Telotristat, the active metabolite of telotristat ethyl, is an inhibitor of tryptophan hydroxylase, which mediates the rate limiting step in serotonin biosynthesis. The *in vitro* inhibitory potential of telotristat towards tryptophan hydroxylase is 29 times higher than that of telotristat ethyl. Serotonin plays a role in mediating secretion, motility, inflammation, and sensation of the GI tract and is over-produced in patients with carcinoid syndrome. Through inhibition of tryptophan hydroxylase, telotristat and telotristat ethyl reduce the production of peripheral serotonin and thus reduce the frequency of carcinoid syndrome diarrhea.

Contraindication(s): None.

Warnings and Precautions:
- Constipation: Telotristat ethyl reduces bowel movement frequency. In a 12-week, placebo-controlled trial, in which patients had four or greater bowel movements per day, two out of 45 patients treated with a higher than recommended dose of telotristat ethyl reported constipation. In one patient, the constipation was serious, resulting in hospitalization. During the 36-week extension period with higher than recommended dosage, 10 out of 115 patients reported constipation: one developed intestinal perforation and one developed obstruction. In another 12-week, placebo-controlled trial in which patients had less than four bowel movements per day, four out of 25 patients treated with the recommended dosage of telotristat ethyl reported constipation. Given that patients with metastatic carcinoid tumors may have impaired integrity of the GI tract wall, it is recommended to monitor for the development of constipation and/or severe, persistent, or worsening abdominal pain in patients taking telotristat ethyl. Telotristat ethyl should be discontinued if severe constipation or severe persistent or worsening abdominal pain develops.

Adverse Reactions: In clinical trials, the most common adverse reactions reported in at least 5% of patients in the telotristat ethyl-treated group and at an incidence that was greater than placebo were nausea, headache, increased gamma-glutamyl-transferase (GGT), depression, peripheral edema, flatulence, decreased appetite, and pyrexia.

Drug Interactions:
- CYP3A4 Substrates: Concomitant use of telotristat ethyl may decrease the efficacy of drugs that are CYP3A4 substrates (e.g., midazolam) by decreasing their systemic exposure. Patients should be monitored for suboptimal efficacy and increasing the dose for concomitant CYP3A4 substrates should be considered, if necessary.

- Short-Acting Octreotide: Concurrent administration of short-acting octreotide with telotristat ethyl significantly decreased the systemic exposure of telotristat ethyl and telotristat, the active metabolite. If treatment with short-acting octreotide is needed in combination with telotristat ethyl, short-acting octreotide should be administered at least 30 minutes after administration of telotristat ethyl.

Use in Specific Populations:

- Pregnancy: There are no human data with telotristat ethyl use in pregnant women to inform a drug-associated risk. In animal reproduction studies, no effects on embryo-fetal development were observed with the administration of oral telotristat ethyl to rats during organogenesis at doses up to approximately nine times the recommended human dose (RHD). Treatment of pregnant rabbits with oral telotristat ethyl during organogenesis produced maternal toxicity and post-implantation loss at doses of approximately 15 times the RHD, and reduced fetal weight at doses of approximately 33 times the RHD. In a pre/postnatal development study, an increased incidence of mortality in rat offspring was observed during postnatal days 0 to 4 at the maternal oral dose of approximately five times the RHD, given during organogenesis through lactation.
- Lactation: There are no data on the presence of telotristat ethyl in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The effects of local GI and systemic exposure to telotristat ethyl on breastfed infants are unknown.
- Pediatric Use: The safety and effectiveness of telotristat ethyl in pediatric patients have not been established.
- Geriatric Use: Of 45 patients in a clinical trial of telotristat ethyl, 42% were 65 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Efficacy: The efficacy of telotristat ethyl was established in a 12-week double-blind, placebo-controlled, randomized, multicenter trial that was conducted in adult patients with a well-differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months.

- Patients were randomized to placebo or treatment with telotristat ethyl 250mg three times daily. All patients were required to stay on their baseline SSA regimen and were allowed to use rescue medication (short-acting octreotide) and antidiarrheals (e.g., loperamide) for symptomatic relief.
- Baseline daily bowel movements were assessed over the 3 to 4 week screening/run-in period.
- A total of 90 patients were evaluated for efficacy. The primary efficacy endpoint was the change from baseline in the number of daily bowel movements averaged over the 12-week period (*see analysis results in the following table*).
- In the 12-week study, a difference in average weekly reductions in bowel movement frequency between telotristat ethyl and placebo was observed as early as 1 to 3 weeks, and persisted for the remaining 9 weeks of the study.

Change from Baseline in Daily Bowel Movements		
Parameter	**Telotristat Ethyl 250mg TID**	**Placebo**
Number of Patients	45	45
Baseline Mean (SD); Median (Min, Max)	6.1 (2.1); 5.5 (3.5, 13)	5.2 (1.4); 5.1 (3.5, 9)
±Change Averaged Over 12 Weeks: Mean (SD); Median (Min, Max)	-1.4 (1.4); -1.3 (-6.1, 1.6)	-0.6 (0.8); -0.6 (-2.7, 0.8)
±Estimate of Treatment Difference (97.5% CL)α	-0.8* (-1.3, -0.3)	——

*p-value <0.001
TID = three times daily, BM = bowel movement, SD = standard deviation, CL = confidence limit
±BMs/Day averaged over 12 weeks
αStatistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. CLs were based on the Hodges-Lehmann estimator of the median paired difference.

Cost: The WAC of Xermelo™ is $61.48 per tablet, resulting in a monthly cost of $5,533.20.

Symproic® (Naldemedine) Product Summary[24,25]

Indication(s): Symproic® (naldemedine) is indicated for the treatment of OIC in adult patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

Dosing:

- Symproic® is available as oral tablets containing 0.2mg of naldemedine.
- The recommended dosage of naldemedine is 0.2mg orally once daily with or without food.
- Patients receiving opioids for less than 4 weeks may be less responsive to naldemedine.
- Naldemedine should be discontinued if treatment with the opioid pain medication is also discontinued.

Mechanism of Action: Naldemedine is an opioid antagonist with binding affinities for mu-, delta-, and kappa-opioid receptors. Naldemedine functions as a PAMORA in tissues such as the GI tract, thereby decreasing the constipating effects of opioids. Naldemedine is a derivative of naloxone to which a side chain has been added that increases the molecular weight and the polar surface area, thereby reducing its ability to cross the blood-brain barrier (BBB). Naldemedine is also a substrate of the P-glycoprotein (P-gp) efflux transporter. Based on these properties, the central nervous system (CNS) penetration of naldemedine is expected to be negligible at the recommended dose levels, limiting the potential for interference with centrally-mediated opioid analgesia.

Contraindication(s):

- Patients with known or suspected GI obstruction and patients at increased risk of recurrent obstruction, due to the potential for GI perforation
- Patients with a history of a hypersensitivity reaction to naldemedine (reactions have included bronchospasm and rash)

Warnings and Precautions:

- GI Perforation: Cases of GI perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the GI tract (e.g., peptic ulcer disease, Ogilvie's syndrome, diverticular disease, infiltrative GI tract malignancies, peritoneal metastases). When using naldemedine in patients with these conditions or other conditions which might result in impaired integrity of the GI tract wall (e.g., Crohn's disease), the overall risk-benefit profile should be taken into account.
- Opioid Withdrawal: Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, increased lacrimation, hot flush/flushing, pyrexia, sneezing, feeling cold, abdominal pain, diarrhea, nausea, and vomiting have occurred in patients treated with naldemedine. Patients having disruptions to the BBB may be at increased risk for opioid withdrawal or reduced analgesia. The overall risk-benefit profile should be taken into account when using naldemedine in such patients, and such patients should be monitored for opioid withdrawal.

Adverse Reactions: In clinical trials, the most common adverse reactions reported in at least 2% of patients receiving naldemedine and at an incidence greater than placebo were abdominal pain, diarrhea, nausea, vomiting, and gastroenteritis.

Drug Interactions:

- Strong CYP3A Inducers: The co-administration of naldemedine with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) significantly decreased plasma naldemedine concentrations, which may reduce efficacy. Use of naldemedine with strong CYP3A inducers should be avoided.
- Other Opioid Antagonists: The co-administration of naldemedine with other opioid antagonists has the potential for an additive effect of opioid receptor antagonism and an increased risk of opioid withdrawal. Use of naldemedine with other opioid antagonists should be avoided.
- Moderate and Strong CYP3A Inhibitors: The co-administration of naldemedine with moderate (e.g., fluconazole, atazanavir, aprepitant, diltiazem, erythromycin) and strong (e.g., itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir) CYP3A inhibitors increased plasma naldemedine concentrations. Patients should be monitored for potential naldemedine-related adverse reactions.
- P-gp Inhibitors: The co-administration of naldemedine with P-gp inhibitors (e.g., amiodarone, captopril, cyclosporine, quercetin, quinidine, verapamil) increased plasma naldemedine concentrations. Patients should be monitored for potential naldemedine-related adverse reactions.

Use in Specific Populations:

- Pregnancy: There are no available data with naldemedine in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. There is a potential for opioid withdrawal in a fetus when naldemedine is used in pregnant women.

- Lactation: There is no information regarding the presence of naldemedine in human milk, the effects on the breastfed infant, or the effects on milk production. Naldemedine was present in the milk of rats.
- Pediatric Use: The safety and effectiveness of naldemedine have not been established in pediatric patients.
- Geriatric Use: Of 1,163 patients in clinical studies exposed to naldemedine, 16% were 65 years of age and older, while 3% were 75 years of age and older. No overall differences in safety or effectiveness between these patients and younger patients were observed, but greater sensitivity of some older individuals cannot be ruled out.
- Hepatic Impairment: The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naldemedine has not been evaluated. Use of naldemedine should be avoided in patients with severe hepatic impairment.

Efficacy: The efficacy of naldemedine was evaluated in two replicate, 12-week, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2) in which naldemedine was used without laxatives in patients with OIC and chronic non-cancer pain.

- Patients receiving a stable opioid morphine equivalent daily dose of at least 30mg for at least 4 weeks before enrollment and self-reported OIC were eligible for clinical trial participation. Patients with evidence of significant structural abnormalities of the GI tract were not eligible for the trials.
- A total of 547 patients in Study 1 and 553 patients in Study 2 were randomized in a 1:1 ratio to receive naldemedine 0.2mg once daily or placebo for 12 weeks.
- The efficacy of naldemedine was assessed using a responder analysis. A responder was defined as a patient who had at least three SBMs per week and a change from baseline of at least one SBM per week for at least 9 out of the 12 weeks and 3 out of the last 4 weeks (*see responder rates in the table below*).

Efficacy Responder Rates						
	Study 1			Study 2		
	Naldemedine 0.2mg QDay (N=273)	Placebo (N=272)	Treatment Difference [95% CI]	Naldemedine 0.2mg QDay (N=276)	Placebo (N=274)	Treatment Difference [95% CI]
Responder	130 (48%)	94 (35%)	13% [5%, 21%]	145 (53%)	92 (34%)	19% [11%, 27%]
p-value			0.0020			<0.0001

QDay = once daily, N = number, CI = confidence interval

Cost: The anticipated release date and cost information for Symproic® are not currently available.

Cost Comparison: Constipation Medications

Medication	Recommended Dose	Cost/Month*
Chronic Idiopathic Constipation (CIC) Indication		
Amitiza® (lubiprostone) 24mcg cap	24mcg PO BID	$336.60
Linzess® (linaclotide) 145mcg cap	72mcg or 145mcg PO QDay	$340.20
Trulance™ (plecanatide) 3mg tab	3mg PO QDay	$337.80
Irritable Bowel Syndrome with Constipation (IBS-C) Indication		
Amitiza® (lubiprostone) 8mcg cap	8mcg PO BID	$336.60
Linzess® (linaclotide) 290mcg cap	290mcg PO QDay	$339.60
Opioid-Induced Constipation (OIC) Indication⁺		
Amitiza® (lubiprostone) 24mcg cap	24mcg PO BID	$336.60
Movantik® (naloxegol) 25mg tab	12.5mg or 25mg PO QDay	$301.20
Relistor® (methylnaltrexone) 150mg tab	450mg PO QDay	$1,431.00
Relistor® (methylnaltrexone) 12mg/0.6mL inj¥	12mg subQ QDay	$2,876.76α
Symproic® (naldemedine) 0.2mg tab	0.2mg PO QDay	n/a

cap = capsule, tab = tablet, inj = injection, PO = by mouth, BID = twice daily, QDay = once daily, subQ = subcutaneous, n/a = not available

*Costs are based on National Average Drug Acquisition Costs (NADAC) and do not reflect rebated prices or net costs.

⁺Medications included in the table are indicated for the treatment of OIC in adults patients with chronic non-cancer pain, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation.

¥Relistor® injection is also indicated for the treatment of OIC in patients with severe terminal disease who are receiving only palliative care, with recommended dosing of weight-based every other day subcutaneous injections as needed.

αCost/month for Relistor® injection is based on once daily use of 12mg/0.6mL syringes.

Recommendations

The College of Pharmacy recommends the prior authorization of Trulance™ (plecanatide), Xermelo™ (telotristat ethyl), Symproic® (naldemedine), and Motofen® (difenoxin/atropine) with the following criteria:

Trulance™ (Plecanatide) Approval Criteria:

1. An FDA approved diagnosis of chronic idiopathic constipation (CIC) in members 18 years of age or older; and
2. Documentation that constipation-causing therapies for other disease states have been discontinued (excluding opioid pain medications for cancer patients); and
3. Documented and updated colon screening for members older than 50 years of age; and
4. 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
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.

6. A quantity limit of 30 tablets for a 30 day supply will apply.

Xermelo™ (Telotristat Ethyl) Approval Criteria:

1. An FDA approved diagnosis of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy; and
2. Member must be 18 years of age or older; and
3. Member must have been taking a stable dose of SSA therapy for the last three months and be inadequately controlled (4 or more bowel movements per day); and
4. Prescriber must verify member will continue taking SSA therapy in combination with Xermelo™; and
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
6. A quantity limit of 90 tablets for a 30 day supply will apply.

Symproic® (Naldemedine) 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, including patients with chronic pain related to prior cancer or its treatment who do not require frequent (e.g., weekly) opioid dosage escalation; 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 older 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. Symproic® must be discontinued if treatment with the opioid pain medication is also discontinued.
9. A quantity limit of 30 tablets for a 30 day supply will apply.

Motofen® (Difenoxin/Atropine) Approval Criteria:

1. An FDA approved diagnosis of acute nonspecific diarrhea or acute exacerbations of chronic functional diarrhea; and
2. Member must not be 2 years of age or younger; and
3. Member must not have diarrhea associated with organisms that penetrate the intestinal mucosa (e.g., toxigenic *Escherichia coli, Salmonella species, Shigella*) or pseudomembranous colitis associated with broad spectrum antibiotics; and

4. A patient-specific, clinically significant reason why the member cannot use Lomotil® (diphenoxylate/atropine) and loperamide must be provided; and
5. A quantity limit of 16 tablets per 2 days will apply.

Additionally, the College of Pharmacy recommends updating the current approval criteria for Xifaxan® (rifaximin) 200mg to remove from the approval criteria the required reason why the member cannot use a fluoroquinolone antibiotic, which addresses the FDA Drug Safety Communication that updated the warnings for fluoroquinolone antibiotics, and recommends updating the current approval criteria for Viberzi® (eluxadoline) to exclude members with any contraindications to taking Viberzi®, which addresses the recent FDA Drug Safety Communication regarding use of Viberzi® in patients without a gallbladder. The proposed changes can be seen in red in the following criteria:

Xifaxan® (Rifaximin) 200mg Approval Criteria:

1. An FDA approved diagnosis of traveler's diarrhea (TD); and
2. Member must be 12 years of age or older; and
3. TD must be due to noninvasive strains of *Escherichia coli*; and
4. ~~A patient-specific, clinically significant reason why the member cannot use a fluoroquinolone antibiotic (e.g., ciprofloxacin, levofloxacin) must be provided.~~
5. A quantity limit of 9 tablets for a 3 day supply will apply.

Viberzi® (Eluxadoline) Approval Criteria:

1. An FDA approved diagnosis of irritable bowel syndrome with diarrhea (IBS-D); and
2. Member must be 18 years of age or older; and
3. Member must not have any of the contraindications for use of Viberzi® (e.g., removed gallbladder; biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, or alcohol addiction; history of pancreatitis or structural diseases of the pancreas; severe hepatic impairment; history of chronic or severe constipation; mechanical gastrointestinal obstruction); and
4. Documentation of trials of two of the following three medications that failed to relieve diarrhea: loperamide, dicyclomine, or diphenoxylate/atropine (each trial should be for at least 10 to 14 consecutive days at the recommended dosing). Trials must be within the past 90 days. Documentation should be provided including dates, dosing, and reason for trial failure.
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment.
6. A quantity limit of 60 tablets for a 30 day supply will apply.

Utilization Details of Constipation and Diarrhea Medications: Fiscal Year 2017

Constipation and Diarrhea Medications

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
LINACLOTIDE PRODUCTS						
LINZESS CAP 290MCG	231	40	$76,729.43	$11.21	$332.16	25.51%
LINZESS CAP 145MCG	224	53	$74,060.86	$11.07	$330.63	24.62%
LINZESS CAP 72MCG	8	6	$2,831.40	$12.00	$353.93	0.94%
SUBTOTAL	**463**	**99**	**$153,621.69**	**$11.15**	**$331.80**	**51.07%**
LUBIPROSTONE PRODUCTS						
AMITIZA CAP 24MCG	188	37	$61,631.89	$10.35	$327.83	20.49%
AMITIZA CAP 8MCG	48	14	$18,045.08	$11.79	$375.94	6.00%
SUBTOTAL	**236**	**51**	**$79,676.97**	**$10.64**	**$337.61**	**26.49%**
NALOXEGOL PRODUCTS						
MOVANTIK TAB 25MG	78	27	$23,834.66	$10.19	$305.57	7.92%
MOVANTIK TAB 12.5MG	8	3	$2,448.26	$10.20	$306.03	0.81%
SUBTOTAL	**86**	**30**	**$26,282.92**	**$10.19**	**$305.62**	**8.74%**
ELUXADOLINE PRODUCTS						
VIBERZI TAB 100MG	21	7	$18,653.36	$33.61	$888.26	6.20%
VIBERZI TAB 75MG	4	3	$4,039.93	$33.67	$1,009.98	1.34%
SUBTOTAL	**25**	**10**	**$22,693.29**	**$33.62**	**$907.73**	**7.54%**
METHYLNALTREXONE PRODUCTS						
RELISTOR INJ 12/0.6ML	10	3	$15,502.30	$72.10	$1,550.23	5.15%
RELISTOR TAB 150MG	2	2	$3,013.10	$50.22	$1,506.55	1.00%
SUBTOTAL	**12**	**5**	**$18,515.40**	**$67.33**	**$1,542.95**	**6.16%**
TOTAL	**822**	**177***	**$300,790.27**	**$12.13**	**$365.92**	**100.00%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Please note, the above data does not include Xifaxan® (rifaximin).

Xifaxan® (Rifaximin)

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
XIFAXAN TAB 550MG	1,108	263	$1,977,947.21	$62.86	$1,785.15	99.90%
XIFAXAN TAB 200MG	5	4	$2,004.47	$41.76	$400.89	0.10%
TOTAL	**1,113**	**266***	**$1,979,951.68**	**$62.83**	**$1,778.93**	**100.00%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Xifaxan® was first FDA approved in 2004 and has a significant federal rebate. Please note, the majority of utilization of rifaximin 550mg was for the reduction in risk of overt hepatic encephalopathy (HE) recurrence.

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Appendix O

Fiscal Year 2017 Annual Review of Thrombopoietin (TPO) Receptor Agonists and 30-Day Notice to Prior Authorize Promacta® (Eltrombopag)

Oklahoma Health Care Authority
October 2017

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

Primary immune thrombocytopenia (ITP), also called idiopathic thrombocytopenic purpura, is an acquired thrombocytopenia that is due to autoimmune platelet destruction and is one of the more common causes of thrombocytopenia in otherwise asymptomatic adults. ITP in children is a clinically distinct condition from that in adults and has a lower incidence of underlying diseases and comorbidities. Additionally, ITP in children has a higher likelihood of spontaneous remission. Many patients with ITP are asymptomatic, but for patients who do have symptoms, the symptoms are related to thrombocytopenia and/or bleeding. The goal of ITP treatment is not to normalize the platelet count, but to provide a safe platelet count in order to prevent clinically important bleeding. For patients who require treatment for ITP, the most commonly used treatment options are glucocorticoids or intravenous immune globulin (IVIG). Other treatment options include splenectomy, rituximab, thrombopoietin (TPO) receptor agonists, or immunosuppressive therapy.

Thrombocytopenia in patients with chronic hepatitis C virus (HCV) remains a major problem and has a multifactorial pathophysiology. The greatest challenge with thrombocytopenia in patients with chronic HCV is the difficulty in maintaining or initiating interferon (IFN) containing anti-viral therapy. However, the recent shift in HCV treatment regimens to direct-acting antivirals (DAAs) without IFN as frontline therapy avoids the dilemma associated with IFN-based anti-viral therapy.

Aplastic anemia (AA) is characterized by diminished or absent hematopoietic precursors in the bone marrow. In patients with AA, red blood cell (RBC), white blood cell (WBC), and platelet counts are low. AA can be acquired or inherited; however, most cases are acquired. AA is classified as moderate, severe, or very severe. Severe and very severe AA are typically treated aggressively while moderate AA may be observed in certain situations. For patients with severe AA, treatment with immune system suppressing therapy or a stem cell transplant is necessary.

Current Prior Authorization Criteria

Nplate® (Romiplostim) Approval Criteria:

1. An FDA approved indication of chronic immune (idiopathic) thrombocytopenia purpura (ITP); and
2. Previous insufficient response with at least two of the following treatments:
    a. Corticosteroids; or
    b. Immunoglobulins; or

c. Splenectomy; and

3. Recent platelet count of < 50 x 10^9/L; and
4. Initial dosing of 1mcg/kg once weekly as a subcutaneous injection with recent patient weight in kilograms provided.
5. Continuation criteria:
   a. Weekly CBCs with platelet count and peripheral blood smears until stable platelet count (≥ 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved, then obtain monthly thereafter; and
   b. Dosing adjustments:
      i. Platelets < 50 x 10^9/L, increase dose by 1mcg/kg.
      ii. Platelets > 200 x 10^9/L for 2 consecutive weeks, reduce dose by 1mcg/kg.
      iii. Platelets > 400 x 10^9/L, do not dose. Continue to assess platelet count weekly. When platelets < 200 x 10^9/L, resume at a dose reduced by 1mcg/kg.
6. Discontinuation criteria:
   a. Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum weekly dose of 10mcg/kg.
7. Approval period will be for four weeks initially, and then quarterly.

Utilization of TPO Receptor Agonists: Fiscal Year 2017

Comparison of Fiscal Years: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	9	68	$286,158.79	$4,208.22	$296.54	908	965
2017	14	66	$479,717.62	$7,268.45	$244.01	1,858	1,966
% Change	**55.60%**	**-2.90%**	**67.60%**	**72.70%**	**-17.70%**	**104.60%**	**103.70%**
Change	**5**	**-2**	**$193,558.83**	**$3,060.23**	**-$52.53**	**950**	**1,001**

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

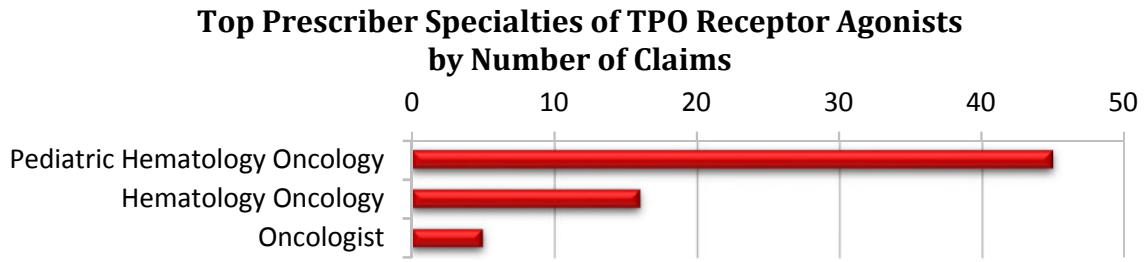
Fiscal Year 2017 Utilization of Nplate®: Medical Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
2017	3	31	$116,293.54	$3,751.41	1,836

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

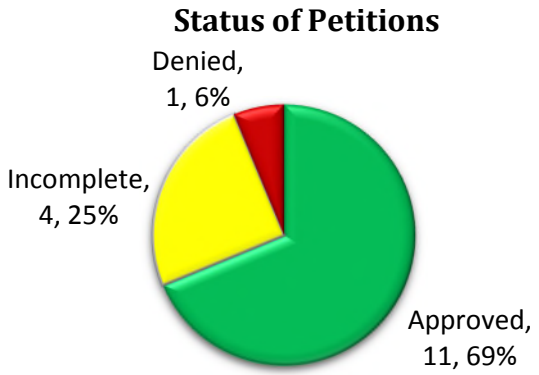
Demographics of Members Utilizing TPO Receptor Agonists

- Due to the small number of members utilizing TPO receptor agonists during fiscal year 2017, detailed demographic information could not be provided.



Prior Authorization of TPO Receptor Agonists

There were 16 prior authorization requests submitted for Nplate® during fiscal year 2017. The following chart shows the status of the submitted petitions.



Market News and Updates[6,7,8,9]

Anticipated Patent Expiration(s):

- Promacta® (eltrombopag): February 2028

Pipeline:

- **Avatrombopag:** Avatrombopag is an investigational second-generation oral TPO receptor agonist that stimulates platelet production. The medication has completed two Phase 3 randomized, double-blind, placebo-controlled, clinical studies evaluating its use as a potential treatment for thrombocytopenia in patients with chronic liver disease undergoing a planned medical procedure. Dova Pharmaceuticals plans to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in the third quarter of 2017.

Other News:

- **April 2017:** Data from a study conducted by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH) was published in *The New England Journal of Medicine*. The Phase 1-2, non-randomized study included 92 patients with treatment-naïve severe aplastic anemia (SAA). Patients received immunosuppressive therapy plus eltrombopag. The three consecutively enrolled cohorts differed with regard to the timing of initiation and the duration of the eltrombopag therapy. In cohort 1, patients received eltrombopag on day 14 to six

months; in cohort 2, patients received eltrombopag on day 14 to three months; in cohort 3, patients received eltrombopag on day one to six months. The study's primary efficacy endpoint was hematologic complete response at six months. A complete response was defined as an absolute neutrophil count of at least 1,000/mm^3, a hemoglobin level of at least 10g/dL, and a platelet count of at least 100,000/mm^3. The overall response rate corresponded to the proportion of patients who had a partial or complete response. The rate of complete response at six months was 33% in cohort 1, 26% in cohort 2, and 58% in cohort 3. The overall response rate at six months was 80% in cohort 1, 87% in cohort 2, and 94% in cohort 3. In the historical cohort, the rate of complete response was 10% and the overall response rate was 66%. The study found that the addition of eltrombopag to immunosuppressive therapy was associated with markedly higher rates of hematologic response among patients with SAA than in the historical cohort.

Promacta® (Eltrombopag) Product Summary[10]

FDA Approval: 2008

Indication(s): Promacta® (eltrombopag) is a TPO receptor agonist indicated for the treatment of:

- Thrombocytopenia in adult and pediatric patients 1 year of age and older with chronic immune (idiopathic) thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.
  - Limitations of Use: Eltrombopag should only be used in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding.
- Thrombocytopenia in patients with chronic hepatitis C (CHC) to allow initiation and maintenance of IFN-based therapy.
  - Limitations of Use: Eltrombopag should only be used in patients with CHC whose degree of thrombocytopenia prevents the initiation of IFN-based therapy or limits the ability to maintain IFN-based therapy. The safety and efficacy have not been established in combination with DAA agents used without IFN for treatment of CHC infection.
- Patients with severe aplastic anemia (SAA) who have had an insufficient response to immunosuppressive therapy.

Dosing:

- Promacta® is available as 12.5mg, 25mg, 50mg, and 75mg oral tablets.
- It is recommended to take eltrombopag on an empty stomach; 1 hour before or 2 hours after a meal.
- Chronic ITP: The recommended initial oral dose for chronic ITP is 50mg once daily for most adult and pediatric patients 6 years of age and older. For patients 1 to 5 years of age, the recommended initial dose is 25mg once daily. For patients with hepatic impairment and some patients of East Asian ancestry, dose reductions are needed. It is recommended to adjust the dose to maintain a platelet count greater than or equal to 50 x 10^9/L. The maximum recommended dose is 75mg per day.

- CHC-associated Thrombocytopenia: The recommended initial dose for the treatment of CHC-associated thrombocytopenia is 25mg once daily for all patients. The dose should be adjusted to achieve target platelet counts required to initiate antiviral therapy. The maximum recommended dose is 100mg per day.
- SAA: The recommended initial dose for the treatment of SAA is 50mg once daily for most patients. For patients with hepatic impairment and some patients of East Asian ancestry, it is recommended to reduce the initial dose. The dose should be adjusted to maintain a platelet count greater than 50 x 10^9/L. The maximum recommended dose is 150mg per day.

Mechanism of Action: Eltrombopag is an orally bioavailable, small molecule TPO-receptor agonist that interacts with the transmembrane domain of the human TPO-receptor and initiates signaling cascades that induce proliferation and differentiation from bone marrow progenitor cells.

Boxed Warning: Risk for Hepatic Decompensation in Patients with CHC; Risk of Hepatotoxicity

- In patients with CHC, eltrombopag in combination with IFN and ribavirin may increase the risk of hepatic decompensation.
- Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity. It is recommended to monitor hepatic function and discontinue dosing as directed.

Contraindication(s): None.

Warnings and Precautions:

- Hepatic Decompensation in Patients with CHC: In patients with CHC, eltrombopag may increase the risk of hepatic decompensation when used in combination with IFN and ribavirin.
- Hepatotoxicity: Eltrombopag may increase the risk of severe and potentially life-threatening hepatotoxicity. Serum ALT, AST, and bilirubin should be measured prior to initiation of eltrombopag, every two weeks during dose adjustment, and monthly following establishment of a stable dose.
- Thrombotic/Thromboembolic Complications: Thrombotic/thromboembolic complications may result from increases in platelet counts with eltrombopag. Reported complications included both venous and arterial events and were observed at low and at normal platelet counts. The potential for an increased risk of thromboembolism should be considered when administering eltrombopag to patients with known factors for thromboembolism (e.g., Factor V Leiden, ATIII deficiency, antiphospholipid syndrome, chronic liver disease). To minimize the risk for thrombotic/thromboembolic complications, eltrombopag should not be used to normalize platelet counts.
- Cataracts: Cataracts developed or worsened in 15 (7%) of patients who received 50mg of eltrombopag daily in the three controlled clinical trials in adults with chronic ITP and in 8 (7%) of the placebo-group patients. A baseline ocular examination should be performed prior to administration of eltrombopag, and during therapy with eltrombopag, patients should be regularly monitored for signs and symptoms of cataracts.

Adverse Reactions: In adult patients with ITP, the most common adverse reactions (greater than or equal to 5% and greater than placebo) were:

- Nausea
- Diarrhea
- Upper Respiratory Tract Infection
- Vomiting
- Increased ALT
- Urinary Tract Infection
- Myalgia

In patients with CHC-associated thrombocytopenia, the most common adverse reactions (greater than or equal to 10% and greater than placebo) were:

- Anemia
- Pyrexia
- Fatigue
- Headache
- Nausea
- Diarrhea
- Decreased Appetite
- Influenza-like Illness
- Asthenia
- Insomnia
- Cough
- Pruritus
- Chills
- Myalgia
- Alopecia
- Peripheral Edema

Use in Specific Populations:

- Pregnancy: Pregnancy category C. There are no adequate and well-controlled studies of eltrombopag use in pregnancy. There was evidence of embryolethality and reduced fetal weights at maternally toxic doses in animal reproduction and developmental toxicity studies.
- Nursing Mothers: It is not known whether eltrombopag is excreted in human milk.
- Pediatric Use: The safety and efficacy of eltrombopag in pediatric patients 1 year of age and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The safety and efficacy have not been established in pediatric patients with thrombocytopenia associated with CHC, SAA, or patients younger than 1 year of age with ITP.
- Geriatric Use: Of the 106 patients in two randomized clinical trials of eltrombopag 50mg in chronic ITP, 22% were 65 years of age and older and 9% were 75 years of age and older. In the two randomized clinical trials of eltrombopag in patients with CHC and thrombocytopenia, 7% were 65 years of age and older, while fewer than 1% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and younger patients in the placebo-controlled trials, but greater sensitivity of some older individuals cannot be ruled out.
- Hepatic Impairment: Hepatic impairment influences the exposure of eltrombopag. It is recommended to reduce the initial dose of eltrombopag in patients with chronic ITP (adult and pediatric patients 6 years of age and older only) or SAA who also have hepatic impairment (Child-Pugh Class A, B, or C). No dosage adjustment is recommended for patients with CHC and hepatic impairment.
- Renal Impairment: No adjustment in the initial dose of eltrombopag is necessary for patients with renal impairment. Patients with impaired renal function should be closely monitored when administered eltrombopag.
- Ethnicity: Patients of East Asian ethnicity (i.e., Japanese, Chinese, Taiwanese, and Korean) exhibit higher eltrombopag exposures. It is recommended to reduce the initial

dose of eltrombopag for patients of East Asian ancestry with ITP (adult and pediatric patients 6 years of age and older only) or SAA. No dose reduction is recommended for patients of East Asian ethnicity with CHC.

Efficacy:

- Chronic ITP: The efficacy and safety of eltrombopag in adult patients with chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3). The efficacy and safety of eltrombopag in pediatric patients 1 year of age and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. Please refer to the package insert for additional information regarding trials 3, 4, and 5.
  - *Trials 1 and 2:* In Trials 1 and 2, patients who had a platelet count less than 30 x 10^9/L and had completed at least one prior ITP therapy were randomized to receive either eltrombopag or placebo daily for up to six weeks, followed by six weeks off therapy. Eltrombopag or placebo was discontinued during the trial if the platelet count exceeded 200 x 10^9/L. Approximately 70% of the patients had received at least two prior ITP therapies (predominantly corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine) and 40% of the patients had undergone splenectomy. The efficacy was evaluated by response rate, defined as a shift from a baseline platelet count of less than 30 x 10^9/L to greater than or equal to 50 x 10^9/L at any time during the treatment period. The following table shows the platelet count response (≥50 x 10^9/L) rates in adults with chronic ITP in Trials 1 and 2.

Platelet Count Response (≥50 x 10^9/L)		
Trial	**Eltrombopag 50mg Daily***	**Placebo**
1	43/73 (59%)	6/37 (16%)
2	19/27 (70%)	3/27 (11%)

*P value <0.001 for eltrombopag versus placebo

The platelet count response to eltrombopag was similar among patients who had or had not undergone splenectomy. In general, increases in platelet counts were detected one week following initiation of eltrombopag and the maximum response was observed after two weeks of therapy. In the placebo and 50mg dose groups of eltrombopag, the trial drug was discontinued due to an increase in platelet counts to greater than 200 x 10^9/L in 3% and 27% of the patients, respectively. The median treatment duration with the 50mg dose was 42 days in Trial 1 and 43 days in Trial 2.

- CHC-associated Thrombocytopenia: The efficacy and safety of eltrombopag for the treatment of thrombocytopenia in adult patients with CHC were evaluated in two randomized, double-blind, placebo-controlled trials. Trial 1 utilized peginterferon alfa-2a (Pegasys®) plus ribavirin for antiviral treatment and Trial 2 utilized peginterferon alfa-2b (Pegintron®) plus ribavirin. In both trials, patients with a platelet count of less than 75 x 10^9/L were enrolled and stratified by platelet count, screening HCV RNA, and HCV genotype. Patients were excluded if they had evidence of decompensated liver disease

with Child-Pugh score greater than 6 (Class B and C), history of ascites, or hepatic encephalopathy. The trials consisted of two phases: a pre-antiviral treatment phase and an antiviral treatment phase. In the pre-treatment phase, patients received open-label eltrombopag to increase the platelet count to a threshold greater than or equal to 90 x 10^9/L for Trial 1 and greater than or equal to 100 x 10^9/L for Trial 2. Eltrombopag was administered at an initial dose of 25mg once daily for 2 weeks and increased in 25mg increments over 2- to 3-week periods to achieve the optimal platelet count to initiate antiviral therapy. The maximal time patients could receive open-label eltrombopag was 9 weeks. If threshold platelet counts were achieved, patients were randomized (2:1) to the same dose of eltrombopag at the end of the pre-treatment phase or to placebo. Eltrombopag was administered in combination with pegylated IFN and ribavirin per their respective prescribing information for up to 48 weeks. The efficacy of eltrombopag for both trials was evaluated by sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count greater than or equal to 90 x 10^9/L was approximately 2 weeks; 95% of patients were able to initiate antiviral therapy. The results of Trials 1 and 2 are summarized in the following table:

Pre-Antiviral Treatment Phase	**Trial 1 (n=715)**		**Trial 2 (n=805)**	
% patients who achieved target platelet counts and initiated antiviral therapy	95%		94%	
Antiviral Treatment Phase	**Eltrombopag (n=450) %**	**Placebo (n=232) %**	**Eltrombopag (n=506) %**	**Placebo (n=253) %**
Overall SVR*	23	14	19	13
HCV Genotype 2,3	35	24	34	25
HCV Genotype 1,4,6	18	10	13	7

*P value < 0.05 for eltrombopag versus placebo
n = number, HCV = hepatitis C virus; SVR = sustained virologic response

- SAA: Eltrombopag was studied in a single-arm, single-center, open-label trial in 43 patients with SAA who had an insufficient response to at least one prior immunosuppressive therapy and who had a platelet count less than or equal to 30 x 10^9/L. Eltrombopag was administered at an initial dose of 50mg once daily for 2 weeks and increased over 2-week periods up to a maximum of 150mg once daily. The efficacy of eltrombopag in the study was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting one or more of the following criteria:
  1) Platelet count increases to 20 x 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks
  2) Hemoglobin increase by greater than 1.5g/dL, or a reduction in greater than or equal to 4 units of RBC transfusions for 8 consecutive weeks
  3) Absolute neutrophil count (ANC) increase of 100% or an ANC increase greater than 0.5 x 10^9/L

Eltrombopag was discontinued after 16 weeks if no hematologic response was observed. Patients who responded continued therapy in an extension phase of the trial. The following table shows the results of the trial:

Outcome	Eltrombopag (n=43)
Response rate, n (%) 95% CI (%)	17 (40) (25, 56)
Median duration of response in months (95% CI)	NR (3.0, NR)

n = number, NR = not reached due to few events (relapsed); CI = confidence interval

Cost Comparison:

Medication	Cost per Unit	Cost per 28 days*
Promacta® 12.5mg tablet	**$122.46**	**$3,428.88**
Promacta® 25mg tablet	**$114.56**	**$3,207.68**
Promacta® 50mg tablet	**$213.13**	**$5,967.64**
Promacta® 75mg tablet	**$319.70**	**$8,951.60**
Nplate® 250mcg vial	$1,439.38	$11,515.04
Nplate® 500mcg vial	$3,328.75	$13,315.00

Unit = tablet or vial
Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or Specialty Pharmaceutical Allowable Cost (SPAC), if NADAC unavailable. Costs listed in the table above do not take into account federal or supplemental rebate participation; therefore, do not reflect net costs.
*Promacta® dosing based on one tablet per day. Nplate® dosing based on maximum weekly dose of 10mcg/kg for a 50kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Promacta® (eltrombopag) with the following criteria:

Promacta® (Eltrombopag) Approval Criteria:

1. An FDA approved indication of chronic immune (idiopathic) thrombocytopenia (ITP); and
    a. Previous insufficient response to at least one of the following:
        i. Corticosteroids; or
        ii. Immunoglobulins; or
        iii. Splenectomy; and
    b. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
    c. Must be prescribed by, or in consultation with, a hematologist or oncologist; or
2. An FDA approved indication of thrombocytopenia in patients with chronic hepatitis C (CHC) to allow initiation and maintenance of interferon (IFN)-based therapy; and
    a. Promacta® 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
    b. Patient must be prescribed IFN for treatment of CHC infection; or

3. An FDA approved indication of severe aplastic anemia (SAA); and
    a. Previous insufficient response or documented contraindication or intolerance to immunosuppressive therapy; and
    b. Must be prescribed by, or in consultation with, a hematologist or oncologist; and
4. For the diagnoses of chronic ITP and CHC associated thrombocytopenia, initial approvals will be for the duration of 1 month. For the diagnosis of SAA, initial approvals will be for the duration of 4 months. Subsequent approvals may be authorized if the prescriber documents the member is responding well to therapy and the following criteria is met, based upon member's diagnosis:
    a. For All Diagnosis:
        i. Must not have excessive platelet count responses. Promacta® should be discontinued if platelets exceed 400 x 10^9/L after two weeks of therapy at lowest dose; and
        ii. Prescriber documents liver function tests are being monitored and levels are acceptable to the prescriber.
    b. Chronic ITP:
        i. Documentation that platelet count has increased to a level sufficient to avoid clinically important bleeding or that a dose increase is planned, if not already on maximum dose. Promacta® should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after four weeks of therapy at the maximum daily dose of 75mg.
    c. CHC-associated Thrombocytopenia:
        i. Documentation that member continues to be on antiviral therapy. Promacta® should be discontinued when antiviral therapy is discontinued.
    d. SAA:
        i. Documentation that member has had a hematologic response (e.g., increase in platelet count, increase in hemoglobin, increase in absolute neutrophil count, reduction in frequency of platelet or RBC transfusions). Promacta® should be discontinued if no hematologic response has occurred after 16 weeks of therapy.

Additionally, the College of Pharmacy recommends to update the Nplate® (romiplostim) prior authorization criteria with the following changes noted in red:

Nplate® (Romiplostim) Approval Criteria:

1. An FDA approved indication of chronic immune (idiopathic) thrombocytopenia purpura (ITP); and
2. Previous insufficient response with at least ~~two~~ one of the following treatments:
    a. Corticosteroids; or
    b. Immunoglobulins; or
    c. Splenectomy; and
~~3. Recent platelet count of < 50 x 10^9/L; and~~
4. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
5. Nplate® (romiplostim) is not being used in an attempt to normalize platelet counts; and

6. Must be prescribed by, or in consultation with, a hematologist or oncologist; and
7. Initial dosing of 1mcg/kg once weekly as a subcutaneous injection with recent patient weight in kilograms provided.
8. Continuation criteria:
    a. Weekly CBCs with platelet count and peripheral blood smears until stable platelet count (≥ 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved; then obtain monthly thereafter; and
    b. Dosing adjustments:
        i. Platelets < 50 x 10^9/L, increase dose by 1mcg/kg.
        ii. Platelets > 200 x 10^9/L for 2 consecutive weeks, reduce dose by 1mcg/kg.
        iii. Platelets > 400 x 10^9/L, do not dose. Continue to assess platelet count weekly. When platelets < 200 x 10^9/L, resume at a dose reduced by 1mcg/kg.
9. Discontinuation criteria:
    a. Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum weekly dose of 10mcg/kg.
10. Approval period will be for four weeks initially, and then quarterly.

Utilization Details of TPO Receptor Agonists: Fiscal Year 2017

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
ELTROMBOPAG PRODUCTS						
PROMACTA TAB 50MG	28	9	$218,456.17	$260.07	$7,802.01	45.54%
PROMACTA TAB 25MG	17	3	$67,828.86	$133.00	$3,989.93	14.14%
PROMACTA TAB 75MG	14	2	$150,669.79	$358.74	$10,762.13	31.41%
SUBTOTAL	**59**	**14**	**$436,954.82**	**$246.87**	**$7,406.01**	**91.09%**
ROMIPLOSTIM PRODUCTS						
NPLATE INJ 250MCG	7	1	$42,762.80	$218.18	$6,108.97	8.91%
SUBTOTAL	**7**	**1**	**$42,762.80**	**$218.18**	**$6,108.97**	**8.91%**
TOTAL	**66**	**14***	**$479,717.62**	**$244.01**	**$7,268.45**	**100.00%**

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

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM
ROMIPLOSTIM PRODUCTS				
NPLATE INJ 250MCG	31	3	$116,293.54	$3,751.40
TOTAL	**31**	**3***	**$116,293.54**	**$3,751.40**

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

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Appendix P

Fiscal Year 2017 Annual Review of Allergen Immunotherapies and 30-Day Notice to Prior Authorize Odactra™ (House Dust Mite Allergen Extract)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Grastek® (Timothy Grass Pollen Allergen Extract) Approval Criteria:

1. Member must be 5 years of age or older; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies for Timothy grass or cross-reactive grass pollen (cool season grasses); and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 12 weeks prior to the start of the grass pollen season (November 15th) and continue throughout the season; and
7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and
9. Initial approvals will be for the duration of six months of therapy to include 12 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Ragwitek® (Short Ragweed Pollen Allergen Extract) Approval Criteria:

1. Member must be 18 years of age or older; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies to short ragweed pollen; and

3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis symptoms; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 12 weeks prior to the start of ragweed pollen season (May 15th) and continue throughout the season; and
7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and
9. Initial approvals will be for the duration of six months of therapy to include 12 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) Approval Criteria:

1. Member must be 10 years of age or older; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies to one of the five grass pollens contained in Oralair®; and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 16 weeks prior to the start of the grass pollen season (October 15th) and continue throughout the season; and

7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and
9. Initial approvals will be for the duration of six months of therapy to include 16 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Utilization of Allergen Immunotherapies: Fiscal Year 2017

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	1	7	$1,855.05	$265.01	$8.83	210	210
2017	2	17	$5,504.21	$323.78	$10.79	510	510
% Change	**100.00%**	**142.90%**	**196.70%**	**22.20%**	**22.20%**	**142.90%**	**142.90%**
Change	**1**	**10**	**$3,649.16**	**$58.77**	**$1.96**	**300**	**300**

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

Demographics of Members Utilizing Allergen Immunotherapies

- Due to the small number of members utilizing allergen immunotherapies during fiscal year 2017, detailed demographic information could not be provided.

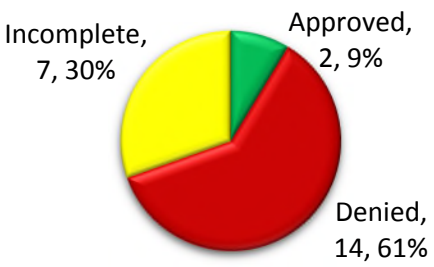
Top Prescriber Specialties of Allergen Immunotherapies by Number of Claims

- The only prescriber specialty listed on paid pharmacy claims for allergen immunotherapies during fiscal year 2017 was an allergist.

Prior Authorization of Allergen Immunotherapies

There were 23 prior authorization requests submitted for allergen immunotherapies during fiscal year 2017. The following chart shows the status of the submitted petitions.

Status of Petitions



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

New FDA Approval(s):

- **March 2017:** The U.S. Food and Drug Administration (FDA) approved Odactra™ for the treatment of house dust mite (HDM)-induced nasal inflammation (allergic rhinitis), with or without eye inflammation (conjunctivitis), in patients 18 to 65 years of age. This is the first approval of an allergen extract to be administered sublingually for this indication. Odactra™ exposes patients to HDM allergens, gradually training the immune system in order to reduce the severity and frequency of eye and nasal allergy symptoms. It is recommended for patients to dissolve one tablet under the tongue daily, and the tablets are taken year round.

Other News:

- **February 2017:** Findings from a clinical trial evaluating the effect of two years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at three years were published in the *Journal of the American Medical Association*. The findings of the trial suggest that three years of treatment with sublingual immunotherapy (SLIT) are necessary for long-term control of moderate-to-severe allergic rhinitis. Two years of SLIT for allergic rhinitis are no more effective than placebo at relieving symptoms one year after the end of treatment for patients with allergy to grass pollen. Subcutaneous immunotherapy (SCIT) is established as a highly effective treatment for rhinitis symptoms and SLIT is a more recent alternative. The authors stated that "three years of continuous treatment with immunotherapy via either delivery method modifies the underlying course of the disease with long-term remission of symptoms for several years after stopping treatment." The researchers designed a randomized, double-blind, placebo-controlled trial to study the effects of two years of SLIT on allergic rhinitis as long-term treatment is expensive and inconvenient for the patient. A total of 106 patients were randomly assigned to one of three groups: SLIT tablets plus placebo injections, SCIT injections plus placebo tablets, or placebo tablets plus placebo injections. Patients had to be 18 to 65 years of age with at least a two year history of moderate-to-severe grass pollen-induced allergic rhinitis. The primary endpoint was the difference between SLIT and placebo to a grass pollen allergen challenge one year after the end of treatment, as measured by the Total Nasal Symptom Score (TNSS), a questionnaire in which patients are asked to rate their symptoms, ranging from 0 (none) to 12 (maximum intensity). Scores of seven or greater are indicative of moderate-to-intense severity. Out of the 106 patients enrolled in the study, 92 continued to the primary end point evaluation three years later. At the 3-year follow-up examination one year after the end of treatment, mean TNSS scores among the 92 patients were 4.55 (95% CI, 3.67 - 5.43) in the SLIT group, 4.82 (95% CI, 3.90 - 5.74) in the placebo group, and 3.96 (95% CI, 3.21 - 4.71) in the SCIT group. There were no significant differences between the placebo group and the treatment groups, or between the two treatment groups.
- **March 2017:** A focused allergen immunotherapy practice parameter update was published in the *Annals of Allergy, Asthma, and Immunology* to provide guidance for effective, safe, and appropriate administration of the FDA-approved SLIT formulations.

At the time of the writing, there were only three FDA approved sublingual tablet formulations (short ragweed, Timothy pollen, and 5-grass pollen). The following recommendations were made:

- Summary Statement 1: It is recommended to only use FDA-approved SLIT products for the treatment of allergic rhinitis/rhinoconjunctivitis and not for other related or unrelated conditions. (Strength of Recommendation: Strong; Evidence: A/B)
- Summary Statement 2: SLIT may not be suitable in patients with certain medical conditions, especially those that may reduce the patient's ability to survive a systemic reaction or the resultant treatment of the systemic reaction. (Strength of Recommendation: Strong; Evidence: D)
- Summary Statement 3: The FDA-approved SLIT-products should be used very cautiously in patients who are pregnant or breastfeeding as there is insufficient data regarding the safety of initiating or continuing SLIT during pregnancy or breastfeeding. (Strength of Recommendation: Weak; Evidence: C)
- Summary Statement 4: There are no direct comparisons between the same allergen extract administered as a SLIT tablet versus an aqueous SLIT extract and it is unknown whether equal efficacy and safety exists when using similar doses of the two preparations. It is recommended not to assume dosing equivalence between SLIT tablets and extracts of the same allergen. (Strength of Recommendation: Weak; Evidence: C)
- Summary Statement 5: The patient's first dose of SLIT should be administered in a medical facility under the supervision of a physician or other health care professional with experience in the diagnosis and treatment of anaphylaxis. (Strength of Recommendation: Strong; Evidence: D)
- Summary Statement 6: Patients receiving SLIT tablets should be prescribed epinephrine and trained how to use the device. (Strength of Recommendation: Strong; Evidence: D)
- Summary Statement 7: A patient's SLIT dose should be reduced if they have missed treatment for more than seven days. (Strength of Recommendation: Weak; Evidence: D)
- Summary Statement 8: Patients receiving SLIT therapy should be scheduled for regular follow-up care with a specialist trained in the evaluation of patients with allergic conditions to monitor efficacy and safety and as a strategy for optimizing adherence. (Strength of Recommendation: Moderate; Evidence: D)
- Summary Statement 9: Off-label use of aqueous SLIT extracts or any other non-FDA approved SLIT formulation is not endorsed. (Strength of Recommendation: Strong; Evidence: D)

- **April 2017:** Circassia Pharmaceuticals announced top-line results from its investigational HDM allergy immunotherapy Phase 2b field study. Both the active treatment and placebo greatly reduced subjects' allergy symptoms and rescue medications during the study. Therefore, the treatment did not show a significant effect compared to placebo and the study did not meet its primary endpoint. The immunotherapy was well

tolerated with a highly favorable safety profile. Following these results, Circassia will make no further investment in its allergy programs.

Odactra™ (House Dust Mite Allergen Extract) Product Summary[5]

Indication(s): Odactra™ (house dust mite allergen extract) is an allergen extract indicated as immunotherapy for HDM-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* HDM, or skin testing to licensed HDM allergen extracts. Odactra™ is approved for use in adults 18 to 65 years of age.

Dosing:

- Odactra™ is supplied as 12 SQ-HDM tablets in three blister packages containing 10 sublingual tablets per package (30 tablets total). SQ-HDM is the dose unit for Odactra™. SQ is a method of standardization of biological potency, major allergen content, and complexity of the allergen extract.
- The recommended dose is one tablet daily. Odactra™ is for sublingual use only.
- The tablet should be placed immediately under the tongue where it will dissolve within 10 seconds. Patients should not swallow for at least one minute.
- The first dose should be administered under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Patients should be observed for at least 30 minutes following the first dose.

Mechanism of Action: The precise mechanism(s) of action of allergen immunotherapy have not been fully established.

Boxed Warning: Severe Allergic Reactions

- Odactra™ can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. Odactra™ should not be administered to patients with severe, unstable, or uncontrolled asthma. Patients should be observed for at least 30 minutes in the office following the initial dose. Patients should be prescribed auto-injectable epinephrine and should receive instruction and training on its appropriate use. Patients should be instructed to seek immediate medical care upon use of epinephrine. Odactra™ may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. Odactra™ may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Contraindication(s):

- Severe, unstable, or uncontrolled asthma
- History of any severe, systemic allergic reaction or any severe, local reaction to sublingual allergen immunotherapy
- History of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients contained in the product

Warnings and Precautions:

- Severe Allergic Reactions: Odactra™ can cause systemic allergic reactions including anaphylaxis, which may be life-threatening. Odactra™ can also cause severe, local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening.
- Epinephrine: Patients receiving Odactra™ should be prescribed auto-injectable epinephrine. Odactra™ may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include, but are not limited to, markedly compromised lung function, unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. Odactra™ may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine, including beta-adrenergic blockers, alpha-adrenergic blockers, ergot alkaloids, tricyclic antidepressants, levothyroxine, monoamine oxidase inhibitors, certain antihistamines, cardiac glycosides, and diuretics.
- Upper Airway Compromise: Odactra™ can cause local reactions in the mouth or throat that could compromise the upper airway. Discontinuation of Odactra™ should be considered in patients who experience persistent or escalating adverse reactions in the mouth or throat.
- Eosinophilic Esophagitis: Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. In patients who experience severe or persistent gastroesophageal symptoms including dysphagia or chest pain, Odactra™ should be discontinued and a diagnosis of eosinophilic esophagitis should be considered.
- Asthma: Odactra™ should be withheld if the patient is experiencing an acute asthma exacerbation. Patients who have recurrent asthma exacerbations should be re-evaluated and discontinuation of Odactra™ should be considered.
- Concomitant Allergen Immunotherapy: Odactra™ has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.
- Oral Conditions: Treatment with Odactra™ should be stopped in patients with oral inflammation or oral wounds to allow complete healing of the oral cavity.

Adverse Reactions: The most common adverse reactions reported in at least 10% of subjects treated with Odactra™ were:

- Throat Irritation/Tickle
- Itching in the Mouth
- Itching in the Ear
- Swelling of the Uvula/Back of the Mouth
- Swelling of the Lips
- Swelling of the Tongue
- Nausea
- Tongue Pain
- Throat Swelling
- Tongue Ulcer/Sore on the Tongue
- Stomach Pain
- Mouth Ulcer/Sore in the Mouth
- Taste Alteration/Food Tastes Different

Use in Specific Populations:

- Pregnancy: The available data on Odactra™ administered to pregnant women are insufficient to inform associated risks in pregnancy. In a fetal/embryo developmental toxicity study performed in mice, administration of Odactra™ during gestation did not reveal adverse developmental outcomes in fetuses.
- Lactation: Data are not available to assess the effects of Odactra™ on the breastfed child or on milk production and excretion in the nursing woman.
- Pediatric Use: The safety and effectiveness of Odactra™ have not been established in persons younger than 18 years of age.
- Geriatric Use: The safety and effectiveness of Odactra™ have not been established in persons older than 65 years of age.

Efficacy:

- The efficacy of Odactra™ for the treatment of HDM-induced allergic rhinitis was investigated in two double-blind, placebo-controlled, randomized clinical field efficacy studies (Studies 1 and 2).
- Study 1 was a 12-month double-blind, placebo-controlled, randomized field efficacy study, that compared the efficacy of Odactra™ (N=741) to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects enrolled in the study were 12 to 85 years of age with a history of symptomatic allergic rhinitis and sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE testing. Subjects were required to be symptomatic and could not be taking symptom-relieving allergy medications at enrollment. The efficacy of Odactra™ was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS), and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms were individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects were allowed to take symptom-relieving allergy medications (i.e., oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid. The primary endpoint was the difference between the treatment and placebo groups in the average TCRS during approximately the last eight weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS.
- Study 2 was a double-blind, placebo-controlled, randomized field efficacy study comparing Odactra™ (N=318) to placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Adult subjects 18 through 66 years of age with a history of symptomatic allergic rhinitis when exposed to house dust and sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE testing were included in the study. At study entry, subjects were required to be

symptomatic despite taking symptom-relieving allergy medications during the baseline period. The primary efficacy endpoint was the difference relative to placebo in the average TCRS during the last eight weeks of treatment.

Study	Primary Endpoint	Odactra™ Score (N)	Placebo Score (N)	Treatment Difference*	Difference Relative to Placebo¥	
					Estimate	(95% CI)
1	TCRS	4.10 (566)	4.95 (620)	-0.80	-17.2%	(-25.0%, -9.7%)
2	TCRS	5.71 (318)	6.81 (338)	-1.09	-16.1%	(-25.8%, -5.7%)

N = number, TCRS = Total Combined Rhinitis Score, CI = confidence interval
*Treatment Difference = Odactra™ - Placebo
¥Difference relative to placebo computed as: (Odactra™ – placebo)/placebo x 100.

Cost: Information regarding the cost of Odactra™ is currently unavailable.

Recommendations[6,7,8]

The College of Pharmacy recommends the prior authorization of Odactra™ (house dust mite allergen extract) with the following criteria:

Odactra™ (House Dust Mite Allergen Extract) Approval Criteria:

1. Member must be 18 to 65 years of age; and
2. Member must have a positive skin test (labs required) to licensed house dust mite allergen extracts or *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites; and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each; and
    b. **Montelukast:** One 14-day trial in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each; and
6. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
7. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
8. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
9. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist; and
10. A quantity limit of one tablet daily will apply.
11. Initial approvals will be for the duration of six months of therapy, at which time the prescriber must verify the patient is responding well to Odactra™ therapy. Additionally, compliance will be evaluated for continued approval.

The College of Pharmacy also recommends updating the existing prior authorization criteria of Grastek® (Timothy grass pollen allergen extract), Ragwitek® (short ragweed pollen allergen extract), and Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue grass mixed pollens allergen extract) to include an upper limit age restriction of 65 years of age, as shown in red, based on FDA approved indication:

Grastek® (Timothy Grass Pollen Allergen Extract) Approval Criteria:

1. Member must be 5 to 65 years of age; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies for Timothy grass or cross-reactive grass pollen (cool season grasses); and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 12 weeks prior to the start of the grass pollen season (November 15th) and continue throughout the season; and
7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and
9. Initial approvals will be for the duration of six months of therapy to include 12 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Ragwitek® (Short Ragweed Pollen Allergen Extract) Approval Criteria:

1. Member must be 18 to 65 years of age; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies to short ragweed pollen; and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis symptoms; and

5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 12 weeks prior to the start of ragweed pollen season (May 15th) and continue throughout the season; and
7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and
9. Initial approvals will be for the duration of six months of therapy to include 12 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as "allergy shots"; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Allergen Extract) Approval Criteria:

1. Member must be 10 to 65 years of age; and
2. Member must have a positive skin test (labs required) or *in vitro* testing for pollen specific IgE antibodies to one of the five grass pollens contained in Oralair®; and
3. Member must not have severe uncontrolled asthma; and
4. Member must have failed conservative attempts to control allergic rhinitis; and
5. Member must have failed pharmacological agents used to control allergies including the following (dates and duration of trials must be indicated on the prior authorization request):
    a. **Antihistamines:** Trials of two different products for 14 days each during a previous season; and
    b. **Montelukast:** One 14-day trial during a previous season in combination with an antihistamine; and
    c. **Intranasal corticosteroids:** Trials of two different products for 21 days each during a previous season; and
6. Treatment must begin greater than or equal to 16 weeks prior to the start of the grass pollen season (October 15th) and continue throughout the season; and
7. The first dose must be given in the physician's office, and the member must be observed for at least 30 minutes post dose; and
8. A quantity limit of one tablet daily will apply; and

9. Initial approvals will be for the duration of six months of therapy to include 16 weeks prior to the season and continue throughout the season; and
10. Member must not be allergic to other allergens for which they are receiving treatment via subcutaneous immunotherapy also known as “allergy shots”; and
11. Member or family member must be trained in the use of an auto-injectable epinephrine device and have such a device available for use at home; and
12. Prescriber must be an allergist, immunologist, or be an advanced care practitioner with a supervising physician that is an allergist or immunologist.

Utilization Details of Allergen Immunotherapies: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
GRASTEK SUB 2800BAU	10	1	$2,746.35	$9.15	$274.64
ORALAIR SUB 300 IR	7	1	$2,757.86	$13.13	$393.98
TOTAL	**17**	**2***	**$5,504.21**	**$10.79**	**$323.78**

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

[1] U.S. Food and Drug Administration (FDA). FDA News Release: FDA Approved Odactra for House Dust Mite Allergies. Available online at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm544330.htm. Issued 03/01/2017. Last accessed 07/07/2017.
[2] MacReady, Norra. Allergic Rhinitis: 3 Years of Immunotherapy Needed. *Medscape*. Available online at: http://www.medscape.com/viewarticle/875799. Issued 02/14/2017. Last accessed 08/15/2017.
[3] Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual Immunotherapy: A Focused Allergen Immunotherapy Practice Parameter Update. *Annals of Allergy, Asthma, & Immunology* 2017; 118(2017):276-282.
[4] Circassia Press Release. Circassia Announces Top-Line Results from House Dust Mite Allergy Field Study. Available online at: http://www.circassia.com/media/press-releases/circassia-announces-top-line-results-from-house-dust-mite-allergy-field-study/. Issued 04/18/2017. Last accessed 07/07/2017.
[5] Odactra™ Prescribing Information. Merck & Co., Inc. Available online at: https://www.fda.gov/downloads/biologicsbloodvaccines/allergenics/ucm544382.pdf. Last revised 03/2017. Last accessed 09/06/2017.
[6] Grastek® Prescribing Information. Merck & Co., Inc. Available online at: https://www.grastek.com/app/uploads/sites/3/2016/12/grastek_pi.pdf. Last revised 09/2016. Last accessed 09/19/2017.
[7] Ragwitek® Prescribing Information. Merck & Co., Inc. Available online at: https://www.ragwitek.com/app/uploads/sites/4/2016/12/ragwitek_pi.pdf. Last revised 09/2016. Last accessed 09/19/2017.
[8] Oralair® Prescribing Information. Stallergenes S.A. Available online at: https://www.oralairhcp.com/wp-content/uploads/2017/06/ORALAIR_Prescribing_Information.pdf. Last accessed 09/19/2017.

Appendix Q

Fiscal Year 2017 Annual Review of Topical Corticosteroids and 30-Day Notice to Prior Authorize MiCort™ HC (Hydrocortisone Acetate 2.5% Cream)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Tier-1 products are covered with no prior authorization necessary.

Tier-2 Topical Corticosteroid Approval Criteria:

1. Documented trials of all Tier-1 topical corticosteroids of similar potency in the past 30 days that did not yield adequate relief; and
2. If Tier-1 trials are completed and do not yield adequate relief, the member must also provide a patient-specific, clinically significant reason for requesting a Tier-2 in the same potency instead of trying a higher potency; and
3. When the same medication is available in Tier-1, a patient-specific, clinically significant reason must be provided for using a special dosage formulation of that medication in Tier-2 (foams, shampoos, sprays, kits, etc.); and
4. Topical corticosteroid kits require tier trials and a patient-specific, clinically significant reason for use of the kit over other standard formulations.

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**
halobetasol propionate (**Ultravate®**)	**C**	clobetasol propionate 0.05% (**Olux®**)	**F**
		clobetasol propionate 0.05% (**Olux-E®**)	**F**
		clobetasol propionate 0.05% (**Temovate®**)	**C,O,G,So**
		desoximetasone 0.25% (**Topicort®**)	**C,O,Spr**
		desoximetasone 0.05% (**Topicort®**)	**G**
		diflorasone diacetate 0.05% (**Apexicon®**)	**C**
		diflorasone diacetate 0.05% (**Apexicon E®**)	**C,O**
		fluocinonide 0.05%	**G**
		fluocinonide 0.1% (**Vanos®**)	**C**
		flurandrenolide tape (**Cordran®**)	**Tape**
		halcinonide (**Halog®**)	**C,O**
		halobetasol propionate 0.05% (**Ultravate®**)	**L,O**

Topical Corticosteroids			
Tier-1		**Tier-2**	
		halobetasol propionate/lactic acid (**Ultravate X®**)	**C**
Medium/High to Medium Potency			
betamethasone dipropionate	**L**	betamethasone dipropionate 0.05% (**Sernivo™**)	**Spr**
betamethasone valerate 0.1% (**Beta-Val®**)	**C,O,L**	betamethasone dipropionate/calcipotriene	**O,Sus,Spr**
fluticasone propionate (**Cutivate®**)	**C,O**	betamethasone valerate 0.12% (**Luxiq®**)	**F**
mometasone furoate (**Elocon®**)	**C,L**	calcipotriene/betamethasone dipropionate (**Enstilar®**)	**F**
triamcinolone acetonide	**C,O,L**	desoximetasone 0.05% (**Topicort LP®**)	**C,O**
		fluocinolone acetonide 0.025% (**Synalar®**)	**C,O**
		fluocinonide emollient (**Lidex E®**)	**C**
		flurandrenolide 0.05%	**C,L,O**
		fluticasone propionate (**Cutivate®**)	**L**
		hydrocortisone butyrate 0.1%	**C,O,So**
		hydrocortisone probutate (**Pandel®**)	**C**
		hydrocortisone valerate 0.2% (**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,L**
hydrocortisone acetate 2.5%	**C,O,L**	desonide 0.05% (**Desonate®**)	**G**
hydrocortisone/urea (**U-Cort®**)	**C**	desonide 0.05% (**Verdeso®**)	**F**
		desonide emollient	**C,O**
		fluocinolone acetonide 0.01% (**Capex®**)	**Sh**
		fluocinolone acetonide 0.01%	**Oil**
		fluocinolone acetonide 0.01% (**Synalar®**)	**So**
		hydrocortisone 2.5% (**Texacort®**)	**So**
		hydrocortisone/pramoxine (**Pramosone®**)	**C,L**

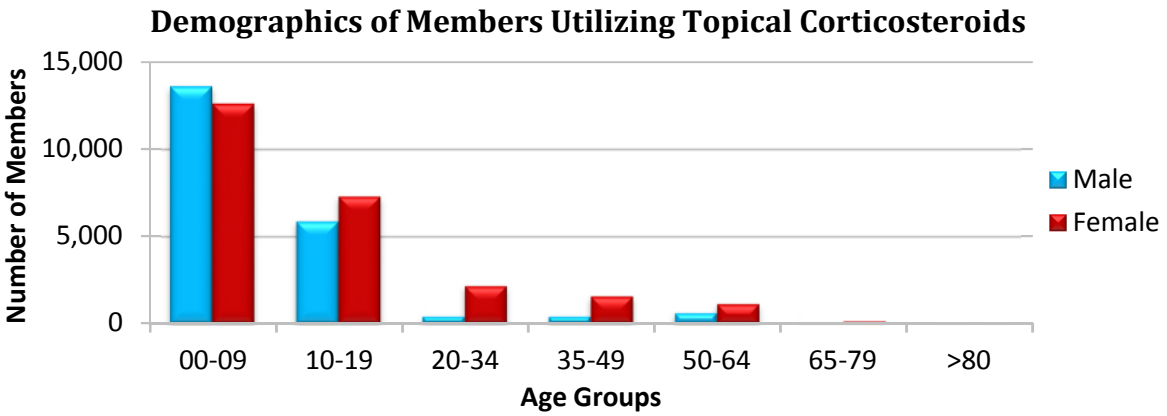
C= Cream; O = Ointment; L = Lotion; G = Gel, Sh = Shampoo; So = Solution; Spr = Spray; Sus = Suspension; F = Foam
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

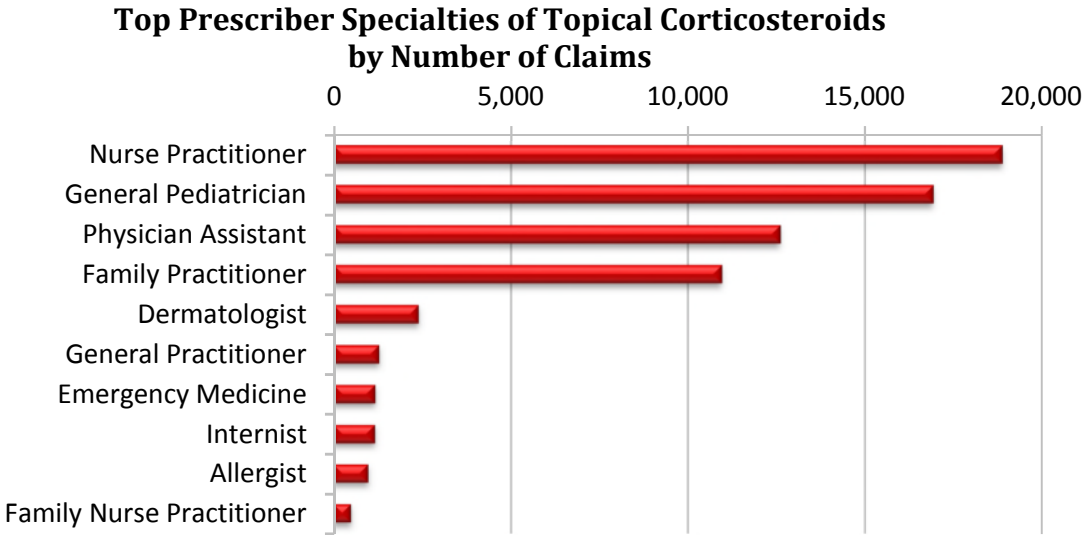
Utilization of Topical Corticosteroids: Fiscal Year 2017

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	46,501	70,951	$1,549,800.82	$21.84	$1.36	4,406,459	1,140,457
2017	45,843	69,158	$1,230,301.46	$17.79	$1.13	4,232,610	1,093,377
% Change	**-1.40%**	**-2.50%**	**-20.60%**	**-18.50%**	**-16.90%**	**-3.90%**	**-4.10%**
Change	**-658**	**-1,793**	**-$319,499.36**	**-$4.05**	**-$0.23**	**-173,849**	**-47,080**

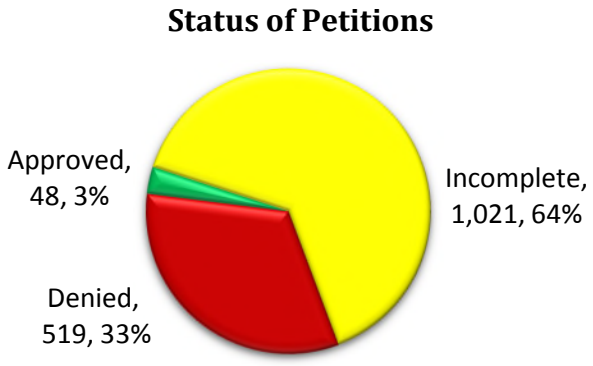
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.





Prior Authorization of Topical Corticosteroids

There were 1,588 prior authorization requests submitted for topical corticosteroids during fiscal year 2017. The following chart shows the status of the submitted petitions.



Market News and Updates[1,2,3]

Patent Expiration(s):

- Capex® shampoo, Texacort® 2.5% topical solution, Halog®, Cordran®, Pandel®, and U-Cort® are not available generically, but have no unexpired patents or exclusivities.
- Desonate® (desonide 0.05% gel): August 2020
- Topicort® (desoximetasone 0.25% spray): September 2028
- Verdeso® (desonide 0.05% foam): November 2028
- Sernivo™ (betamethasone dipropionate topical spray 0.05%): August 2030
- Ultravate® (halobetasol lotion 0.05%): June 2033

Product Update:

MiCort™ HC (hydrocortisone acetate) 2.5% cream was approved by the U.S. Food and Drug Administration (FDA) as an abbreviated new drug application (ANDA) in February 2001; however, the market start date for MiCort™ HC was September of 2016. MiCort™ HC is a topical corticosteroid indicated for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses. It is available as a topical external 2.5% w/w cream and should be applied to the affected area as a thin film two to four times daily depending on the severity of the condition. The wholesale acquisition cost (WAC) for MiCort™ HC is $7.42 per gram or $210.73 per 28.4 gram tube with applicator. Proctosol-HC® (hydrocortisone) 2.5% cream comparatively has a national average drug acquisition cost (NADAC) of $1.40 per gram or $39.69 for a 28.35 gram tube with applicators and is currently available without prior authorization.

Recommendations

The College of Pharmacy recommends the prior authorization of MiCort™ HC (hydrocortisone acetate) 2.5% cream with the criteria noted in red:

MiCort™ HC (Hydrocortisone Acetate) 2.5% Cream Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use Proctosol-HC® (hydrocortisone) 2.5% cream.

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

Topical Corticosteroid PBPA Tier Chart and Criteria Recommendations:

1. The creation of a third Tier to account for very high net cost products.
2. Move Aclovate® (alclometasone dipropionate cream and ointment) from Tier-1 to Tier-2 under Low Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.
3. Move Derma-Smooth® and Derma-Smooth FS® (fluocinolone acetonide 0.01% oil) from Tier-2 to Tier-3 under Low Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.
4. Move Desonate® (desonide 0.05% gel) and Capex® (fluocinolone acetonide 0.01% shampoo) from Tier-2 to Tier-1 under Low Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.

5. Move Sernivo™ (betamethasone dipropionate 0.05% spray) spray and Westcort® (hydrocortisone valerate 0.2% cream and ointment) from Tier-2 to Tier-3 under Medium/High to Medium Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.
6. Move Temovate® (clobetasol propionate 0.05% cream and solution) from Tier-2 to Tier-1 under the Ultra-high to High Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.
7. Move Clobex® (clobetasol propionate 0.05% shampoo and spray), Olux-E® and Olux® (clobetasol propionate 0.05% foam), Temovate® (clobetasol propionate 0.05% ointment), Topicort® (desoximetasone 0.25% cream, ointment, and spray) from Tier-2 to Tier-3 under the Ultra-high to High Potency of the Topical Corticosteroid PBPA Tier Chart based on cost.

Tier-1 products are covered with no prior authorization necessary.

Tier-2 Topical Corticosteroid Approval Criteria:

1. Documented trials of all Tier-1 topical corticosteroids of similar potency in the past 30 days that did not yield adequate relief; and
2. If Tier-1 trials are completed and do not yield adequate relief, the member must also provide a patient-specific, clinically significant reason for requesting a Tier-2 in the same potency instead of trying a higher potency; and
3. When the same medication is available in Tier-1, a patient-specific, clinically significant reason must be provided for using a special dosage formulation of that medication in Tier-2 (foams, shampoos, sprays, kits, etc.); and
4. Topical corticosteroid kits require tier trials and a patient-specific, clinically significant reason for use of the kit over other standard formulations.

Tier-3 Topical Corticosteroid Approval Criteria:

1. Documented trials of all Tier-1 and Tier-2 topical corticosteroids of similar potency in the past 90 days that did not yield adequate relief; and
2. If Tier-1 and Tier-2 trials are completed and do not yield adequate relief, the member must also provide a patient-specific, clinically significant reason for requesting a Tier-3 in the same potency instead of trying a higher potency; and
3. When the same medication is available in Tier-1 or Tier-2, a patient-specific, clinically significant reason must be provided for using a special dosage form of that medication in Tier-3 (foams, shampoos, sprays, kits, etc.); and
4. Topical corticosteroid kits require tier trials and a patient-specific, clinically significant reason for use of the kit over other standard formulations.

Topical Corticosteroids					
Tier-1		**Tier-2**		**Tier-3**	
Ultra-High to High Potency					
augmented betamethasone dipropionate (**Diprolene AF®**)	**C**	amcinonide	**C,O,L**	**clobetasol propionate 0.05% (Clobex®)**	**Sh,Spr**
augmented betamethasone dipropionate (**Diprolene®**)	**G**	augmented betamethasone dipropionate (**Diprolene®**)	**O,L**	**clobetasol propionate 0.05% (Olux®, Olux-E®)**	**F**
betamethasone dipropionate (**Diprosone®**)	**O**	betamethasone dipropionate (**Diprosone®**)	**C**	**clobetasol propionate 0.05% (Temovate®)**	**O**
clobetasol propionate 0.05% (Temovate®)	**C,So**	clobetasol propionate 0.05% (**Clobex®**)	**L**	**desoximetasone 0.25% (Topicort®)**	**C,O,Spr**
fluocinonide 0.05%	**C,O,So**	clobetasol propionate 0.05% (**Temovate®**)	**G**		
halobetasol propionate (**Ultravate®**)	**C**	desoximetasone 0.05% (**Topicort®**)	**G**		
		diflorasone diacetate 0.05% (**Apexicon®**)	**C**		
		diflorasone diacetate 0.05% (**Apexicon E®**)	**C,O**		
		fluocinonide 0.05%	**G**		
		fluocinonide 0.1% (**Vanos®**)	**C**		
		flurandrenolide tape (**Cordran®**)	**Tape**		
		halcinonide (**Halog®**)	**C,O**		
		halobetasol propionate 0.05% (**Ultravate®**)	**L,O**		
		halobetasol propionate/lactic acid (**Ultravate X®**)	**C**		
Medium/High to Medium Potency					
betamethasone dipropionate	**L**	betamethasone dipropionate/calcipotriene (**Taclonex®**)	**O,Sus, Spr**	**betamethasone dipropionate 0.05% (Sernivo™)**	**Spr**
betamethasone valerate 0.1% (**Beta-Val®**)	**C,O,L**	betamethasone valerate 0.12% (**Luxiq®**)	**F**	**hydrocortisone valerate 0.2% (Westcort®)**	**C,O**
fluticasone propionate (**Cutivate®**)	**C,O**	calcipotriene/betamethasone dipropionate (**Enstilar®**)	**F**		
mometasone furoate (**Elocon®**)	**C,L**	desoximetasone 0.05% (**Topicort LP®**)	**C,O**		
triamcinolone acetonide	**C,O,L**	fluocinolone acetonide 0.025% (**Synalar®**)	**C,O**		
		fluocinonide emollient (**Lidex E®**)	**C**		
		flurandrenolide 0.05%	**C,L,O**		
		fluticasone propionate	**L**		
		hydrocortisone butyrate 0.1%	**C,O,So**		
		hydrocortisone probutate (**Pandel®**)	**C**		
		mometasone furoate 0.1%	**O**		
		prednicarbate (**Dermatop®**)	**O,C**		

Topical Corticosteroids					
Tier-1		**Tier-2**		**Tier-3**	
		triamcinolone acetonide (**Kenalog®**)	**Spr**		
Low Potency					
desonide 0.05% (Desonate®)	**G**	**alclometasone dipropionate (Aclovate®)**	**C,O**	**fluocinolone acetonide 0.01% (Derma-Smoothe®; Derma-Smoothe FS®)**	**Oil**
fluocinolone acetonide 0.01% (Capex®)	**Sh**	clocortolone pivalate (**Cloderm®**)	**C**		
fluocinolone acetonide 0.01% (**Synalar®**)	**C**	desonide 0.05% (**Verdeso®**)	**F**		
hydrocortisone acetate 2.5%	**C,O,L**	desonide emollient	**C,O**		
hydrocortisone/urea (**U-Cort®**)	**C**	fluocinolone acetonide 0.01% (**Synalar®**)	**So**		
		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
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Utilization Details of Topical Corticosteroid Products: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
TIER-1 MEDICATIONS						
LOW-POTENCY PRODUCTS						
HYDROCORT CRE 2.5%	4,339	3,428	$39,973.64	$0.65	$9.21	3.25%
HYDROCORT OIN 2.5%	2,562	1,719	$28,269.00	$0.91	$11.03	2.30%
HYDROCORT CRE 1%	2,019	1,730	$17,985.26	$0.95	$8.91	1.46%
HYDROCORT LOT 2.5%	453	380	$10,437.95	$1.39	$23.04	0.85%
ALCLOMETASON CRE 0.05%	434	357	$36,924.70	$3.29	$85.08	3.00%
HYDROCORT OIN 1%	357	315	$3,674.18	$1.01	$10.29	0.30%
ALCLOMETASON OIN 0.05%	228	139	$15,371.22	$3.27	$67.42	1.25%
SUBTOTAL	**10,392**	**8,068**	**$152,635.95**	**$1.10**	**$14.69**	**12.41%**
MEDIUM-HIGH TO MEDIUM POTENCY PRODUCTS						
TRIAMCINOLON CRE 0.1%	26,064	20,045	$308,634.44	$0.74	$11.84	25.09%
TRIAMCINOLON OIN 0.1%	10,547	7,757	$142,510.04	$0.79	$13.51	11.58%
TRIAMCINOLON CRE 0.025%	5,802	4,644	$63,231.82	$0.74	$10.90	5.14%
TRIAMCINOLON CRE 0.5%	2,932	2,303	$46,670.49	$1.21	$15.92	3.79%
TRIAMCINOLON OIN 0.025%	2,515	1,995	$33,724.55	$0.92	$13.41	2.74%
MOMETASONE CRE 0.1%	2,117	1,529	$40,034.91	$1.12	$18.91	3.25%
FLUTICASONE CRE 0.05%	1,330	979	$32,461.21	$1.43	$24.41	2.64%
TRIAMCINOLON OIN 0.5%	1,030	791	$21,489.44	$1.57	$20.86	1.75%
TRIAMCINOLON LOT 0.1%	632	513	$24,510.11	$2.05	$38.78	1.99%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
BETAMETH VAL CRE 0.1%	543	394	$17,555.09	$1.83	$32.33	1.43%
FLUTICASONE OIN 0.005%	426	257	$14,300.72	$1.64	$33.57	1.16%
TRIAMCINOLON LOT 0.025%	330	286	$12,836.15	$1.78	$38.90	1.04%
MOMETASONE SOL 0.1%	170	108	$3,106.40	$0.79	$18.27	0.25%
BETAMETH DIP LOT 0.05%	128	100	$5,586.73	$2.25	$43.65	0.45%
BETAMETH VAL OIN 0.1%	70	58	$2,449.43	$1.92	$34.99	0.20%
TRIANEX OIN 0.05%	27	18	$1,139.59	$1.52	$42.21	0.09%
BETAMETH VAL LOT 0.1%	16	13	$791.88	$2.47	$49.49	0.06%
SUBTOTAL	**54,679**	**41,790**	**$771,033.00**	**$0.88**	**$14.10**	**62.65%**
ULTRA-HIGH TO HIGH POTENCY PRODUCTS						
AUG BETAMET CRE 0.05%	911	653	$17,128.24	$1.09	$18.80	1.39%
FLUOCINONIDE CRE 0.05%	564	377	$33,263.75	$2.81	$58.98	2.70%
FLUOCINONIDE OIN 0.05%	533	302	$49,346.96	$4.56	$92.58	4.01%
BETAMETH DIP OIN 0.05%	518	366	$41,507.54	$4.57	$80.13	3.37%
FLUOCINONIDE SOL 0.05%	433	292	$32,551.90	$3.31	$75.18	2.65%
HALOBETASOL CRE 0.05%	196	123	$19,082.25	$5.55	$97.36	1.55%
FLUOCIN ACET CRE 0.01%	58	41	$5,066.34	$6.13	$87.35	0.41%
AUG BETAMET GEL 0.05%	21	16	$2,344.01	$4.72	$111.62	0.19%
SUBTOTAL	**3,234**	**2,170**	**$200,290.99**	**$3.23**	**$61.93**	**16.27%**
TIER-2 MEDICATIONS						
LOW-POTENCY PRODUCTS						
FLUOCIN ACET OIL SCALP	15	9	$2,337.82	$5.95	$155.85	0.19%
FLUOCIN ACET OIL 0.01%	8	6	$1,102.99	$4.95	$137.87	0.09%
DESONIDE LOT 0.05%	7	2	$1,886.96	$34.31	$269.57	0.15%
DESONIDE CRE 0.05%	3	1	$525.95	$5.84	$175.32	0.04%
DESOXIMETAS CRE 0.05%	3	2	$856.07	$15.56	$285.36	0.07%
DESOXIMETAS OIN 0.05%	3	2	$806.51	$13.44	$268.84	0.07%
FLUOCIN ACET SOL 0.01%	3	2	$348.02	$6.96	$116.01	0.03%
DESONATE GEL 0.05%	2	1	$1,011.16	$16.85	$505.58	0.08%
FLUOCIN ACET OIL 0.01% BDY	1	1	$163.20	$5.44	$163.20	0.01%
CAPEX SHA 0.01%	1	1	$407.04	$27.14	$407.04	0.03%
SUBTOTAL	**46**	**27**	**$9,445.72**	**$9.16**	**$205.34**	**0.76%**
MEDIUM-HIGH TO MEDIUM POTENCY PRODUCTS						
HC BUTYRATE SOL 0.1%	44	32	$5,201.94	$5.63	$118.23	0.42%
FLUOCINONIDE CRE-E 0.05%	22	17	$1,563.41	$3.64	$71.06	0.13%
HC BUTYRATE OIN 0.1%	3	1	$424.59	$4.72	$141.53	0.03%
HC VALERATE OIN 0.2%	1	1	$171.19	$11.41	$171.19	0.01%
SUBTOTAL	**70**	**51**	**$7,361.13**	**$5.05**	**$105.16**	**0.59%**
ULTRA-HIGH TO HIGH POTENCY PRODUCTS						
CLOBETASOL SOL 0.05%	496	350	$50,915.17	$5.14	$102.65	4.14%
CLOBETASOL GEL 0.05%	133	106	$19,910.99	$7.96	$149.71	1.62%
CLOBETASOL E CRE 0.05%	93	64	$8,574.71	$5.58	$92.20	0.70%
CLOBETASOL OIN 0.05%	6	1	$8,308.78	$50.66	$1,384.80	0.68%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
CLOBETASOL AER 0.05%	3	2	$649.98	$8.12	$216.66	0.05%
FLUOCINONIDE GEL 0.05%	2	1	$75.48	$3.77	$37.74	0.01%
TOPICORT SPR 0.25%	1	1	$517.51	$17.25	$517.51	0.04%
CLOBETASOL CRE 0.05%	1	1	$129.94	$18.56	$129.94	0.01%
CLOBETASOL AER 0.05%	1	1	$223.72	$15.98	$223.72	0.02%
CLOBETASOL SHA 0.05%	1	1	$228.39	$7.61	$228.39	0.02%
SUBTOTAL	**737**	**528**	**$89,534.67**	**$6.27**	**$121.49**	**7.29%**
TOTAL	**69,158**	**45,843***	**$1,230,301.46**	**$1.13**	**$17.79**	**100%**

*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: https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm?resetfields=1. Last revised 07/2017. Last accessed 08/25/2017.
[2] Drugs@FDA: FDA Approved Drug Products. Micort-HC. Available online at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=040396. Last accessed 09/11/17.
[3] MiCort™ HC Prescribing Information. Sebela Pharmaceuticals Inc. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3c634bbe-cf9b-0db5-e054-00144ff8d46c. Last revised 09/2016. Last accessed 09/11/2017.

Appendix R

Fiscal Year 2017 Annual Review of Bladder Control Medications and 30-Day Notice to Prior Authorize Noctiva™ (Desmopressin Acetate Nasal Spray)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Bladder Control Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
fesoterodine (Toviaz®)	tolterodine (Detrol®)	darifenacin (Enablex®)	oxybutynin patch (Oxytrol®)+
oxybutynin (Ditropan®)	trospium (Sanctura®)	mirabegron (Myrbetriq®)	
oxybutynin ER (Ditropan XL®)		oxybutynin gel (Gelnique®)	
		solifenacin (VESIcare®)	
		tolterodine ER (Detrol LA®)	
		trospium ER (Sanctura XR®)	

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
ER = extended release
+Unique criteria specific to Oxytrol® (oxybutynin patch) applies.

Bladder Control Medications Tier-2 Approval Criteria:

1. A trial of all Tier-1 medications that yielded an inadequate clinical response or adverse effects; or
2. A unique indication which the Tier-1 medications lack.

Bladder Control Medications Tier-3 Approval Criteria:

1. A trial of all Tier-1 and Tier-2 medications that yielded inadequate clinical response or adverse effects; or
2. A unique indication which the Tier-1 and Tier-2 medications lack.

Bladder Control Medications Special Prior Authorization (PA) Criteria:

1. **Oxytrol® (Oxybutynin Patch) Approval Criteria:**
   a. An FDA approved diagnosis of overactive bladder; and
   b. A patient-specific, clinically significant reason why all lower tiered medications are not appropriate for the member; and
   c. A quantity limit of 8 patches every 30 days will apply.

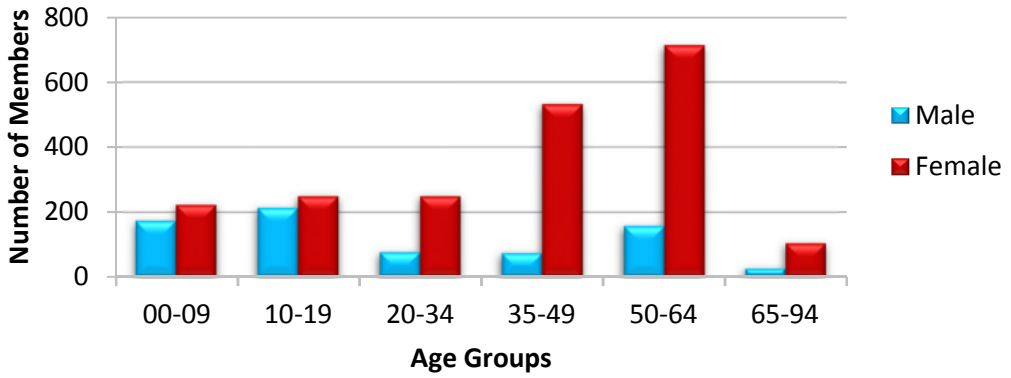
Utilization of Bladder Control Medications: Fiscal Year 2017

Comparison of Fiscal Years

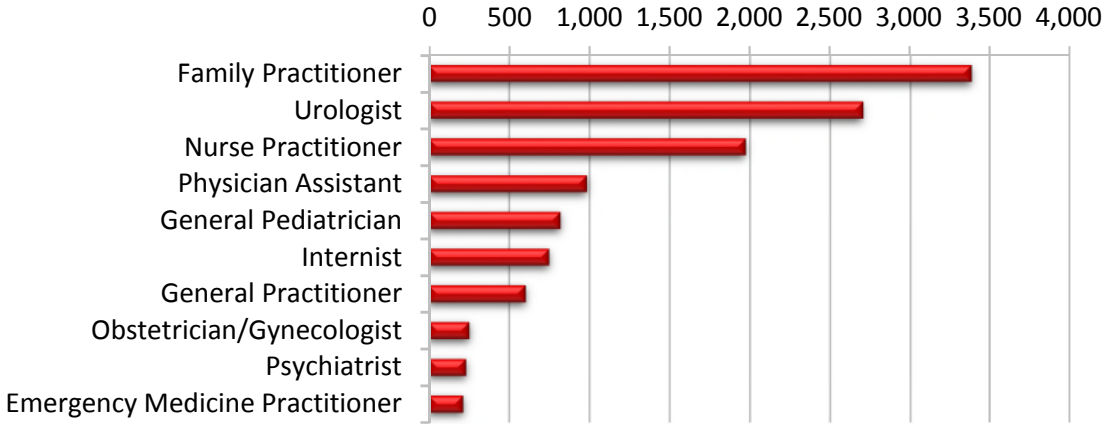
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	2,828	12,448	$671,254.32	$53.92	$1.69	900,663	397,805
2017	2,778	12,324	$657,578.02	$53.36	$1.66	878,601	397,267
% Change	**-1.80%**	**-1.00%**	**-2.00%**	**-1.00%**	**-1.80%**	**-2.40%**	**-0.10%**
Change	**-50**	**-124**	**-$13,676.30**	**-$0.56**	**-$0.03**	**-22,062**	**-538**

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

Demographics of Members Utilizing Bladder Control Medications



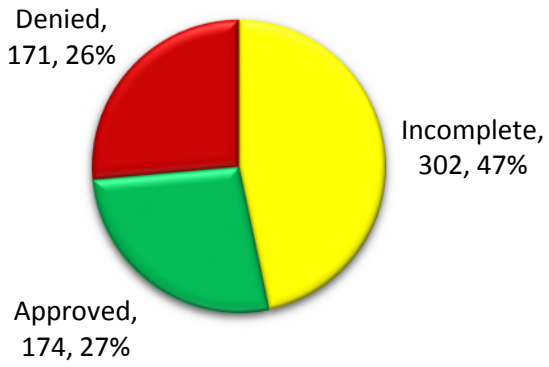
Top Prescriber Specialties of Bladder Control Medications by Number of Claims



Prior Authorization of Bladder Control Medications

There were 647 prior authorization requests submitted for the bladder control medications during fiscal year 2017. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2]

Anticipated Patent Expiration(s):

- VESIcare® (solifenacin): November 2018
- Oxytrol® (oxybutynin patch): April 2020
- Myrbetriq® (mirabegron): November 2023
- Toviaz® (fesoterodine): June 2027
- Gelnique® (oxybutynin gel): March 2031

News:

- **April 2017:** *The Journal of Clinical Pharmacology* published the results of a retrospective cohort study that examined the association between antimuscarinic use and the subsequent risk of depressive disorder. The study included 1,952 women with overactive bladder (OAB) syndrome who received antimuscarinics as the study cohort and 9,760 matched women with OAB who did not receive antimuscarinics as the comparison cohort. The mean ages of the study cohort and comparison cohort were 51.5 ± 16.7 and 51.5 ± 16.9 years, respectively. This population-based retrospective cohort study showed that women with OAB who received antimuscarinics were 1.38 times more likely to be diagnosed with subsequent depressive disorder compared with those women with OAB who did not receive antimuscarinics. The authors concluded that women with OAB who received antimuscarinics had a significantly higher risk of subsequent depressive disorder compared with those women with OAB who did not receive antimuscarinics. Based on this finding, the authors recommended that clinicians be alert to the relationship between antimuscarinic usage and depressive disorder in women with OAB.

Nocturnal Polyuria[3]

The normal pattern of urination is a decrease in urine output at nighttime, relative to daytime. Overproduction of urine at night, with a normal 24-hour urine output, is called nocturnal polyuria. The definition of nocturnal polyuria is age-dependent, and for older adults (greater than 65 years of age) it is defined as nocturnal urine volume greater than 33% of the 24-hour urine volume. Nocturnal polyuria may be due to age-related changes in the secretion and

action of arginine vasopressin (AVP). AVP, a peptide hormone secreted by the neurohypophyseal system, targets receptors in the renal distal tubules which control urine concentration. There is a daily cycle of AVP release in young, healthy subjects, with higher AVP plasma levels in the evening contributing to decreased nighttime urine output. The daily variation in AVP release is absent in many older individuals. Decreased solute excretion at night is another factor accounting for relatively low nocturnal urine output in healthy adults. Disorders in solute diuresis, associated with certain disease states, can lead to nocturnal polyuria. For example, heart failure or other edematous states causes third spacing of fluids which can mobilize into the vascular space at night (due to supine position) and lead to solute diuresis. Obstructive sleep apnea (OSA) may also cause nocturnal polyuria by release of atrial natriuretic peptide (ANP) due to negative intrathoracic pressure and stretching of the myocardium. ANP release causes vasodilation and inhibits aldosterone, resulting in increased sodium and water excretion. ANP levels are, however, reduced with use of continuous positive airway pressure (CPAP).

The link of inadequate nighttime levels of AVP or inadequate daily variation in AVP to nocturnal polyuria, makes desmopressin (1-deamino-8-D-arginine vasopressin, ddAVP) a logical treatment choice. As a neuropeptide differing from endogenous vasopressin by a two-amino acid substitution, ddAVP is a potent antidiuretic. Taken orally two hours prior to bedtime, ddAVP reduces nighttime urine production via increase in urine osmolality and resultant decrease in urine volume. However, with ongoing therapy or in patients 65 years of age or older, the risk of hyponatremia may be severe. Currently, Noctiva™ (desmopressin acetate nasal spray) is the only U.S. Food and Drug administration (FDA) approved treatment for nocturnal polyuria. While not FDA approved for nocturnal polyuria, oral desmopressin tablets are used off-label for the treatment of this condition.

Noctiva™ (Desmopressin Acetate Nasal Spray) Product Summary[4,5]

Indication(s): Noctiva™ (desmopressin acetate nasal spray) is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation of Use: Not studied in patients younger than 50 years of age.

Dosing:

- Noctiva™ is preservative-free nasal spray delivering 0.83mcg of desmopressin acetate or 1.66mcg of desmopressin acetate in each spray (0.1mL).
- It is available in a 3.5mL amber glass bottle containing 30 doses in addition to the initial priming (5 actuations) amount.
- It is recommended that Noctiva™ be stored upright and refrigerated before opening. After opening, it may be stored upright at room temperature. Noctiva™ should be discarded 60 days after opening.
- For patients younger than 65 years of age who are not at increased risk for hyponatremia, the recommended dose is one spray of 1.66mcg in either nostril nightly approximately 30 minutes before going to bed.

- For patients 65 years of age and older or younger patients at risk for hyponatremia, the recommended starting dose is one spray of 0.83mcg nightly in either nostril, which can be increased to one spray of 1.66mcg after at least 7 days, if needed, provided the serum sodium concentration has remained normal.
- Within 7 days and approximately one month after initiating, resuming, or increasing the dose of Noctiva™ serum sodium concentrations should be checked.
- Two sprays of Noctiva™ 0.83mcg are not interchangeable with one spray of Noctiva™ 1.66mcg.

Mechanism of Action: Desmopressin acetate is a synthetic analog of vasopressin, and acts as a selective agonist at V2 receptors on renal cells in the collecting ducts. This increases water re-absorption in the kidneys and reduces urine production.

Boxed Warning: Hyponatremia

- Noctiva™ can cause hyponatremia. Severe hyponatremia can be life-threatening, leading to seizures, coma, respiratory arrest, or death.
- Noctiva™ is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.
- Prescribers should ensure serum sodium concentrations are normal before patients start or resume Noctiva™. Serum sodium should be measured within seven days and approximately one month after initiating therapy or increasing the dose, and periodically during treatment. Serum sodium should be monitored more frequently in patients 65 years of age and older and in patients at increased risk of hyponatremia.
- If hyponatremia occurs, Noctiva™ may need to be temporarily or permanently discontinued.

Contraindication(s):

- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics
- Concomitant use with systemic or inhaled glucocorticoids
- Renal impairment with an estimated glomerular filtration rate (eGFR) below 50mL/min/1.73m^2
- Known or suspected syndrome of inappropriate antidiuretic hormone (SIADH) secretion
- During illnesses that can cause fluid or electrolyte imbalance, such as gastroenteritis, salt-wasting nephropathies, or systemic infection
- Congestive heart failure (CHF)
- Uncontrolled hypertension

Warnings and Precautions:

- <u>Risk of Hyponatremia:</u> Noctiva™ can cause hyponatremia. It is recommended that serum sodium levels be monitored. The frequency of monitoring should be based on the patient's risk for hyponatremia. Additionally, when Noctiva™ is administered, fluid

intake in the evening and night-time hours should be moderated to decrease the risk of hyponatremia.

- Fluid Retention: Noctiva™ can cause fluid retention, which can worsen underlying conditions that are susceptible to volume status, such as CHF.
- Concurrent Nasal Conditions: It is recommended that Noctiva™ be discontinued in patients with concurrent nasal conditions that may increase systemic absorption of Noctiva™ (e.g., atrophy of nasal mucosa, acute or chronic rhinitis), because the increased absorption may increase the risk of hyponatremia. Noctiva™ is not recommended for use in patients who require treatment with other drugs via the nasal route.

Adverse Reactions: The most common adverse reactions reported by at least 2% of patients with nocturia due to nocturnal polyuria who were treated with Noctiva™ and at a higher incidence with the 1.66mcg dose than with placebo include the following:

- Nasal Discomfort
- Nasopharyngitis
- Nasal Congestion
- Sneezing
- Hypertension/Blood Pressure Increased
- Back Pain
- Epistaxis
- Bronchitis
- Dizziness

Use in Specific Populations:

- Pregnancy: There are no data with Noctiva™ use in pregnant women to inform any drug-associated risks. Noctiva™ is not recommended for the treatment of nocturia in pregnant women. Nocturia during pregnancy is usually related to normal, physiologic changes during pregnancy that do not require treatment with Noctiva™.
- Lactation: Desmopressin (the active ingredient of Noctiva™) is present in small amounts in human milk and is poorly absorbed orally by an infant. There is no information on the effects of Noctiva™ on the breastfed infant or on milk production.
- Pediatric Use: Noctiva™ is contraindicated for the treatment of primary nocturnal enuresis because of reports of hyponatremic-related seizures in pediatric patients treated with other intranasal formulations of desmopressin.
- Geriatric Use: Patients 65 years of age and older treated with Noctiva™ had a higher incidence of hyponatremia compared to patients younger than 65 years of age treated with Noctiva™.
- Renal Impairment: Noctiva™ is mainly excreted in the urine. The area under the concentration-time curve (AUC) and terminal half-life of Noctiva™ in renally impaired patients with an eGFR below 50mL/min/1.73m^2 is 3-to 4-fold greater than in patients with an eGFR above 50mL/min/1.73m^2.

Efficacy: The efficacy of Noctiva™ in patients with nocturia due to nocturnal polyuria was established in two 12-week randomized, double-blind, placebo-controlled, multi-center trials in adults 50 years of age and older. At baseline, patients were required to have a six-month history of at least two nocturic episodes per night, on average, and at least 13 documented nocturia episodes over 6 nights during screening. The majority of patients in these trials were

Caucasian (79%). The mean age was 67 years (range 50 to 90 years), 57% were men, and 43% were women. In both trials, nocturnal polyuria was defined as a night-time urine production exceeding one-third of the 24-hour urine production confirmed with a 24-hour urine frequency/volume chart. Each trial had two co-primary efficacy endpoints. One endpoint was the change in mean number of nocturic episodes per night from baseline during the 12-week treatment period. The other endpoint was the percentage of patients who achieved at least a 50% reduction from baseline in the mean number of nocturia episodes per night during the 12-week treatment period.

- Trial 1: A total of 612 patients with nocturia due to nocturnal polyuria were randomized to receive either Noctiva™ 1.66mcg, Noctiva™ 0.83mcg, or placebo. The change in mean number of nocturic episodes per night from baseline was -1.5 for both the 1.66mcg ($p=0.01$) and 0.83mcg groups ($p<0.01$). For placebo, the change in mean number of episodes was -1.2. Both treatment groups had statistically significant changes from baseline. The percentage of patients achieving at least 50% reduction in nocturic episodes per night from baseline was 47% for the 1.66mcg group ($p <0.0001$), 35% for the 0.83mcg group ($p=0.08$), and 27% for the placebo group. Statistical significance was only achieved in the 1.66mcg group.
- Trial 2: A total of 433 patients were randomized to receive Noctiva™ 1.66mcg, Noctiva™ 0.83mcg, or placebo. The change in mean number of nocturic episodes per night from baseline was -1.5 for the 1.66mcg group ($p<0.0001$) and -1.4 for the 0.83mcg group ($p<0.01$). Both treatment groups had statistically significant changes from baseline. For placebo, the change in mean number of episodes was -1.1. The percentage of patients achieving at least 50% reduction in nocturic episodes per night from baseline was 49% for the 1.66mcg group ($p<0.001$), 41% for the 0.83mcg group ($p=0.03$), and 29% for the placebo group.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 30 days
Noctiva™ (desmopressin acetate nasal spray)	**Unknown**	**Unknown**
desmopressin 0.1mg tablet	$0.78	$23.40*

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.
*Cost per 30 days based on off-label dosing for nocturia of 100mcg at bedtime.

Recommendations[6]

The College of Pharmacy recommends placement of Noctiva™ (desmopressin acetate) into the Special Prior Authorization (PA) Tier of the Bladder Control Medications Product Based Prior Authorization (PBPA) category with the following criteria:

Noctiva™ (Desmopressin Acetate) Approval Criteria:

1. An FDA approved diagnosis of nocturia due to nocturnal polyuria in adults 50 years of age and older; and

2. All other causes of nocturia have been ruled out or adequately treated (e.g., benign prostatic hyperplasia [BPH], overactive bladder [OAB], obstructive sleep apnea [OSA]); and
3. The prescriber must confirm the member has a 6-month history of at least two nocturic episodes per night; and
4. Member has failed behavior modifications including reducing caffeine intake, alcohol intake, and nighttime fluid intake; and
5. Member has failed a trial of DDAVP® (desmopressin) tablets or has a patient-specific, clinically significant reason why the tablet formulation cannot be used; and
6. The prescriber must be willing to measure serum sodium levels within 7 days of anticipated start of treatment and document levels are acceptable; and
7. The prescriber must agree to monitor serum sodium levels within one month of starting treatment or increasing the dose; and
8. The prescriber must confirm the member is not taking any of the following:
    a. Other medications via the nasal route; or
    b. Loop diuretics; or
    c. Inhaled or systemic glucocorticoids; and
9. The prescriber must confirm the member does not have renal impairment with estimated glomerular filtration rate (eGFR) below 50mL/min/1.73m^2; and
10. Initial approvals will be for 3 months, for continued authorization the prescriber must provide the following:
    a. Serum sodium levels and documentation levels are acceptable; and
    b. Documentation that the member is responding to treatment.

Bladder Control Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
fesoterodine (Toviaz®)	tolterodine (Detrol®)	darifenacin (Enablex®)	oxybutynin patch (Oxytrol®)+
oxybutynin (Ditropan®)	trospium (Sanctura®)	mirabegron (Myrbetriq®)	**desmopressin acetate nasal spray (Noctiva™)+**
oxybutynin ER (Ditropan XL®)		oxybutynin gel (Gelnique®)	
		solifenacin (VESIcare®)	
		tolterodine ER (Detrol LA®)	
		trospium ER (Sanctura XR®)	

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
ER = extended release
+Unique criteria specific to Oxytrol® (oxybutynin patch) and Noctiva™ (desmopressin acetate nasal spray) applies.

Utilization Details of Bladder Control Medications: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
TIER-1 PRODUCTS					
OXYBUTYNIN PRODUCTS					
OXYBUTYNIN TAB 5MG	5,463	1,380	$149,405.51	$0.89	$27.35
OXYBUTYNIN TAB 10MG ER	1,801	479	$62,504.93	$0.96	$34.71
OXYBUTYNIN TAB 5MG ER	1,202	395	$43,687.26	$1.09	$36.35
OXYBUTYNIN SYP 5MG/5ML	1,074	305	$12,401.17	$0.41	$11.55
OXYBUTYNIN TAB 15MG ER	802	172	$32,070.51	$1.08	$39.99
SUBTOTAL	**10,342**	**2,731**	**$300,069.38**	**$0.90**	**$29.01**
FESOTERODINE PRODUCTS$^{\Delta}$					
TOVIAZ TAB 4MG	106	59	$31,134.60	$9.94	$293.72
TOVIAZ TAB 8MG	92	33	$25,831.75	$9.41	$280.78
SUBTOTAL	**198**	**92**	**$56,966.35**	**$9.69**	**$287.71**
TIER-1 SUBTOTAL	**10,540**	**2,823**	**$357,035.73**	**$1.05**	**$33.87**
TIER-2 PRODUCTS					
TOLTERODINE PRODUCTS					
TOLTERODINE TAB 2MG	351	56	$26,031.72	$2.53	$74.16
TOLTERODINE TAB 1MG	75	10	$7,269.22	$3.28	$96.92
SUBTOTAL	**426**	**66**	**$33,300.94**	**$2.66**	**$78.17**
TROSPIUM PRODUCTS					
TROSPIUM CL TAB 20MG	66	19	$5,057.75	$2.44	$76.63
SUBTOTAL	**66**	**19**	**$5,057.75**	**$2.44**	**$76.63**
TIER-2 SUBTOTAL	**492**	**85**	**$38,358.69**	**$2.63**	**$77.96**
TIER-3 PRODUCTS					
TROSPIUM PRODUCTS					
TROSPIUM CHL CAP 60MG ER	704	132	$115,877.11	$4.73	$164.60
SUBTOTAL	**704**	**132**	**$115,877.11**	**$4.73**	**$164.60**
TOLTERODINE PRODUCTS					
TOLTERODINE CAP 4MG ER	238	30	$28,846.48	$4.07	$121.20
TOLTERODINE CAP 2MG ER	23	5	$2,939.23	$4.35	$127.79
SUBTOTAL	**261**	**35**	**$31,785.71**	**$4.10**	**$121.78**
SOLIFENACIN PRODUCTS					
VESICARE TAB 5MG	102	16	$37,445.52	$10.23	$367.11
VESICARE TAB 10MG	93	13	$35,576.22	$11.30	$382.54
SUBTOTAL	**195**	**29**	**$73,021.74**	**$10.73**	**$374.47**
MIRABEGRON PRODUCTS					
MYRBETRIQ TAB 50MG	57	11	$18,042.82	$10.55	$316.54
MYRBETRIQ TAB 25MG	28	7	$8,833.67	$10.54	$315.49
SUBTOTAL	**85**	**18**	**$26,876.49**	**$10.55**	**$316.19**
DARIFENACIN PRODUCTS					
DARIFENACIN TAB 15MG ER	47	7	$14,622.55	$9.65	$311.12
SUBTOTAL	**47**	**7**	**$14,622.55**	**$9.65**	**$311.12**

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
TIER-3 SUBTOTAL	**1,292**	**221**	**$262,183.60**	**$6.24**	**$202.93**
TOTAL	**12,324**	**2,778***	**$657,578.02**	**$1.66**	**$53.36**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
[Δ]The fesoterodine products moved from Tier-3 to Tier-1 on January 1, 2017 due to significant rebates. The utilization in the table occurred during fiscal year 2017; however, it is shown under the Tier-1 products to reflect the current tier placement.

[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 07/2017. Last accessed 08/31/2017.
[2] Chung SD, Weng S, Huang C, et al. Antimuscarinic Use in Females With Overactive Bladder Syndrome Increases the Risk of Depressive Disorder: A 3-Year Follow-up Study. *The Journal of Clinical Pharmacology* 2017; 57(8): 1064–1070.
[3] Johnson TM. Nocturia: Clinical Presentation, Evaluation, and Management in Adults. *UpToDate®*. Available online at: http://www.uptodate.com/contents/nocturia-clinical-presentation-evaluation-and-management-in-adults?source=machineLearning&search=nocturnal+polyuria&selectedTitle=1%7E150&sectionRank=1&anchor=H7#H7. Last revised 08/08/2017. Last accessed 09/08/2017.
[4] Noctiva™ Prescribing Information. Serenity Pharmaceuticals. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/201656lbl.pdf. Last revised 03/2017. Last accessed 08/14/2017.
[5] U.S. Food and Drug Administration (FDA): Summary Review for Regulatory Action. https://www.accessdata.fda.gov/drugsatfda_docs/summary_review/2017/201656Orig1s000SumR.pdf. Issued 02/04/2016. Last accessed 09/18/2017.
[6] Bergman AM, Sih AM, Weiss JP. Nocturia: An Overview of Evaluation and Treatment. *Bladder* 2015; 2(2): e13.

Appendix S

Fiscal Year 2017 Annual Review of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and 30-Day Notice to Prior Authorize Sprix® (Ketorolac Tromethamine Nasal Spray) and Cataflam® (Diclofenac Potassium Tablets)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)		
Tier-1	**Tier-2**	**Special PA**
diclofenac ER (Voltaren® XR)	celecoxib (Celebrex®)	diclofenac (Zorvolex®)
diclofenac potassium (Cataflam®)	diclofenac sodium/ misoprostol (Arthrotec®)	diclofenac epolamine (Flector® patch)
diclofenac sodium (Voltaren®) 50mg & 75mg tabs	diclofenac sodium (Voltaren®) 25mg tabs	diclofenac potassium (Cambia® powder pack)
etodolac (Lodine®) 400mg & 500mg tabs	etodolac (Lodine®) 200mg & 300mg caps	diclofenac potassium (Zipsor® caps)
flurbiprofen (Ansaid®)	etodolac ER (Lodine® XL)	diclofenac sodium (Dyloject™)
ibuprofen (Motrin®)	fenoprofen (Nalfon®)	diclofenac sodium (Pennsaid® topical drops)
ketoprofen (Orudis®)	meclofenamate (Meclomen®)	diclofenac sodium (Voltaren Gel®)
meloxicam (Mobic®)	naproxen sodium (Anaprox®) 275mg & 550mg tabs	ibuprofen/famotidine (Duexis®)
nabumetone (Relafen®)	oxaprozin (Daypro®)	indomethacin susp & ER caps (Indocin®)
naproxen (Naprosyn®)	piroxicam (Feldene®)	indomethacin (Tivorbex®)
naproxen EC (Naprosyn®)	tolmetin (Tolectin®)	ketoprofen ER (Oruvail®)
sulindac (Clinoril®)		mefenamic acid (Ponstel®)
		meloxicam caps (Vivlodex®)
		naproxen sodium ER (Naprelan®)
		naproxen/esomeprazole (Vimovo®)

ER = extended-release, EC = enteric coated, caps = capsules, tabs = tablets, susp = suspension
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

NSAIDs Tier-2 Approval Criteria:

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

NSAIDs Special Prior Authorization (PA) Approval Criteria:

1. A unique indication for which a Tier-1 or Tier-2 medication is not appropriate; or

2. Previous use of at least two Tier-1 NSAID products (from different product lines); and
3. A patient-specific, clinically-significant reason why a special formulation is needed over a Tier-1 product.
4. Additionally, use of Tivorbex® will require a patient-specific, clinically significant reason why the member cannot use all other available generic indomethacin products.

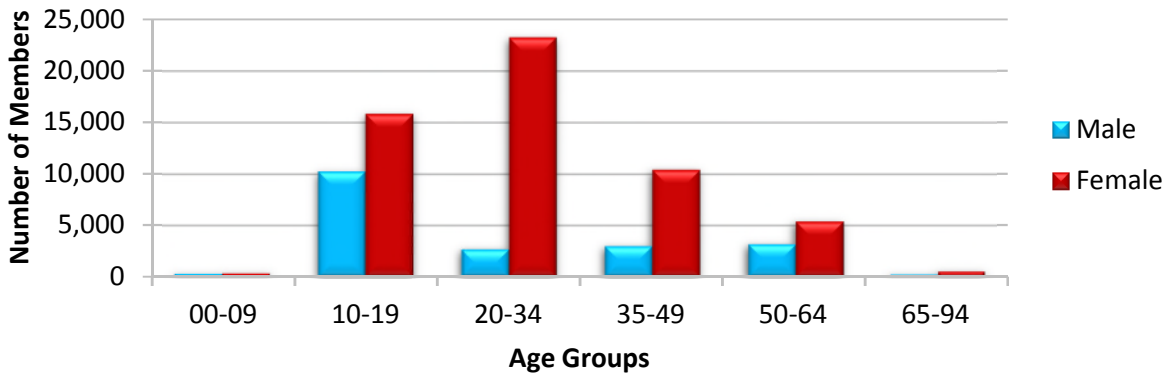
Utilization of NSAIDs: Fiscal Year 2017

Comparison of Fiscal Years

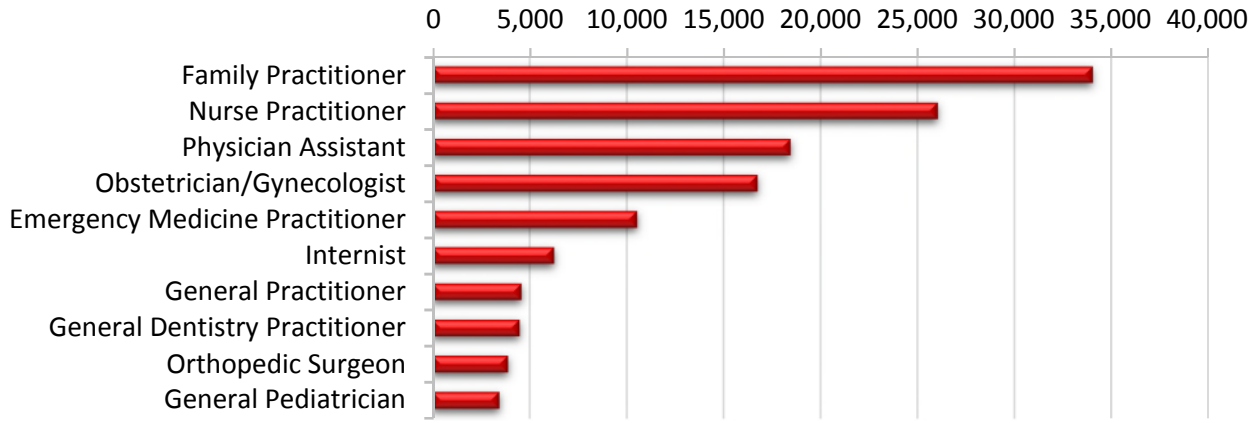
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	84,009	148,940	$1,507,195.70	$10.12	$0.46	8,051,039	3,285,202
2017	75,261	141,957	$1,657,863.21	$11.68	$0.51	6,822,256	3,241,816
% Change	**-10.40%**	**-4.70%**	**10.00%**	**15.40%**	**10.90%**	**-15.30%**	**-1.30%**
Change	**-8,748**	**-6,983**	**$150,667.51**	**$1.56**	**$0.05**	**-1,228,783**	**-43,386**

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

Demographics of Members Utilizing NSAIDs

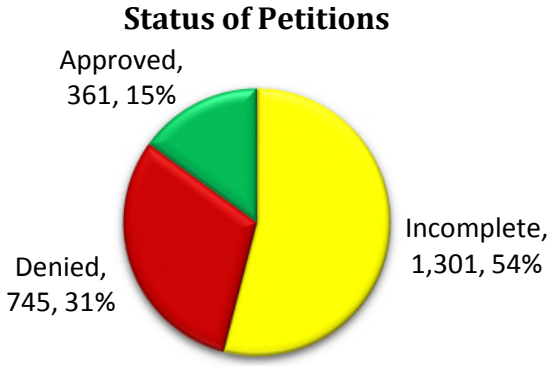


Top Prescriber Specialties of NSAIDs by Number of Claims



Prior Authorization of NSAIDs

There were 2,407 prior authorization requests submitted for the NSAID category during fiscal year 2017. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.



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

Anticipated Patent Expiration(s):

- Flector® (diclofenac epolamine topical patches): April 2019
- Cambia® (diclofenac potassium powder packs): June 2026
- Duexis® (ibuprofen/famotidine tablets): July 2026
- Dyloject™ (diclofenac sodium for injection): March 2027
- Zipsor® (diclofenac potassium capsules): February 2029
- Tivorbex® (indomethacin capsules): April 2030
- Zorvolex® (diclofenac capsules): April 2030
- Pennsaid® (diclofenac sodium 2% topical drops): August 2030
- Vimovo® (naproxen/esomeprazole tablets): October 2031
- Vivlodex® (meloxicam capsules): March 2035

News:

- **November 2016:** The results of the Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen (PRECISION) were simultaneously formally presented at the American Heart Association 2016 Scientific Sessions and published in *The New England Journal of Medicine*. The trial suggests the selective cyclooxygenase-2 (COX-2) inhibitor celecoxib has similar cardiovascular (CV) safety as naproxen and ibuprofen in arthritis patients at increased cardiovascular disease (CVD) risk. Celecoxib achieved noninferiority for the primary CV endpoint, the first occurrence of an adverse event that met the Antiplatelet Trialists Collaboration (APTC) criteria [i.e., death from CV cardiovascular causes, including hemorrhagic death, nonfatal myocardial infarction (MI), or nonfatal stroke]. As compared with naproxen and ibuprofen, celecoxib was associated with numerically fewer CV events, which resulted in noninferiority P-values of less than 0.001. Additionally, secondary and tertiary outcomes also included clinically significant gastrointestinal (GI) events, clinically significant renal events, iron deficiency anemia of GI origin, and hospitalization for heart failure (HF) or hypertension

(HTN). Celecoxib treatment resulted in lower rates of GI events than did either comparator drug and in lower rates of renal adverse events than did ibuprofen. Some of the limitations of the trial included: adherence and retention were lower than in most trials that assess CV outcomes, and results reflect the relative safety of only these three drugs (not the effects of the more than two dozen other marketed NSAIDs).

- **July 2017:** Horizon Pharmaceuticals received U.S. Food and Drug Administration (FDA) approval for new and expanded indications for Vimovo® (esomeprazole magnesium/naproxen). The new indications include adults and adolescent patients 12 years of age or older weighing 38kg or more, who require naproxen for symptomatic relief of arthritis and esomeprazole magnesium to decrease the risk of developing naproxen-associated gastric ulcers. Additionally, the naproxen component of Vimovo® is indicated for relief of signs and symptoms of juvenile idiopathic arthritis (JIA) in adolescent patients. Prior to the new indications, Vimovo® was only approved in adult patients for the relief of signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and to decrease the risk of developing gastric ulcers in patients at risk of developing NSAID-associated gastric ulcers.

Sprix® (Ketorolac Tromethamine Nasal Spray) Product Summary[5]

Indication(s): Sprix® (ketorolac tromethamine nasal spray) is indicated for use in adults for the short-term (up to 5 days) management of moderate-to-moderately severe pain that requires analgesia at the opioid level.

Limitation of Use: The total duration of use of Sprix® alone or sequentially with other forms of ketorolac is not to exceed 5 days. Sprix® must not be used concomitantly with other forms of ketorolac or other NSAIDs.

Dosing:

- Sprix® is supplied in single-day, preservative-free spray bottles containing eight sprays per bottle.
- Each spray delivers 15.75mg of ketorolac tromethamine in precisely metered doses of 100µL per spray.
- Sprix® nasal spray bottles should be discarded within 24 hours of taking the first dose, even if medication remains.
- The recommended dose for adults younger than 65 years of age is 31.5mg (one 15.75mg spray in each nostril) every 6 to 8 hours with a maximum daily dose of 126mg (four doses or eight sprays).
- The recommended dose for adults 65 years of age and older, renally impaired patients, and adult patients weighing less than 50kg (110lbs) is 15.75mg (one 15.75mg spray in only one nostril) every 6 to 8 hours with a maximum daily dose of 63mg (four doses or four sprays).

Boxed Warning: Risk of Serious CV and GI Events

CV Thrombotic Events:

- NSAIDs cause an increased risk of serious CV thrombotic events, including MI and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.

- Sprix® is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.

GI Bleeding, Ulceration, and Perforation:

- NSAIDs cause an increased risk of serious GI adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.

Efficacy: The effect of Sprix® on acute pain was evaluated in two multi-center, randomized, double-blind, placebo-controlled studies.

- In one study, 300 adult patients who had undergone elective abdominal or orthopedic surgery were randomized to receive Sprix® or placebo administered every eight hours. Patients in both groups also received morphine administered via patient controlled analgesia on an as needed basis. Efficacy was demonstrated as a statistically significant greater reduction in the summed pain intensity difference over 48 hours in patients who received Sprix® as compared to those receiving placebo. The clinical relevance of this is reflected in the finding that patients treated with Sprix® required 36% less morphine over 48 hours than patients treated with placebo.
- In another study, 321 adults who had undergone elective abdominal surgery, were randomized to receive Sprix® or placebo administered every six hours. Patients in both groups also received morphine administered via patient controlled analgesia on an as needed basis. Efficacy was demonstrated using the same measure as in the study above, and was demonstrated as a statistically significant greater reduction in the summed pain intensity difference over 48 hours in patients who received Sprix® as compared to those receiving placebo. The clinical relevance of this is reflected in the finding that patients treated with Sprix® required 26% less morphine over 48 hours than patients treated with placebo.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 5 days
Sprix® (ketorolac tromethamine 15.75mg nasal spray)*	**$295.85**	**$1,479.25**
ketorolac injection 30mg/1mL	$3.48	$69.60
ketorolac 10mg tablet	$0.98	$19.60

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.
*Sprix® is dispensed exclusively through Cardinal Health Specialty Pharmacy.

Cost Comparison

There are several cost-effective, generic options available for SoonerCare members who require NSAID therapy. As shown in the following tables, several generic medications cost significantly more than similar medications. In the Tier-1 products table below, the national average drug acquisition cost (NADAC) of diclofenac potassium 50mg is $0.48 per tablet resulting in a 30-day supply costing $43.20. The cost of a similar product, diclofenac sodium 75mg, is $0.14 per tablet with a 30-day supply costing $8.40. The Tier-2 products table shows additional substantial cost differences between similar medications. The NADAC for fenoprofen

600mg tablets is $312.00 for a 30 day supply, while the wholesale acquisition cost (WAC) for meclofenamate 100mg capsules is $742.80 for a 30-day supply. This compares to etodolac 300mg capsules with a NADAC of $94.50 for a 30-day supply.

Tier-1 Products:

Medication	Cost Per Unit	Cost for 30 Days of Therapy*
Cataflam® (diclofenac potassium) 50mg tablet	**$0.48**	**$43.20**
Voltaren® (diclofenac sodium) 75mg tablet	$0.14	$8.40
Mobic® (meloxicam) 15mg tablet	$0.02	$0.60

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.
*Cost for 30 days of therapy based on recommended dosing for osteoarthritis.
Unit = tablet

Tier-2 Products:

Medication	Cost Per Unit	Cost for 30 Days of Therapy*
Nalfon® (fenoprofen) 600mg tablet	**$2.60**	**$312.00**
Meclomen® (meclofenamate) 100mg capsule	**$6.19**	**$742.80**
Lodine® (etodolac) 300mg capsule	$1.05	$94.50
Anaprox® (naproxen sodium) 550mg tablet	$1.17	$70.20

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.
*Cost for 30 days of therapy based on recommended dosing for osteoarthritis.
Unit = tablet or capsule

There are several strengths of celecoxib available for patients requiring treatment with an NSAID. The cost of celecoxib 400mg differs greatly from the cost of other strengths of celecoxib. The NADAC of celecoxib 400mg is $1.82 per capsule. This results in a 30-day supply costing $54.60. As shown in the following table, a 30-day supply of the other available strengths of celecoxib, at an equivalent dose, is significantly less. For example, the cost of two 200mg celecoxib capsules (400mg total dose) is $25.20 for a 30-day supply.

Medication	Cost Per Unit	Cost for 30 Days of Therapy*
Celebrex® (celecoxib) 400mg capsule	**$1.82**	**$54.60**
Celebrex® (celecoxib) 200mg capsule	$0.42	$25.20
Celebrex® (celecoxib) 100mg capsule	$0.38	$45.60

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.
*30 days of therapy based on 400mg/day of celecoxib.
Unit = capsule

Recommendations

The College of Pharmacy recommends the following:

1. The placement of Cataflam® (diclofenac potassium tablets) into Tier-2 of the NSAID Product Based Prior Authorization (PBPA) category based on national average drug acquisition cost (NADAC).
2. The placement of Sprix® (ketorolac tromethamine nasal spray), Nalfon® (fenoprofen), Meclomen® (meclofenamate), and Celebrex® (celecoxib) 400mg capsules into the

Special Prior Authorization (PA) Tier of the NSAID PBPA category based on wholesale acquisition cost (WAC) and NADAC. Current Special PA Tier criteria will apply. Additionally, for Celebrex® (celecoxib) 400mg capsules the following criteria will apply:

   a. **Celebrex® (Celecoxib 400mg Capsules) Approval Criteria:**
      i. A patient-specific, clinically significant reason why the member cannot use two celecoxib 200mg capsules to achieve a 400mg dose.

3. Move Celebrex® (celecoxib) 50mg, 100mg, and 200mg capsules from Tier-2 to Tier-1 based on NADAC.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)		
Tier-1	**Tier-2**	**Special PA**
celecoxib 50mg, 100mg, & 200mg caps (Celebrex®)	**diclofenac potassium (Cataflam®)**	**celecoxib 400mg caps (Celebrex®)**
diclofenac ER (Voltaren® XR)	diclofenac sodium/ misoprostol (Arthrotec®)	diclofenac (Zorvolex®)
diclofenac sodium (Voltaren®) 50mg & 75mg tabs	diclofenac sodium (Voltaren®) 25mg tabs	diclofenac epolamine (Flector® patch)
etodolac (Lodine®) 400mg & 500mg tabs	etodolac (Lodine®) 200mg & 300mg caps	diclofenac potassium (Cambia® powder pack)
flurbiprofen (Ansaid®)	etodolac ER (Lodine® XL)	diclofenac potassium (Zipsor® caps)
ibuprofen (Motrin®)	naproxen sodium (Anaprox®) 275mg & 550mg tabs	diclofenac sodium (Dyloject™)
ketoprofen (Orudis®)	oxaprozin (Daypro®)	diclofenac sodium (Pennsaid® topical drops)
meloxicam (Mobic®)	piroxicam (Feldene®)	diclofenac sodium (Voltaren Gel®)
nabumetone (Relafen®)	tolmetin (Tolectin®)	**fenoprofen (Nalfon®)**
naproxen (Naprosyn®)		ibuprofen/famotidine (Duexis®)
naproxen EC (Naprosyn®)		indomethacin susp & ER caps (Indocin®)
sulindac (Clinoril®)		indomethacin (Tivorbex®)
		ketoprofen ER (Oruvail®)
		ketorolac tromethamine (Sprix® nasal spray)
		meclofenamate (Meclomen®)
		mefenamic acid (Ponstel®)
		meloxicam caps (Vivlodex®)
		naproxen sodium ER (Naprelan®)
		naproxen/esomeprazole (Vimovo®)

ER = extended-release, EC = enteric coated, caps = capsules, tabs = tablets, susp = suspension
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

NSAIDs Tier-2 Approval Criteria:

1. Previous use of at least two Tier-1 NSAID products (from different product lines) plus a proton pump inhibitor (PPI) within the last 120 days.

NSAIDs Special Prior Authorization (PA) Approval Criteria:

1. A unique indication for which a Tier-1 or Tier-2 medication is not appropriate; or

2. Previous use of at least two Tier-1 NSAID products (from different product lines); and
3. A patient-specific, clinically-significant reason why a special formulation is needed over a Tier-1 product.
4. Additionally, use of Tivorbex® will require a patient-specific, clinically significant reason why the member cannot use all other available generic indomethacin products.
5. Additionally, use of Celebrex® (celecoxib) 400mg capsules will require a patient-specific, clinically significant reason why the member cannot use two celecoxib 200mg capsules to achieve a 400mg dose.

Utilization Details of NSAIDs: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TIER-1 NSAIDS					
IBUPROFEN PRODUCTS					
IBUPROFEN TAB 800MG	45,887	30,907	$430,786.52	1.48	$0.51
IBUPROFEN TAB 600MG	13,753	11,062	$118,428.95	1.24	$0.62
IBUPROFEN TAB 400MG	3,929	2,901	$35,510.43	1.35	$0.60
IBUPROFEN POW	4	3	$288.61	1.33	$2.45
SUBTOTAL	**63,573**	**44,873**	**$585,014.51**	**1.46**	**$0.53**
MELOXICAM PRODUCTS					
MELOXICAM TAB 15MG	20,342	9,441	$121,199.62	2.15	$5.96
MELOXICAM TAB 7.5MG	10,044	5,321	$62,708.16	1.89	$6.24
MELOXICAM SUS 7.5/5ML	25	17	$2,214.35	1.47	$88.57
MOBIC SUS 7.5/5ML	2	1	$359.20	2	$179.60
SUBTOTAL	**30,413**	**14,780**	**$186,481.33**	**2.14**	**$6.13**
NAPROXEN PRODUCTS					
NAPROXEN TAB 500MG	19,795	13,467	$163,436.16	1.47	$8.26
NAPROXEN TAB 375MG	2,647	1,990	$23,141.18	1.33	$8.74
NAPROXEN TAB 250MG	1,847	1,280	$17,330.47	1.44	$9.38
NAPROXEN DR TAB 500MG	933	542	$15,577.75	1.72	$16.70
NAPROXEN SUS 125/5ML	442	262	$53,452.21	1.69	$120.93
NAPROXEN DR TAB 375MG	154	113	$2,129.48	1.36	$13.83
SUBTOTAL	**25,818**	**17,654**	**$275,067.25**	**1.49**	**$10.65**
DICLOFENAC PRODUCTS					
DICLOFENAC TAB 75MG DR	5,772	2,953	$68,950.67	1.95	$11.95
DICLOFENAC TAB 50MG DR	1,542	901	$25,716.71	1.71	$16.68
DICLOFEN POT TAB 50MG	1,513	931	$51,649.79	1.63	$34.14
DICLOFENAC TAB 100MG ER	354	166	$6,950.40	2.13	$19.63
SUBTOTAL	**9,181**	**4,951**	**$153,267.57**	**1.92**	**$16.69**
NABUMETONE PRODUCTS					
NABUMETONE TAB 500MG	1,491	779	$22,795.05	1.91	$15.29
NABUMETONE TAB 750MG	1,265	514	$22,897.90	2.46	$18.10
SUBTOTAL	**2,756**	**1,293**	**$45,692.95**	**2.17**	**$16.58**
KETOROLAC PRODUCTS					
KETOROLAC TAB 10MG	2,562	2,238	$58,995.39	1.14	$23.03
KETOROLAC INJ 60MG/2ML	27	19	$546.64	1.42	$20.25
KETOROLAC INJ 30MG/ML	17	9	$807.07	1.89	$47.47
SUBTOTAL	**2,606**	**2,266**	**$60,349.10**	**1.15**	**$23.16**
ETODOLAC PRODUCTS					
ETODOLAC TAB 400MG	1,763	1,052	$65,946.38	1.68	$37.41

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
ETODOLAC TAB 500MG	686	301	$31,947.65	2.28	$46.57
SUBTOTAL	**2,449**	**1,353**	**$97,894.03**	**1.82**	**$39.97**
KETOPROFEN PRODUCTS					
KETOPROFEN CAP 75MG	1,011	885	$19,487.08	1.14	$19.28
KETOPROFEN CAP 50MG	172	134	$3,718.44	1.28	$21.62
KETOPROFEN POW	35	28	$338.89	1.25	$9.68
SUBTOTAL	**1,218**	**1,047**	**$23,544.41**	**1.16**	**$19.33**
INDOMETHACIN PRODUCTS					
INDOMETHACIN CAP 50MG	345	232	$4,023.24	1.49	$11.66
INDOMETHACIN CAP 25MG	218	162	$2,147.57	1.35	$9.85
SUBTOTAL	**563**	**394**	**$6,170.81**	**1.46**	**$10.96**
SULINDAC PRODUCTS					
SULINDAC TAB 200MG	240	111	$3,787.92	2.16	$15.78
SULINDAC TAB 150MG	69	30	$1,035.74	2.3	$15.01
SUBTOTAL	**309**	**141**	**$4,823.66**	**2.19**	**$15.61**
FLURBIPROFEN PRODUCTS					
FLURBIPROFEN TAB 100MG	77	37	$1,841.09	2.08	$23.91
FLURBIPROFEN TAB 50MG	6	2	$120.31	3	$20.05
SUBTOTAL	**83**	**39**	**$1,961.40**	**2.13**	**$23.63**
TIER-1 SUBTOTAL	**138,969**	**88,791**	**$1,440,267.02**	**1.57**	**$10.36**
TIER-2 NSAIDS					
CELECOXIB PRODUCTS					
CELECOXIB CAP 200MG	1,239	369	$51,751.41	3.36	$41.77
CELECOXIB CAP 100MG	330	103	$12,725.48	3.2	$38.56
CELECOXIB CAP 50MG	14	4	$478.65	3.5	$34.19
CELEBREX CAP 200MG	9	1	$5,749.82	9	$638.87
CELECOXIB CAP 400MG	3	2	$215.31	1.5	$71.77
SUBTOTAL	**1,595**	**479**	**$70,920.67**	**3.45**	**$44.46**
ETODOLAC PRODUCTS					
ETODOLAC CAP 300MG	177	120	$9,335.18	1.48	$52.74
ETODOLAC CAP 200MG	103	51	$4,591.40	2.02	$44.58
ETODOLAC ER TAB 600MG	22	5	$2,156.44	4.4	$98.02
ETODOLAC ER TAB 500MG	15	10	$1,768.14	1.5	$117.88
ETODOLAC ER TAB 400MG	13	5	$1,020.57	2.6	$78.51
SUBTOTAL	**330**	**191**	**$18,871.73**	**1.74**	**$57.19**
NAPROXEN PRODUCTS					
NAPROXEN SOD TAB 550MG	290	191	$19,059.05	1.52	$65.72
NAPROXEN SOD TAB 275MG	36	18	$1,731.62	2	$48.10
SUBTOTAL	**326**	**209**	**$20,790.67**	**1.57**	**$63.78**
DICLOFENAC PRODUCTS					
DICLO/MISOPR TAB 75-0.2MG	89	26	$11,322.53	1.93	$127.22
DICLOFENAC TAB 25MG DR	58	37	$3,005.20	1.71	$51.81
DICLO/MISOPR TAB 50-0.2MG	13	7	$1,867.18	2	$143.63
SUBTOTAL	**160**	**70**	**$16,194.91**	**1.86**	**$101.22**
OXAPROZIN PRODUCTS					
OXAPROZIN TAB 600MG	39	11	$3,708.38	3.55	$95.09
SUBTOTAL	**39**	**11**	**$3,708.38**	**3.55**	**$95.09**
PIROXICAM PRODUCTS					
PIROXICAM CAP 20MG	12	5	$815.69	2.4	$67.97
PIROXICAM CAP 10MG	5	1	$234.17	5	$46.83

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBTOTAL	**17**	**6**	**$1,049.86**	**2.83**	**$61.76**
MECLOFENAMATE PRODUCTS					
MECLOFEN SOD CAP 50MG	11	1	$1,172.65	11	$106.60
MECLOFEN SOD CAP 100MG	1	1	$94.36	1	$94.36
SUBTOTAL	**12**	**2**	**$1,267.01**	**6**	**$105.58**
FENOPROFEN PRODUCTS					
FENOPROFEN CAP 400MG	6	4	$1,793.19	1.5	$298.87
FENOPROFEN TAB 600MG	4	3	$434.58	1.33	$108.65
NALFON CAP 400MG	3	3	$1,679.50	1	$559.83
SUBTOTAL	**13**	**10**	**$3,907.27**	**1.3**	**$300.56**
TOLMETIN PRODUCTS					
TOLMETIN SOD CAP 400MG	9	2	$1,449.64	4.5	$161.07
SUBTOTAL	**9**	**2**	**$1,449.64**	**4.5**	**$161.07**
TIER-2 SUBTOTAL	**2,501**	**980**	**$138,160.14**	**2.64**	**$55.24**
SPECIAL PA NSAIDS					
DICLOFENAC PRODUCTS					
DICLOFENAC GEL 1%	380	228	$44,099.66	1.67	$116.05
VOLTAREN GEL 1%	39	15	$3,802.57	2.6	$97.50
PENNSAID SOL 2%	4	4	$8,568.69	1	$2,142.17
DICLOFENAC SOL 1.5%	4	2	$503.07	2	$125.77
FLECTOR DIS 1.3%	2	2	$652.89	1	$326.45
CAMBIA POW 50MG	1	1	$492.29	1	$492.29
SUBTOTAL	**430**	**252**	**$58,119.17**	**1.71**	**$135.16**
INDOMETHACIN PRODUCTS					
INDOCIN SUS 25MG/5ML	43	6	$20,366.74	7.17	$473.65
INDOMETHACIN CAP 75MG ER	13	7	$928.64	1.86	$71.43
SUBTOTAL	**56**	**13**	**$21,295.38**	**4.31**	**$380.27**
KETOPROFEN PRODUCTS					
KETOPROFEN CAP 200MG ER	1	1	$21.50	1	$21.50
SUBTOTAL	**1**	**1**	**$21.50**	**1**	**$21.50**
SPECIAL PA SUBTOTAL	**487**	**266**	**$79,436.05**	**1.83**	**$163.11**
TOTAL	**141,957**	**75,261***	**$1,657,863.21**	**1.89**	**$11.68**

*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 06/2017. Last accessed 07/26/2017.

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[3] Nissen SE, Neville YD, Solomon DH, et al. Cardiovascular Safety of Celecoxib, Naproxen, or Ibuprofen for Arthritis. *N Engl J Med* 2016; 375(26):2519-2529.

[4] Vimovo® (esomeprazole magnesium/naproxen) – New and Expanded Indications. OptumRx. Available online at: https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/clinical-updates/clinicalupdates_vimovo_2017-0710.pdf. Last accessed 08/14/2017.

[5] National Institute of Health. Sprix® (ketorolac tromethamine spray, metered). *U.S. National Library of Medicine: DailyMed*. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=97005a1c-167e-4676-bae7-e49b38c36f9e. Last revised 07/08/2016. Last accessed 08/02/2017.

Appendix T

Fiscal Year 2017 Annual Review of Anti-Ulcer Medications and 30-Day Notice to Prior Authorize Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets)

Oklahoma Health Care Authority
October 2017

Current Prior Authorization Criteria

Anti-Ulcer Medications*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
omeprazole (Prilosec® caps)	dexlansoprazole (Dexilant® caps)	esomeprazole (Nexium® caps, packets, I.V.)	famotidine (Pepcid® susp)
pantoprazole (Protonix® tabs)	lansoprazole (Prevacid® caps, ODT)	esomeprazole strontium caps	omeprazole/sodium bicarbonate (Zegerid®)
	rabeprazole sodium (Aciphex® tabs)	dexlansoprazole (Dexilant® SoluTab)	ranitidine (caps, Zantac® Effervescent Tabs)
		omeprazole (Prilosec® susp, powder)	sucralfate susp unit dose cups
		pantoprazole (Protonix® susp, I.V.)	
		rabeprazole sodium (Aciphex® Sprinkles)	

ODT = orally disintegrating tablets; caps = capsules; tabs = tablets; I.V. = intravenous; susp = suspension
*Special formulations including ODTs, granules, suspension, sprinkle capsules, and solution for I.V. require special reason for use.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Anti-Ulcer Medications Tier-2 Approval Criteria:

1. A 14-day trial of all available Tier-1 medications titrated up to the recommended dose that has resulted in inadequate relief of symptoms or intolerable adverse effects; or
2. Contraindication(s) to all available Tier-1 medications; or
3. An indication not covered by lower tiered medications.
4. Special formulations including orally disintegrating tablets (ODTs), sprinkle capsules, granules, suspensions, and intravenous (I.V.) solutions require special reason(s) for use.

Anti-Ulcer Medications Tier-3 Approval Criteria:

1. A 14-day trial of all available Tier-1 and Tier-2 medications that has resulted in inadequate relief of symptoms or intolerable adverse effects; or
2. Contraindication(s) to all available Tier-1 and Tier-2 medications; or
3. An indication not covered by lower tiered medications.
4. Special formulations including orally disintegrating tablets (ODTs), sprinkle capsules, granules, suspensions, and intravenous (I.V.) solutions require special reason(s) for use.

Proton Pump Inhibitors for Pediatric Members Approval Criteria:

1. A recent 14-day trial of an H_2 receptor antagonist that has resulted in inadequate relief of symptoms or intolerable adverse effects; or
2. Recurrent or severe disease such as:
    a. Gastrointestinal (GI) bleed; or
    b. Zollinger-Ellison Syndrome or similar disease.

Special Prior Authorization Approval Criteria:

1. **Pepcid® suspension (famotidine):** Pepcid® suspension (famotidine) will have an age restriction of 6 years of age and younger. Members older than 6 years of age will require a reason why the member needs the liquid formulation and cannot use the oral tablet formulation.
2. **Zegerid® (omeprazole/sodium bicarbonate):** A patient-specific, clinically significant reason why the member cannot use omeprazole and OTC sodium bicarbonate separately.
3. **Ranitidine capsules:** A patient-specific, clinically significant reason why the member cannot use ranitidine tablets.
4. **Sucralfate suspension unit dose cups:** A patient-specific, clinically significant reason why the member cannot use the bulk medication.

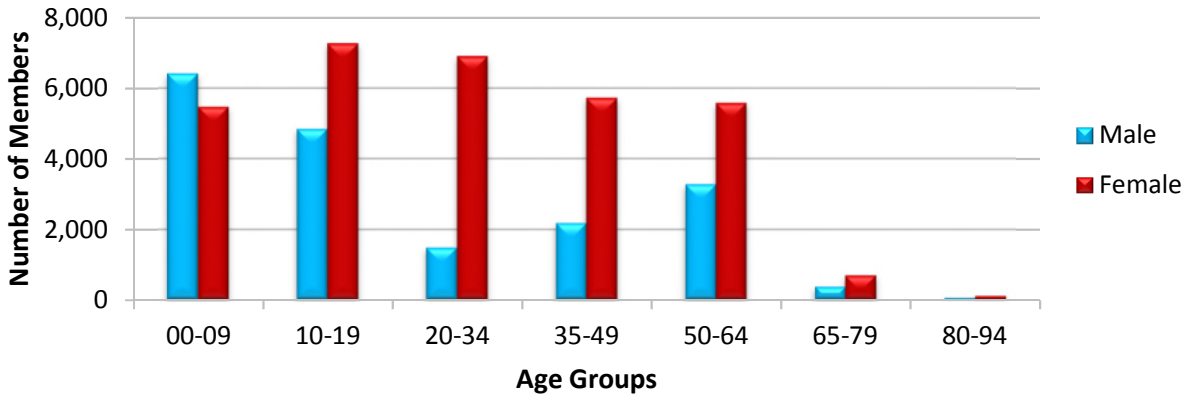
Utilization of Anti-Ulcer Medications: Fiscal Year 2017

Comparison of Fiscal Years

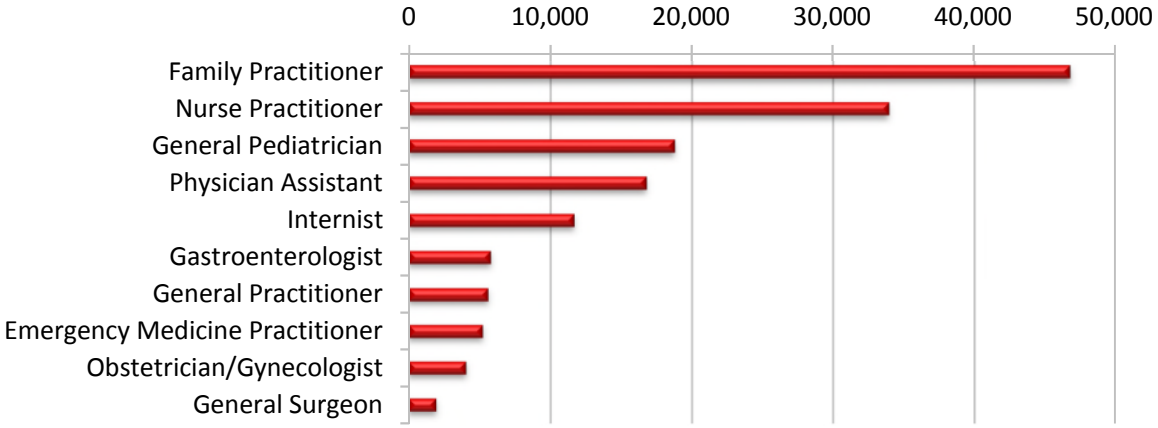
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	48,170	167,896	$3,077,404.61	$18.33	$0.56	10,576,772	5,471,265
2017	48,188	164,386	$3,392,460.72	$20.64	$0.62	10,697,842	5,484,267
% Change	**0.00%**	**-2.10%**	**10.20%**	**12.60%**	**10.70%**	**1.10%**	**0.20%**
Change	**18**	**-3,510**	**$315,056.11**	**$2.31**	**$0.06**	**121,070**	**13,002**

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

Demographics of Members Utilizing Anti-Ulcer Medications



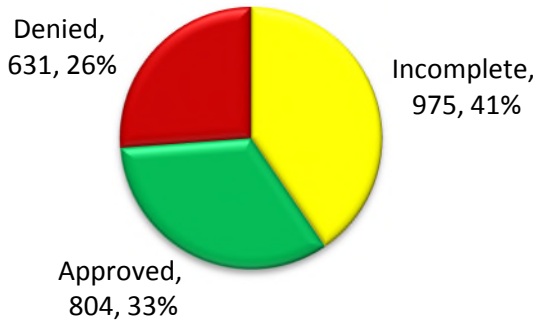
Top Prescriber Specialties of Anti-Ulcer Medications by Number of Claims



Prior Authorization of Anti-Ulcer Medications

There were 2,410 prior authorization requests submitted for anti-ulcer medications during fiscal year 2017. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions for fiscal year 2017.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14]

Anticipated Patent Expiration(s):

- Dexilant® (dexlansoprazole orally disintegrating tablets [ODT]): May 2018
- Nexium® (esomeprazole suspension): May 2018
- Prevacid® (lansoprazole ODT): May 2018
- Prilosec® (omeprazole suspension): November 2019
- Dexilant® (dexlansoprazole capsules): June 2020
- Protonix® (pantoprazole intravenous [I.V.]): November 2021
- Yosprala™ (aspirin/omeprazole tablets): May 2022
- Protonix® (pantoprazole suspension): September 2024

New FDA Approval(s):

- **September 2016:** Yosprala™ (aspirin/omeprazole delayed-release tablets) was approved by the U.S. Food and Drug Administration (FDA) for patients who require aspirin for

secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin-associated gastric ulcers.

- **July 2017:** Omeprazole delayed-release 20mg ODT was approved by the FDA for the over-the-counter (OTC) treatment of frequent heartburn (occurring two or more days a week). This is the first ODT dosage formulation of omeprazole.

News:

- **October 2016:** The FDA announced Zantac® (ranitidine HCl) effervescent tablets 25mg and 150mg and Zantac® (ranitidine HCl) effervescent granules 150mg have been discontinued from marketing effective November 3, 2016 and that the products were not discontinued or withdrawn for safety or efficacy reasons.
- **October 2016:** The FDA approved an update to the prescribing information of all proton pump inhibitors (PPIs) based on reports of cutaneous and systemic lupus erythematosus (SLE) associated with these drugs, with events having occurred in patients as both new onset and as an exacerbation of existing autoimmune disease. The most common form of cutaneous lupus erythematosus (CLE) reported has been subacute CLE, generally without organ involvement, and has occurred within weeks to years after continuous use of PPIs. Reports of PPI-associated SLE indicated that it is milder than non-drug induced SLE, with onset typically occurring within days to years after starting PPI therapy. Most patients presented with rash, however arthralgia and cytopenia were also reported. The updated labeling recommends that use of PPIs for longer than medically indicated should be avoided, and patients who show signs of CLE or SLE should discontinue PPI treatment and be referred to a specialist for follow up.
- **November 2016:** A study by the Danish Heart Foundation reported an association of PPI use with stroke. The study reviewed almost 250,000 medical records of patients undergoing gastric endoscopy from 1997 to 2012. The results showed the risk of stroke was 21% higher in patients taking a PPI. The study noted that while patients tended to also be older and sicker to start with, the level of risk was associated with the dose of the PPI. Patients taking the lowest doses did not have a higher risk; however, the highest doses, such as more than 60mg/day of lansoprazole carried a 30% higher risk and more than 80mg/day of pantoprazole carried a 94% higher risk, with the omeprazole and esomeprazole stroke risk falling within that range.
- **January 2017:** A population-based study from Scotland showed a link between acid suppression medications, including PPIs, and an increased risk of intestinal infections with *Clostridium difficile* (*C. difficile)* and *Campylobacter* bacteria. The study showed that compared to individuals in the community who did not take acid suppression medications, those who did had 1.7-times and 3.7-times increased risk of *C. difficile* and *Campylobacter* infections, respectively. The study also showed that among hospitalized patients, those using acid suppression medications had 1.4-times and 4.5-times increased risk, respectively.
- **February 2017:** A study by the Veterans Affairs Saint Louis Health Care System showed that among new users of acid suppression therapy, the incident PPI users have increased risk of chronic renal outcomes including chronic kidney disease (CKD), CKD progression, and end-stage renal disease (ESRD) in the absence of intervening acute kidney injury (AKI). The researchers analyzed data on 125,596 new users of PPIs and

183,436 new users of histamine H_2 receptor antagonists (H_2 blockers) for five years to compare renal outcomes between groups. Compared with new users of H_2 blockers, new users of PPIs had a greater risk of having an estimated glomerular filtration rate (eGFR) of less than 60mL/min/1.73m^2 [hazard ratio (HR) 1.19; 95% confidence interval (95% CI) 1.15-1.24], incident CKD (HR 1.26; 95% CI 1.20-1.33), a greater than 30% decrease in eGFR (HR 1.22; 95% CI 1.16-1.28), and ESRD or a greater than 50% decrease in eGFR (HR 1.30; 95% CI 1.15-1.48) after adjusting for demographic factors and comorbidities. The study also showed 18.24% of new PPI users developed AKI during this time compared to 12.67% of new users of H_2 blockers. When the researches excluded those patients with AKI, PPI users still had an excess risk of chronic renal outcomes compared to those taking H_2 blockers including a 22% higher risk for incident eGFR less than 60mL/min/1.73m^2, 29% higher risk for CKD, 26% higher risk for a greater than 30% decrease in eGFR, and a 35% higher risk for ESRD or a greater than 50% decrease in eGFR.

- **March 2017:** The American Gastroenterological Association (AGA) released a clinical practice update reviewing the risks and benefits of long-term PPI use. The clinical practice update noted the long-term use of PPIs in patients with gastroesophageal reflux disease (GERD), Barrett's esophagus, and non-steroidal anti-inflammatory drug (NSAID) bleeding prophylaxis doubled in the United States from 1999 to 2012, along with a doubling of adverse events in the same period. The clinical practice update includes ten best practice recommendations including the following:
  - Prescribers should prescribe PPIs to patients with GERD, erosive esophagitis, and peptic stricture to assist in short-term healing and long-term control of symptoms.
  - Prescribers should attempt to stop or reduce the dose of PPIs in patients with uncomplicated GERD if they respond to short-term PPIs.
  - Prescribers should prescribe long-term PPIs to patients with Barrett's esophagus and symptomatic GERD.
  - Consideration should be given to long-term PPIs in patients with asymptomatic Barrett's esophagus.
- **May 2017:** In a simulation-based survey of a cross-section of the American College of Physicians with 487 physician respondents, 68% of clinicians would continue giving PPIs to patients at low risk for gastrointestinal (GI) bleeding, but 62% of clinicians would discontinue the drug in patients at highest risk of lethal bleeding. Dr. Jacob Kurlander, of the University of Michigan in Ann Arbor, stated that 80 to 85% of patients with the least risk of serious bleeding should discontinue PPIs because their side effects outweigh possible benefits. On the other hand, the benefits of PPIs outweigh their adverse event risks in patients with intermediate and high risk of fatal bleeds, and discontinuation of PPIs in these patients should be zero, according to Dr. Kurlander. However, in the simulation, 47% of physicians would have discontinued treatment in the intermediate risk patients and 64% would have discontinued in the highest risk group.
- **May 2017:** A new guideline for deprescribing PPIs was published in *Canadian Family Physician*. The new recommendations focus on adults 18 years of age and older with upper GI symptoms who have received PPIs for a minimum of four weeks and have experienced symptom resolution. The guidelines recommend clinicians either reduce

the daily dose of the PPI or stop the drug and switch to as needed PPI use (strong recommendation). Alternatively, the guidelines suggest consideration of step down to an H_2 blocker (weak recommendation). The new guideline notes the evidence base used to develop the guideline was predominantly related to GERD or esophagitis, but they state the data can be extrapolated to apply to patients with other upper GI disorders, such as peptic ulcer disease, and that these guidelines work in conjunction with current treatment guidelines.

- **June 2017:** A new study showed that PPIs did not increase the risk of dementia or Alzheimer's disease (AD). An observational, longitudinal study using data from the National Alzheimer's Coordinating Center database from 2005 to 2015 set to evaluate the risk of mild cognitive impairment, dementia, and AD associated with PPIs. The study looked at patients 50 years of age and older with two to six annual visits with baseline normal cognition or mild cognitive impairment, with the researchers controlling for various demographic factors, vascular comorbidities, mood, and use of anticholinergics and H_2 blockers. The data indicated continuous PPI use was tied to a reduced risk of cognitive function decline compared to never using a PPI (HR 0.78; 95% CI 0.66-0.93; p=0.005) and linked to a reduced risk of progressing to mild cognitive impairment or AD (HR 0.82; 95% CI 0.69-0.98; p=0.001). The results also showed that intermittent PPI use was associated with a reduced risk of cognitive function decline (HR 0.84; 95% CI 0.76-0.93; p=0.001) and risk of progressing to mild cognitive impairment or AD (HR 0.82; 95% CI 0.74-0.91; p=0.001). The study also showed that a significantly higher proportion of PPI users regularly or occasionally had heart disease, diabetes, hypertension, stroke or transient ischemic attack, and depression compared to non-users, as well as more PPI users were regularly or occasionally taking more anticholinergic drugs, which are associated with cognitive impairment. This study's data contrasts other recent reports of higher risk of dementia or AD with PPI use; additional studies will be required to validate these findings.
- **July 2017:** An observational study by the U.S. Department of Veterans Affairs showed that patients on long-term PPIs are at a higher risk of death compared to patients taking H_2 blockers. The study reviewed medical records of 275,933 patients taking a PPI and 73,355 patients taking an H_2 blocker between October 2006 and September 2008, tracking deaths up to five years. The results showed a 25% increased risk of death in patients who took a PPI compared to patients who took H_2 blockers, and that the risk of death increased the longer the patient took the PPI. Since this study was only observational, it was unable to determine a cause-and-effect relationship.

Pipeline:

- **IW-3718:** In July 2017, Ironwood Pharmaceuticals announced positive top-line data from a randomized, double-blind, placebo-controlled Phase 2b trial evaluating IW-3718, a novel, gastric retentive formulation of a bile acid sequestrant, in adult patients with uncontrolled GERD. The trial met its primary efficacy endpoint, percent change in weekly heartburn severity from baseline to week 8, with patients treated with IW-3718 1,500mg plus a PPI showing a mean decrease of 58.0% from baseline in heartburn severity compared to 46.0% in patients treated with a PPI alone (p=0.04). In addition, 52.9% of patients treated with IW-3718 1,500mg plus a PPI were heartburn responders,

compared to 37.1% of patients treated with a PPI alone (heartburn responder was defined as a patient who experienced at least a 45% reduction from baseline in heartburn severity for at least four out of eight weeks, including at least one of the last two weeks). IW-3718 1,500mg plus a PPI also showed a mean decrease of 55.4% from baseline in regurgitation frequency compared to 37.9% in patients treated with a PPI alone (among patients with baseline regurgitation; p=0.01).

Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets) Product Summary[15]

FDA Approved: September 2016

Indication(s): Yosprala™, a combination of aspirin and omeprazole, is indicated for patients who require aspirin for secondary prevention of cardiovascular and cerebrovascular events and who are at risk of developing aspirin-associated gastric ulcers.

Dosing:

- Yosprala™ is available as delayed-release combination tablets in the following strengths:
  - 81mg delayed-release aspirin and 40mg immediate-release omeprazole
  - 325mg delayed-release aspirin and 40mg immediate-release omeprazole
- The recommended dose is one tablet by mouth once daily to be taken at least 60 minutes prior to a meal.
- The tablets should be swallowed whole with liquid and should not be split, crushed, or dissolved.

Mechanism of Action: Aspirin is an inhibitor of both prostaglandin synthesis and platelet aggregation. Omeprazole suppresses gastric acid secretion by specific inhibition of the $[H^+/K^+]$-ATPase enzyme system at the secretory surface of the gastric parietal cells.

Contraindication(s):

- Patients with known allergy or hypersensitivity to aspirin or other NSAIDs, omeprazole, substituted benzimidazoles, or any excipients in the formulation
- Patients with the syndrome of asthma, rhinitis, and nasal polyps
- Pediatric patients with suspected viral infections (with or without fever)
- Patients receiving rilpivirine-containing products

Warnings and Precautions:

- Coagulation Abnormalities: Patients should be monitored for signs of increased bleeding as even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time.
- Gastrointestinal (GI) Adverse Reactions: Aspirin is associated with serious GI adverse reactions, including inflammation, bleeding, ulceration, and perforation of the upper and lower GI tract. Other adverse reactions with aspirin include stomach pain, heartburn, nausea, and vomiting.
- Bleeding Risk with Use of Alcohol: Patients who consume three or more alcoholic beverages a day should be counseled about bleeding risks involved with chronic, heavy alcohol use while taking Yosprala™.

- Interaction with Clopidogrel: Concomitant use of Yosprala™ and clopidogrel should be avoided.
- Interaction with Ticagrelor: Concomitant use of Yosprala™ 325mg/40mg and ticagrelor should be avoided.
- Renal Failure: Yosprala™ should be avoided in patients with severe renal failure (GFR less than 10mL/min/1.73^2).
- Presence of Gastric Malignancy: GI follow-up and diagnostic testing should be considered in adult patients who experience gastric symptoms during treatment, or have a symptomatic relapse after completing treatment.
- Acute Interstitial Nephritis: Acute interstitial nephritis has been observed in patients taking PPIs, including omeprazole. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction.
- *C. difficile*-Associated Diarrhea: PPI-containing therapies may be associated with an increased risk of *C. difficile*-associated diarrhea, especially in hospitalized patients. The lowest dose and shortest duration of Yosprala™ appropriate to trest the condition should be used.
- Bone Fracture: PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The lowest dose and shortest duration of Yosprala™ appropriate for the condition should be used.
- CLE and SLE: CLE and SLE have been reported in patients taking PPIs, including omeprazole. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. Administration of PPIs for longer than medically indicated should be avoided.
- Hepatic Impairment: Long-term moderate-to-high doses of aspirin may result in elevations in serum ALT levels, which rapidly resolve with discontinuation of aspirin. Systemic exposure to omeprazole is increased in patients with hepatic impairment. Yosprala™ should be avoided in patients with any degree of hepatic impairment.
- Cyanocobalamin Deficiency: Daily treatment with any acid suppressing medication over a long period of time (e.g., longer than three years) may lead to malabsorption of cyanocobalamin.
- Hypomagnesemia: Hypomagnesemia has been reported rarely in patients treated with PPIs for at least three months. Magnesium levels in patients who are expected to be on Yosprala™ long-term or who will be taking it with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics) should be monitored prior to initiation of Yosprala™ and periodically during treatment.
- Reduced Effect of Omeprazole with St. John's Wort or Rifampin: Drugs which induce the CYP2C19 or CYP3A4 can substantially decrease concentrations of omeprazole. Concomitant use of Yosprala™ and St. John's wort or rifampin should be avoided
- Interactions with Diagnostic Investigations for Neuroendocrine Tumors: Serum chromogranin A (CgA) levels increase secondary to omeprazole-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic interventions for neuroendocrine tumors.

- Interaction with Methotrexate: Concomitant use of PPIs with methotrexate (primarily at high doses) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities.
- Abnormal Laboratory Tests: Aspirin has been associated with elevated hepatic enzymes, blood urine nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.

Adverse Reactions: The most common adverse reactions in adults (≥2%) were gastritis, nausea, diarrhea, gastric polyps, and non-cardiac chest pain.

Use in Specific Populations:

- Pregnancy: Use of NSAIDs, including Yosprala™, during the 3rd trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Yosprala™ should be avoided in pregnant women starting at 30 weeks gestation.
- Nursing Mothers: There is no information about the presence of Yosprala™ in human milk; however, the individual components (aspirin and omeprazole) are present in human milk. Based on limited data, aspirin in human milk poses a potential risk for serious adverse reactions, including metabolic acidosis, thrombocytopenia, hemolysis, or Reye's syndrome. Yosprala™ is not recommended in patients who are breastfeeding.
- Females of Reproductive Potential: Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including Yosprala™, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women.
- Pediatric Use: The safety and efficacy of Yosprala™ have not been established in pediatric patients.
- Geriatric Use: No overall differences in safety or effectiveness were observed between subjects 65 years of age and older and younger subjects, however greater sensitivity of some older individuals cannot be ruled out.
- Renal Impairment: No dose reduction is necessary in patients with mild-to-moderate renal impairment. Yosprala™ should be avoided in patients with severe renal impairment (GFR less than 10mg/mL/1.73^2) due to the aspirin component.
- Hepatic Impairment: Yosprala™ should be avoided in patients with any degree of hepatic impairment.
- Asian Population: In studies of healthy subjects, Asians had approximately a four-fold higher exposure to omeprazole than Caucasians. Approximately 15% to 20% of Asians are CYP2C19 poor metabolizers. Yosprala™ should be avoided in Asian patients with unknown CYP2C19 genotype or those who are known to be poor metabolizers.

Efficacy: Two randomized, multi-center, double-blind trials evaluated the omeprazole component by comparing the incidence of gastric ulcer formation in 524 patients randomized to Yosprala™ 325mg/40mg tablets and 525 patients randomized to enteric coated (EC)-aspirin 325mg. Patients were included with a cerebro- or cardiovascular diagnosis if they had been taking daily aspirin 325mg for at least three months, were expected to require daily aspirin 325mg therapy for at least six months, and were older than 55 years of age. Subjects between 18 and 55 years of age were also required to have a documented history of gastric or duodenal ulcer within the past five years. The majority of patients were male (71%), white (90%), and

≥65 years of age (57%). Approximately 11% were also on chronic NSAID therapy. The results from the study are seen in the table below.

Table 1. Cumulative Incidence of Gastric Ulcers (GU) at 1, 3, and 6 Months

	STUDY 1		STUDY 2	
	Yosprala™ N=265 Number (%)	EC-aspirin N=265 Number (%)	Yosprala™ N=259 Number (%)	EC-aspirin N=260 Number (%)
0-1 Month	3 (1.1)	10 (3.8)	1 (0.4)	8 (3.1)
0-3 Months	8 (3.0)	18 (6.8)	1 (0.4)	17 (6.5)
0-6 Months‡	10 (3.8)	23 (8.7)	7 (2.7)	22 (8.5)

‡ Study 1: p=0.020 and Study 2: p=0.005 for treatment comparison of cumulative GU incidence at 6 months.

Cost Comparison:

Medication	Cost Per Unit	Cost for 30 Days of Therapy*
Yosprala™ (aspirin/omeprazole delayed-release tablets)	**$5.00**	**$150.00**
aspirin 81mg enteric-coated tablets◊	$0.05	$1.50
omeprazole 40mg capsules	$0.09	$2.70

*30 days of therapy based on usual dose of medication

◊Cost based off of Walgreens generic 120-count bottle from walgreens.com, last checked 6/26/2017.

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

Recommendations

The College of Pharmacy recommends the following changes to the Anti-Ulcer Medication Product Based Prior Authorization (PBPA) category:

1. Place Yosprala™ (aspirin/omeprazole delayed-release tablets) into the Special Prior Authorization (PA) Tier of the Anti-Ulcer PBPA category. The following criteria will apply:
   a. A patient-specific, clinically significant why the separate products (aspirin and omeprazole) cannot be used in place of this combination product.
2. Place nizatidine solution (Axid®) into the Special PA Tier of the Anti-Ulcer PBPA category based on net cost. The following criteria will apply:
   a. A previous trial of ranitidine syrup or a patient-specific, clinically significant reason why ranitidine syrup is not appropriate for the member.
3. Place cimetidine tablets (Tagamet®) and nizatidine capsules (Axid®) into the Special PA Tier of the Anti-Ulcer PBPA category based on net costs. The following criteria will apply:
   a. A previous trial of ranitidine and famotidine or a patient-specific, clinically significant reason why ranitidine and famotidine are not appropriate for the member.
4. Move esomeprazole (Nexium® packets) and pantoprazole (Protonix® I.V.) to Tier-2 based on net costs. Current Tier-2 criteria and special formulation criteria will apply.

5. For famotidine suspension (Pepcid®), add a previous trial of ranitidine syrup or a patient-specific, clinically significant reason why ranitidine syrup is not appropriate for the member.

The proposed changes can be seen in red in the following criteria and tier chart:

Tagamet® (Cimetidine Tablets) Approval Criteria:

1. A previous 14-day trial of ranitidine and famotidine or a patient-specific, clinically significant reason why ranitidine and famotidine are not appropriate for the member.

Pepcid® (Famotidine Suspension) Approval Criteria:

1. A previous 14-day trial of ranitidine syrup or a patient-specific, clinically significant reason why ranitidine syrup is not appropriate for the member; and
2. Famotidine suspension (Pepcid®) will have an age restriction of 6 years of age and younger. Members older than 6 years of age will require a reason why the member needs the liquid formulation and cannot use the oral tablet formulation.

Axid® (Nizatidine Capsules) Approval Criteria:

1. A previous 14-day trial of ranitidine and famotidine or a patient-specific, clinically significant reason why ranitidine and famotidine are not appropriate for the member.

Axid® (Nizatidine Solution) Approval Criteria:

1. A previous 14-day trial of ranitidine syrup or a patient-specific, clinically significant reason why ranitidine syrup is not appropriate for the member; and
2. Nizatidine (Axid®) will have an age restriction of 6 years of age and younger. Members older than 6 years of age will require a reason why the member needs the liquid formulation and cannot use the oral capsule formulation.

Yosprala™ (Aspirin/Omeprazole Delayed-Release Tablets) Approval Criteria:

1. A patient-specific, clinically significant why the separate products (aspirin and omeprazole) cannot be used in place of this combination product.

Anti-Ulcer Medications*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA***
omeprazole (Prilosec® caps)	dexlansoprazole (Dexilant® caps)	esomeprazole (Nexium® caps, packets, I.V.)	**aspirin/omeprazole DR tabs (Yosprala™)**
pantoprazole (Protonix® tabs)	**esomeprazole (Nexium® packets)**	esomeprazole strontium caps	**cimetidine tabs (Tagamet®)**
	lansoprazole (Prevacid® caps, ODT)	dexlansoprazole (Dexilant® SoluTab)	famotidine (Pepcid® susp)
	pantoprazole (Protonix® I.V.)	omeprazole (Prilosec® susp, powder)	**nizatidine caps & sol (Axid®)**
	rabeprazole sodium (Aciphex® tabs)	pantoprazole (Protonix® susp, I.V.)	omeprazole/sodium bicarbonate (Zegerid®)
		rabeprazole sodium (Aciphex® Sprinkles)	ranitidine (caps, ~~**Zantac® Effervescent Tabs**~~)
			sucralfate susp UD cups

ODT = orally disintegrating tablets; caps = capsules; tabs = tablets; I.V. = intravenous; susp = suspension; sol = solution; DR = delayed-release; UD = unit dose

*Special formulations including ODTs, granules, suspension, sprinkle capsules, and solution for I.V. require special reason for use.

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or

Utilization Details of Anti-Ulcer Medications: Fiscal Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TIER-1 UTILIZATION					
CIMETIDINE PRODUCTS					
CIMETIDINE SOL 300/5ML	426	283	$8,448.29	1.51	$19.83
CIMETIDINE TAB 400MG	393	191	$12,850.65	2.06	$32.70
CIMETIDINE TAB 300MG	189	126	$4,944.43	1.5	$26.16
CIMETIDINE TAB 800MG	149	72	$6,341.46	2.07	$42.56
CIMETIDINE TAB 200MG	115	65	$2,868.87	1.77	$24.95
SUBTOTAL	**1,272**	**725**	**$35,453.70**	**1.75**	**$27.87**
FAMOTIDINE PRODUCTS					
FAMOTIDINE TAB 20MG	7,316	3,001	$61,283.86	2.44	$8.38
FAMOTIDINE TAB 40MG	1,384	641	$13,524.87	2.16	$9.77
FAMOTIDINE INJ 40MG/4ML	26	2	$412.90	13	$15.88
FAMOTIDINE INJ 20MG/2ML	25	1	$321.59	25	$12.86
FAMOTIDINE INJ 10MG/ML	1	1	$10.52	1	$10.52
SUBTOTAL	**8,752**	**3,607**	**$75,553.74**	**2.43**	**$8.63**
LANSOPRAZOLE PRODUCTS					
LANSOPRAZOLE POW	117	34	$2,036.24	3.44	$17.40
SUBTOTAL	**117**	**34**	**$2,036.24**	**3.44**	**$17.40**
NIZATIDINE PRODUCTS					
NIZATIDINE SOL 15MG/ML	1,752	762	$143,606.46	2.3	$81.97
NIZATIDINE CAP 150MG	93	27	$1,912.01	3.44	$20.56
NIZATIDINE CAP 300MG	1	1	$64.76	1	$64.76
SUBTOTAL	**1,846**	**790**	**$145,583.23**	**2.34**	**$78.86**
OMEPRAZOLE PRODUCTS					
OMEPRAZOLE CAP 20MG	44,851	14,639	$406,816.54	3.06	$9.07
OMEPRAZOLE CAP 40MG	24,937	7,933	$281,714.89	3.14	$11.30
OMEPRAZOLE CAP 10MG	2,469	950	$40,800.51	2.6	$16.53
OMEPRAZOLE POW	1,169	384	$50,217.84	3.04	$42.96
SUBTOTAL	**73,426**	**22,645**	**$779,549.78**	**3.24**	**$10.62**
PANTOPRAZOLE PRODUCTS					
PANTOPRAZOLE TAB 40MG	23,833	6,708	$209,091.04	3.55	$8.77
PANTOPRAZOLE TAB 20MG	3,757	1,246	$38,063.38	3.02	$10.13
SUBTOTAL	**27,590**	**7,732**	**$247,154.42**	**3.57**	**$8.96**
RANITIDINE PRODUCTS					
RANITIDINE TAB 150MG	17,137	6,993	$147,141.80	2.45	$8.59
RANITIDINE SYP 75MG/5ML	14,842	7,192	$168,181.74	2.06	$11.33
RANITIDINE SYP 15ML/ML	3,444	2,083	$42,589.62	1.65	$12.37
RANITIDINE TAB 300MG	1,760	762	$18,817.62	2.31	$10.69
ZANTAC TAB 150MG	3	1	$1,589.07	3	$529.69
RANITIDINE POW HCL	1	1	$84.38	1	$84.38
SUBTOTAL	**37,187**	**16,252**	**$378,404.23**	**2.29**	**$10.18**
SUCRALFATE PRODUCTS					
SUCRALFATE TAB 1GM	4,668	2,555	$100,066.47	1.83	$21.44
CARAFATE SUS 1GM/10ML	1,709	961	$381,512.44	1.78	$223.24
SUBTOTAL	**6,377**	**3,403**	**$481,578.91**	**1.97**	**$75.52**
TIER-1 SUBTOTAL	**156,583**	**47,561**	**$2,146,675.90**	**3.29**	**$13.71**
TIER-2 UTILIZATION					
DEXLANSOPRAZOLE PRODUCTS					

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
DEXILANT CAP 60MG DR	1,909	290	$479,527.52	6.58	$251.19
DEXILANT CAP 30MG DR	304	54	$78,557.90	5.63	$258.41
SUBTOTAL	**2,213**	**336**	**$558,085.42**	**6.59**	**$252.19**
LANSOPRAZOLE PRODUCTS					
LANSOPRAZOLE CAP 30MG DR	2,636	374	$45,042.15	7.05	$17.09
PREVACID TAB 15MG STB	791	160	$308,812.22	4.94	$390.41
PREVACID TAB 30MG STB	454	65	$168,551.60	6.98	$371.26
LANSOPRAZOLE CAP 15MG DR	364	67	$9,004.85	5.43	$24.74
SUBTOTAL	**4,245**	**641**	**$531,410.82**	**6.62**	**$125.19**
RABEPRAZOLE PRODUCTS					
RABEPRAZOLE TAB 20MG	415	66	$9,177.33	6.29	$22.11
ACIPHEX SPR CAP 10MG	13	2	$7,063.40	6.5	$543.34
SUBTOTAL	**428**	**68**	**$16,240.73**	**6.29**	**$37.95**
TIER-2 SUBTOTAL	**6,886**	**1,032**	**$1,105,736.97**	**6.67**	**$160.58**
TIER-3 UTILIZATION					
ESOMEPRAZOLE PRODUCTS					
ESOMEPRA MAG CAP 40MG DR	454	55	$26,114.16	8.25	$57.52
NEXIUM GRA 10MG DR	45	10	$11,883.83	4.5	$264.09
NEXIUM GRA 2.5MG DR	33	12	$9,122.96	2.75	$276.45
NEXIUM GRA 5MG DR	32	13	$10,726.15	2.46	$335.19
ESOMEPRA MAG CAP 20MG DR	32	6	$1,962.35	5.33	$61.32
NEXIUM GRA 40MG DR	25	6	$6,292.97	4.17	$251.72
NEXIUM I.V. INJ 40MG	24	1	$7,111.72	24	$296.32
NEXIUM CAP 40MG	22	3	$7,651.15	7.33	$347.78
NEXIUM GRA 20MG DR	15	6	$4,149.93	2.5	$276.66
SUBTOTAL	**682**	**105**	**$85,015.22**	**6.5**	**$124.66**
OMEPRAZOLE PRODUCTS					
PRILOSEC POW 2.5MG	73	31	$17,618.91	2.35	$241.35
PRILOSEC POW 10MG	55	13	$15,795.89	4.23	$287.20
SUBTOTAL	**128**	**44**	**$33,414.80**	**2.91**	**$261.05**
PANTOPRAZOLE PRODUCTS					
PROTONIX PAK	56	8	$20,799.25	7	$371.42
PROTONIX INJ 40MG	51	1	$818.58	51	$16.05
SUBTOTAL	**107**	**9**	**$21,617.83**	**11.89**	**$202.04**
TIER-3 SUBTOTAL	**789**	**114**	**$106,633.05**	**6.92**	**$135.15**
SPECIAL PRIOR AUTHORIZATION (PA) UTILIZATION					
FAMOTIDINE PRODUCTS					
FAMOTIDINE SUS 40MG/5ML	16	4	$1,361.65	4	$85.10
SUBTOTAL	**16**	**4**	**$1,361.65**	**4**	**$85.10**
SPECIAL PA SUBTOTAL	**16**	**4**	**$1,361.65**	**4**	**$85.10**
TOTAL	**164,386**	**48,188***	**$3,392,460.72**	**3.41**	**$20.64**

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

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Appendix U

Industry News and Updates

Oklahoma Health Care Authority
October 2017

Introduction

The following report is an overview of recent issues, important literature, and select guideline updates impacting pharmacy and health care. Information that is expected to have a particular impact in the SoonerCare population has been included for review.

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

News:

- **Abuse-Deterrent Opioids:** Abuse-deterrent formulations (ADFs) have increased in popularity as part of a solution to ending the opioid crisis. However, a review of 10 ADFs shows that the health gains from these formulations are uncertain and they also have a high cost. The Institute for Clinical and Economic Review (ICER), an independent, non-profit research organization, looked at available data for 10 different ADFs to determine their value on health and to perform a cost-benefit analysis. All but one of the products reviewed were extended-release. The current research on the efficacy of ADFs in reducing abuse is limited and uncertain. Pre-market studies showed that recreational drug users said that they were less likely to take the ADF version again and that ADFs are less useful to them than the non-ADF form. However, no threshold exists for measuring abuse potential, and according to ICER, the clinical significance of these findings are unclear. In post-market studies, it was found that drug users were less likely to abuse Oxycontin® after it was reformulated. However, other studies showed an increase in the abuse of other opioids, indicating that abusers just switched to another drug. There is currently limited data available on any ADFs except Oxycontin®. The evidence led ICER to determine that Oxycontin® provided "moderate certainty" of a net health benefit for patients prescribed an opioid. Furthermore, reports for other ADFs were "promising but inconclusive" and the overall evidence was "insufficient to determine a net health benefit of ADFs." Based on the limited evidence available, ICER created a hypothetical model to determine a cost-benefit model using 100,000 non-cancer patients who were prescribed opioids. Based on the information utilized by ICER, in order to attain cost-neutrality relative to non-ADFs, ADFs would need to prevent 35% of abuse cases (operate at 35% effectiveness). However, even at 100% effectiveness the cost of ADFs would be an additional $113 million over five years. The price of ADFs would need to be lowered by 41% to achieve cost-neutrality. The New England Comparative Effectiveness Public Advisory Council (CEPAC), an ICER board consisting of 12 physicians and various health specialists who make recommendations to improve the quality and value of health care, met in July 2017 to discuss the findings. The New England CEPAC made several recommendations to policy makers, payers, and physicians, including the following:

- Reduce barriers to out-of-pocket payments for ADFs
- Need for the development and study of immediate-release ADFs
- Require medical schools to teach the role of ADFs in clinical practice
- Need for health care practitioners to share information on ADFs and non-ADFs with patients

- **Medicaid Spending:** A Kaiser Health News data analysis showed that commonly used medications cost the Medicaid program billions of additional dollars in 2016 compared to 2015. The analysis showed that in 2016 rising costs for 313 brand-name medications increased Medicaid's spending by approximately $3.2 billion. Nine of the brand-name medications have been on the market since before 1970. Other medications contributing to increases in Medicaid spending include commonly used drugs such as generic antidepressants and heartburn medications. For example, generic metformin increased in cost from an average of $0.10 per tablet in 2015 to $0.13 in 2016; the increase in cost per tablet cost Medicaid a combined $8.3 million in 2016. Additionally, the cost increases for the authorized generic extended-release formulation cost the program an additional $6.5 million. Medicaid spending does not include rebates, which drug manufacturers return to states after they pay for the medications up front. Scott Gottlieb, recently named U.S. Food and Drug Administration (FDA) Commissioner, has made increasing generic competition a core mission.
- **FDA Approvals:** According to two new reports in the *Journal of the American Medical Association*, many drugs that are granted accelerated approval by the FDA lack clear evidence of effectiveness and safety. Dr. Huseyin Naci from the London School of Economic and Political Science and his team analyzed the FDA's accelerated approval of 22 medications for the treatment of 24 medical conditions. The FDA generally requires a randomized controlled trial for the standard approval process to demonstrate the drug's safety and effectiveness. However, 14 of the accelerated approvals analyzed were exclusively based on less-rigorous trials. The FDA required 38 more trials after the approval to confirm the benefits of these drugs due to the lower standard of evidence. Most of the later trials used outcomes that would not be acceptable for standard approval, and several of the later trials were discontinued early or failed to show a benefit. For the 10 approvals that eventually met the FDA's established requirements, the time to meet the requirements ranged from one to five years after the accelerated approval. Dr. Naci stated that when the FDA approves medicines through its accelerated approval process, the FDA should clearly state the data limitations and how required confirmatory studies are expected to address these limitations.
- **Lidocaine Patches:** Results from a comparison study published in *Pain Management* found that over-the-counter (OTC) transdermal lidocaine with menthol patches proved noninferior to prescription (Rx) lidocaine patches for efficacy, safety, and quality of life. Transdermal lidocaine has "become a gold standard" in treatment for patients with localized pain. The double-blind, placebo-controlled trial randomized patients (n=87) to three treatment arms: OTC lidocaine 3.6% with menthol 1.25% patches, Rx lidocaine 5%, and placebo. OTC lidocaine with menthol patches demonstrated noninferiority to Rx lidocaine, and compared to placebo, the OTC lidocaine with menthol patches demonstrated superiority for efficacy, general activity, and normal work. The authors

concluded that the lower cost and resource utilization of OTC patches may be favorable for patients and payers. The authors believe that menthol increases skin permeability, which allows for more efficient drug delivery to the area of pain and results in "higher than expected efficacy."

- **Prescription Drug Disposal:** William Simpson, the president of DisposeRX company, believes there is a simpler way to handle diversion of prescription medications. The company's goal was to find a solution to medication disposal that was environmentally safe, inexpensive, and easy. Their solution to the problem of how to properly dispose of medications is a packet of powder that, when mixed with water, renders prescription medications unusable and seals them inside a pill bottle. The powder can also be used to turn liquid medication solid and to encapsulate medication patches. The pill bottle can then be disposed of in the trash. Currently, the packets are available directly from DisposeRx, however the company is working to make the product a part of the dispensing process at pharmacies and hospitals.

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Appendix V

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

FDA NEWS RELEASE

For Immediate Release: August 29th, 2017
FDA approves new antibacterial drug

The U.S. Food and Drug Administration (FDA) approved Vabomere for adults with complicated urinary tract infections (cUTI), including a type of kidney infection, pyelonephritis, caused by specific bacteria. Vabomere is a drug containing meropenem, an antibacterial, and vaborbactam, which inhibits certain types of resistance mechanisms used by bacteria.
The safety and efficacy of Vabomere were evaluated in a clinical trial with 545 adults with cUTI, including those with pyelonephritis. At the end of intravenous (IV) treatment with Vabomere, approximately 98% of patients treated with Vabomere compared with approximately 94% of patients treated with piperacillin/tazobactam, had cure/improvement in symptoms and a negative urine culture test. Approximately seven days after completing treatment, approximately 77% of patients treated with Vabomere compared with approximately 73% of patients treated with piperacillin/tazobactam had resolved symptoms and a negative urine culture.
The most common adverse reactions in patients taking Vabomere were headache, infusion site reactions, and diarrhea. Vabomere is associated with serious risks including allergic reactions and seizures. Vabomere should not be used in patients with a history of anaphylaxis, a type of severe allergic reaction to products in the class of drugs called beta-lactams.
To reduce the development of drug-resistant bacteria and maintain the effectiveness of antibacterial drugs, Vabomere should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.
Vabomere was designated as a qualified infectious disease product (QIDP). This designation is given to antibacterial products that treat serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act. As part of its QIDP designation, Vabomere received a priority review.
The FDA granted approval of Vabomere to Rempex Pharmaceuticals.

FDA NEWS RELEASE

For Immediate Release: August 29th, 2017
FDA approves first U.S. treatment for Chagas disease

The FDA granted accelerated approval to benznidazole for use in children ages 2 to 12 years old with Chagas disease. It is the first treatment approved in the United States for the treatment of Chagas disease.
Chagas disease, or American trypanosomiasis, is a parasitic infection caused by Trypanosoma cruzi and can be transmitted through different routes, including contact with the feces of a certain insect, blood transfusions, or from a mother to her child during pregnancy. After years of infection, the disease can cause serious heart illness, and it also can affect swallowing and digestion. While Chagas disease primarily affects people living in rural parts of Latin America, recent estimates are that there may be approximately 300,000 persons in the United States with Chagas disease.
The safety and efficacy of benznidazole were established in two placebo-controlled clinical trials in pediatric patients 6 to 12 years old. In the first trial, approximately 60% of children treated with benznidazole had an antibody test change from positive to negative compared with approximately 14% of children who received a placebo. Results in the second trial were similar: Approximately 55% of children treated with benznidazole had an antibody test change from positive to negative compared with 5% who received a placebo. An additional study of the safety and pharmacokinetics of benznidazole in pediatric patients 2 to 12 years of age provided information for dosing recommendations down to 2 years of age.
The most common adverse reactions in patients taking benznidazole were stomach pain, rash, decreased weight, headache, nausea, vomiting, abnormal white blood cell count, urticaria (hives), pruritus (itching), and decreased appetite. Benznidazole is associated with serious risks including serious skin reactions, nervous

system effects, and bone marrow depression. Based on findings from animal studies, benznidazole could cause fetal harm when administered to a pregnant woman.
Benznidazole was approved using the Accelerated Approval pathway. The Accelerated Approval pathway allows the FDA to approve drugs for serious conditions where there is unmet medical need and adequate and well-controlled trials establish that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. Further study is required to verify and describe the anticipated clinical benefit of benznidazole.
The FDA granted benznidazole priority review and orphan product designation. These designations were granted because Chagas disease is a rare disease, and until now, there were no approved drugs for Chagas disease in the United States.
With this approval, benznidazole's manufacturer, Chemo Research, S. L., is awarded a Tropical Disease Priority Review Voucher in accordance with a provision included in the FDA Amendments Act of 2007 that aims to encourage development of new drugs and biological products for the prevention and treatment of certain tropical diseases.

FDA NEWS RELEASE

For Immediate Release: August 30th, 2017

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

The FDA issued a historic action making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer and other serious and life-threatening diseases.
The FDA approved Kymriah (tisagenlecleucel) for certain pediatric and young adult patients with a form of acute lymphoblastic leukemia (ALL).
Kymriah, a cell-based gene therapy, is approved in the United States for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.
Kymriah is a genetically-modified autologous T-cell immunotherapy. Each dose of Kymriah is a customized treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. The patient's T-cells are collected and sent to a manufacturing center where they are genetically modified to include a new gene that contains a specific protein (a chimeric antigen receptor or CAR) that directs the T-cells to target and kill leukemia cells that have a specific antigen (CD19) on the surface. Once the cells are modified, they are infused back into the patient to kill the cancer cells.
ALL is a cancer of the bone marrow and blood, in which the body makes abnormal lymphocytes. The disease progresses quickly and is the most common childhood cancer in the United States. The National Cancer Institute estimates that approximately 3,100 patients aged 20 and younger are diagnosed with ALL each year. ALL can be of either T- or B-cell origin, with B-cell the most common. Kymriah is approved for use in pediatric and young adult patients with B-cell ALL and is intended for patients whose cancer has not responded to or has returned after initial treatment, which occurs in an estimated 15-20% of patients.
The safety and efficacy of Kymriah were demonstrated in one multicenter clinical trial of 63 pediatric and young adult patients with relapsed or refractory B-cell precursor ALL. The overall remission rate within three months of treatment was 83 percent.
Treatment with Kymriah has the potential to cause severe side effects. It carries a boxed warning for cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing high fever and flu-like symptoms, and for neurological events. Both CRS and neurological events can be life-threatening. Other severe side effects of Kymriah include serious infections, low blood pressure (hypotension), acute kidney injury, fever, and decreased oxygen (hypoxia). Most symptoms appear within one to 22 days following infusion of Kymriah. Since the CD19 antigen is also present on normal B-cells, and Kymriah will also destroy those normal B cells that produce antibodies, there may be an increased risk of infections for a prolonged period of time.
The FDA also expanded the approval of Actemra (tocilizumab) to treat CAR T-cell-induced severe or life-threatening CRS in patients 2 years of age or older. In clinical trials in patients treated with CAR-T cells, 69% of patients had complete resolution of CRS within two weeks following one or two doses of Actemra.
Because of the risk of CRS and neurological events, Kymriah is being approved with a risk evaluation and mitigation strategy (REMS), which includes elements to assure safe use (ETASU). The FDA is requiring that hospitals and their associated clinics that dispense Kymriah be specially certified. As part of that certification,

staff involved in the prescribing, dispensing, or administering of Kymriah are required to be trained to recognize and manage CRS and neurological events. Additionally, the certified health care settings are required to have protocols in place to ensure that Kymriah is only given to patients after verifying that tocilizumab is available for immediate administration. The REMS program specifies that patients be informed of the signs and symptoms of CRS and neurological toxicities following infusion – and of the importance of promptly returning to the treatment site if they develop fever or other adverse reactions after receiving treatment with Kymriah.
To further evaluate the long-term safety, Novartis is also required to conduct a post-marketing observational study involving patients treated with Kymriah.
The FDA granted Kymriah Priority Review and Breakthrough Therapy designations. The Kymriah application was reviewed using a coordinated, cross-agency approach. The clinical review was coordinated by the FDA's Oncology Center of Excellence, while CBER conducted all other aspects of review and made the final product approval determination.
The FDA granted approval of Kymriah to Novartis Pharmaceuticals Corp. The FDA granted the expanded approval of Actemra to Genentech Inc.

FDA NEWS RELEASE

For Immediate Release: September 1st, 2017
FDA approves Mylotarg for treatment of acute myeloid leukemia

The FDA approved Mylotarg (gemtuzumab ozogamicin) for the treatment of adults with newly diagnosed acute myeloid leukemia whose tumors express the CD33 antigen (CD33-positive AML). The FDA also approved Mylotarg for the treatment of patients aged 2 years and older with CD33-positive AML who have experienced a relapse or who have not responded to initial treatment (refractory).
Mylotarg originally received accelerated approval in May 2000 as a stand-alone treatment for older patients with CD33-positive AML who had experienced a relapse. Mylotarg was voluntarily withdrawn from the market after subsequent confirmatory trials failed to verify clinical benefit and demonstrated safety concerns, including a high number of early deaths. Today's approval includes a lower recommended dose, a different schedule in combination with chemotherapy or on its own, and a new patient population.
AML is a rapidly progressing cancer that forms in the bone marrow and results in an increased number of white blood cells in the bloodstream. The National Cancer Institute of the National Institutes of Health estimates that approximately 21,380 people will be diagnosed with AML this year and that 10,590 patients with AML will die of the disease.
Mylotarg is a targeted therapy that consists of an antibody connected to an anti-tumor agent that is toxic to cells. It is thought to work by taking the anti-tumor agent to the AML cells that express the CD33 antigen, blocking the growth of cancerous cells, and causing cell death.
The safety and efficacy of Mylotarg in combination with chemotherapy for adults were studied in a trial of 271 patients with newly diagnosed CD33-positive AML who were randomized to receive Mylotarg in combination with daunorubicin and cytarabine or to receive daunorubicin and cytarabine without Mylotarg. The trial measured "event-free survival," or how long patients went without certain complications, including failure to respond to treatment, disease relapse, or death, from the date they started the trial. Patients who received Mylotarg in combination with chemotherapy went longer without complications than those who received chemotherapy alone (median, event-free survival 17.3 months vs. 9.5 months).
The safety and efficacy of Mylotarg as a stand-alone treatment were studied in two, separate trials. The first trial included 237 patients with newly diagnosed AML who could not tolerate or chose not to receive intensive chemotherapy. Patients were randomized to receive treatment with Mylotarg or best supportive care. The trial measured "overall survival," or how long patients survived from the date they started the trial. Patients who received Mylotarg survived longer than those who received only best supportive care (median overall survival 4.9 months vs. 3.6 months). The second trial was a single-arm study that included 57 patients with CD33-positive AML who had experienced one relapse of disease. Patients received a single course of Mylotarg. The trial measured how many patients achieved a complete remission. Following treatment with Mylotarg, 26% of patients achieved a complete remission that lasted a median 11.6 months.
Common side effects of Mylotarg include fever (pyrexia), nausea, infection, vomiting, bleeding, low levels of platelets in the blood (thrombocytopenia), swelling and sores in the mouth (stomatitis), constipation, rash, headache, elevated liver function tests, and low levels of certain white blood cells (neutropenia). Severe side effects of Mylotarg include low blood counts, infections, liver damage, blockage of the veins in the liver (hepatic veno-occlusive disease), infusion-related reactions, and severe bleeding (hemorrhage). Women who are

pregnant or breastfeeding should not take Mylotarg, because it may cause harm to a developing fetus or a newborn baby. Patients with hypersensitivity to Mylotarg or any component of its formulation should not use Mylotarg.
The prescribing information for Mylotarg includes a boxed warning that severe or fatal liver damage (hepatotoxicity), including blockage of veins in the liver (veno-occlusive disease or sinusoidal obstruction syndrome), occurred in some patients who took Mylotarg.
Mylotarg received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted the approval of Mylotarg to Pfizer Inc.

FDA NEWS RELEASE

For Immediate Release: September 14th, 2017
FDA approves first biosimilar for the treatment of cancer

The FDA approved Mvasi (bevacizumab-awwb) as a biosimilar to Avastin (bevacizumab) for the treatment of multiple types of cancer. Mvasi is the first biosimilar approved in the U.S. for the treatment of cancer.
Mvasi is approved for the treatment of adult patients with certain colorectal, lung, brain, kidney, and cervical cancers. Specifically, the approved indications include:

- Metastatic colorectal cancer, in combination with IV 5-fluorouracil-based chemotherapy for first- or second-line treatment. Mvasi is not indicated for the adjuvant treatment of surgically resected colorectal cancer.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrmidine-oxaliplatin-based chemotherapy for the second-line treatment of patients who have progressed on a first-line bevacizumab product-containing regimen. Mvasi is not indicated for the adjuvant treatment of surgically resected colorectal cancer.
- Non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment of unresectable, locally advanced, recurrent or metastatic disease.
- Glioblastoma with progressive disease following prior therapy, based on improvement in objective response rate. No data is available demonstrating improvement in disease-related symptoms or survival with bevacizumab products.
- Metastatic renal cell carcinoma, in combination with interferon alfa.
- Cervical cancer that is persistent, recurrent, or metastatic, in combination with paclitaxel and cisplatin or paclitaxel and topotecan.

Health care professionals should review the prescribing information in the labeling for detailed information about the approved uses.
Biological products are generally derived from a living organism and can come from many sources, such as humans, animals, microorganisms or yeast. A biosimilar is a biological product that is approved based on data showing that it is highly similar to an already-approved biological product and has no clinically meaningful differences in terms of safety, purity, and potency (i.e., safety and effectiveness) from the reference product, in addition to meeting other criteria specified by law.
The FDA's approval of Mvasi is based on review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamics data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrated Mvasi is biosimilar to Avastin. It has been approved as a biosimilar, not as an interchangeable product.
Common expected side effects of Mvasi include nose bleeds (epistaxis), headache, high blood pressure (hypertension), inflammation of the nasal cavity (rhinitis), high levels of protein in the urine (proteinuria), taste alteration, dry skin, rectal bleeding (hemorrhage), excessive tear production (lacrimation disorder), back pain, and skin irritation (exfoliative dermatitis).
Serious expected side effects of Mvasi include holes in or abnormal connection between two organs (perforation or fistula), blood clot formation (arterial and venous thromboembolic events), hypertension, problems in brain function or structure (posterior reversible encephalopathy syndrome), proteinuria, infusion-related reactions, and loss of function of the ovaries. Patients should stop using Mvasi if these side effects become severe or life-threatening. Women who are pregnant should not take Mvasi because it may cause harm to a developing fetus.
Like Avastin, the labeling for Mvasi contains a Boxed Warning to alert health care professionals and patients about an increased risk of holes in the stomach and intestines (gastrointestinal perforations); surgery and

wound healing complications; and severe or fatal pulmonary, gastrointestinal, central nervous system, and vaginal bleeding (hemorrhage). Patients should stop using Mvasi if gastrointestinal perforation occurs. Patients should not take Mvasi in the 28 days prior to and after elective surgery, and until the surgical wound is fully healed. Patients should stop using Mvasi if a surgical incision breaks open (wound dehiscence). Mvasi should not be given to patients with severe hemorrhage or in patients who cough up blood (hemoptysis).
The FDA granted approval of Mvasi to Amgen, Inc. Avastin was approved in February 2004 and is manufactured by Genentech, Inc.

FDA NEWS RELEASE

For Immediate Release: September 14th, 2017
FDA approves new treatment for adults with relapsed follicular lymphoma

The FDA granted accelerated approval to Aliqopa (copanlisib) for the treatment of adults with relapsed follicular lymphoma who have received at least two prior treatments known as systemic therapies.
Follicular lymphoma is a slow-growing type of non-Hodgkin lymphoma, a cancer of the lymph system. The lymph system is part of the body's immune system and is made up of lymph tissue, lymph nodes, the spleen, thymus, tonsils, and bone marrow. The National Cancer Institute at the National Insititutes of Health estimates that approximately 72,240 people in the United States will be diagnosed with some form of non-Hodgkin lymphoma this year; approximately 20,140 patients with non-Hodgkin lymphoma will die from the disease in 2017.
Aliqopa is a kinase inhibitor that works by blocking several enzymes that promote cell growth.
Aliqopa received an **Accelerated Approval**, which enables the FDA to approve drugs for serious conditions to fill an unmet medical need using clinical trial data that is thought to predict a clinical benefit to patients. Further clinical trials are required to confirm Aliqopa's clinical benefit and the sponsor is currently conducting these studies.
Approval of Aliqopa was based on data from a single-arm trial that included 104 patients with follicular B-cell non-Hodgkin lymphoma who had relapsed disease following at least two prior treatments. The trial measured how many patients experienced complete or partial shrinkage of their tumors after treatment (overall response rate). In the trial, 59% of patients had a complete or partial response for a median 12.2 months.
Common side effects of Aliqopa include hyperglycemia, diarrhea, decreased general strength and energy, hypertension, low levels of certain white blood cells (leukopenia, neutropenia), nausea, lower respiratory tract infections, and low levels of blood platelets (thrombocytopenia).
Serious side effects include infections, hyperglycemia, hypertension, inflammation of the lung tissue (non-infectious pneumonitis), low levels of certain white blood cells (neutropenia), and severe skin reactions.
Women who are pregnant or breastfeeding should not take Aliqopa because it may cause harm to a developing fetus or newborn baby.
Aliqopa was granted Priority Review designation, under which the FDA's goal is to take action on an application within six months where the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing, or preventing a serious condition.
Aliqopa also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted the approval of Aliqopa to Bayer Healthcare Pharmaceuticals, Inc.

Safety Announcements

FDA Drug Safety Communication: FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs

[9/6/17] The FDA is recommending that patients avoid taking the potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) at the same time as any other medicines taken by mouth. A study found that sodium polystyrene sulfonate binds to many commonly prescribed oral medicines, decreasing the absorption and therefore effectiveness of those oral medicines. To reduce this likelihood, the FDA recommends separating the dosing of sodium polystyrene sulfonate from other orally administered medicines by at least 3 hours. The FDA is updating the sodium polystyrene sulfonate drug labels to include information about this dosing separation.
Sodium polystyrene sulfonate is used to treat hyperkalemia, a serious condition in which the amount of potassium in the blood is too high. It works by binding with potassium in the intestines so it can be removed

from the body. Potassium is a mineral that helps the body function properly. Too much potassium in the blood can cause problems with heart rhythm, which in rare cases can be fatal. Sodium polystyrene sulfonate is available as the brand name Kayexalate, as generic brands, and also as non-branded generics.
Patients should take orally administered prescription and over-the-counter (OTC) medicines at least 3 hours before or 3 hours after sodium polystyrene sulfonate. Patients should not stop taking their potassium-lowering medicines without talking to their health care professional first. If patients have questions or concerns, including about how to take sodium polystyrene sulfonate with other medicines, they should talk to a pharmacist or other health care professional.
When prescribing sodium polystyrene sulfonate, **health care professionals** should advise patients to separate dosing from other orally administered medicines by at least 3 hours. That time should be increased to 6 hours for patients with gastroparesis or other conditions resulting in delayed emptying of food from the stomach into the small intestine.
A laboratory study was conducted to evaluate the binding potential for six orally administered medicines commonly taken together with sodium polystyrene sulfonate. These medicines were the blood pressure medicines amlodipine and metoprolol, the antibiotic amoxicillin, the water pill furosemide, the seizure medicine phenytoin, and the blood-thinner warfarin. The study found significant binding to sodium polystyrene sulfonate occurred with all of these medicines.
Based on the FDA's findings, the FDA has concluded that sodium polystyrene sulfonate would also be likely to bind to many other oral medicines, and separating its dosing from other oral medications by 3 hours (6 hours if the patient has gastroparesis) would reduce the risk of binding. The recommended spacing interval is based on the expected amount of time it would take for either sodium polystyrene sulfonate or the other drugs to pass through the stomach. As a result, the FDA has determined that additional drug interaction studies are no longer needed and will be releasing the manufacturer of Kayexalate, Concordia Pharmaceuticals, Inc., from its requirement to conduct further studies. The FDA is also adding the new information about separating the time of administration of orally administered medicines and sodium polystyrene products to the sodium polystyrene sulfonate drug labels.
The FDA urges patients and health care professionals to report side effects involving sodium polystyrene sulfonate products to the FDA MedWatch program.

Safety Announcements

FDA Drug Safety Communication: FDA warns Meridian Medical Technologies about CGMP violations associated with the manufacture of EpiPen

[9/5/17] The FDA issued a warning letter to a Meridian Medical Technologies facility, located in Brentwood, Missouri, which manufactures Mylan's EpiPen (epinephrine injection). The warning letter identifies significant violations of current good manufacturing practice (CGMP) requirements for its epinephrine auto injectors, including EpiPen and EpiPen Jr, and instructs the company to undertake steps to correct those violations. The FDA understands the importance of epinephrine auto-injectors and will work to ensure that the company's corrections are adequate so that patients can be assured of the safety and efficacy of the products.
The FDA is not aware of defective EpiPens currently on the market and recommends that consumers use their prescribed epinephrine auto injector. As stated on the product label, consumers should always seek emergency medical help right away after using their EpiPens.
The FDA asks health care professionals and consumers to report any adverse reactions or quality problems to the FDA's MedWatch program.

Safety Announcements

FDA Drug Safety Communication: FDA urges caution about withholding opioid addiction medications from patients taking benzodiazepines or CNS depressants: careful medication management can reduce risks

[9/20/17] Based on the FDA's additional review, the FDA is advising that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks. The FDA is requiring this

information to be added to the buprenorphine and methadone drug labels along with detailed recommendations for minimizing the use of medication-assisted treatment (MAT) drugs and benzodiazepines together.

Buprenorphine and methadone help people reduce or stop their abuse of opioids, including prescription pain medications and heroin. Methadone and buprenorphine have been shown to be effective in reducing the negative health effects and deaths associated with opioid addiction and dependency. These medications are often used in combination with counseling and behavioral therapies, and patients can be treated with them indefinitely. Buprenorphine and methadone work by acting on the same parts of the brain as the opioid that the patient is addicted to. The patient taking the medication as directed generally does not feel high, and withdrawal does not occur. Buprenorphine and methadone also help reduce cravings.

Many patients with opioid dependence may also use benzodiazepines or other CNS depressants, either under a health care professional's direction or illicitly. Although there are serious risks with combining these medicines, excluding patients from MAT or discharging patients from treatment because of use of benzodiazepines or CNS depressants is not likely to stop them from using these drugs together. Instead, the combined use may continue outside the treatment setting, which could result in more severe outcomes.

Health care professionals should take several actions and precautions and develop a treatment plan when buprenorphine or methadone is used in combination with benzodiazepines or other CNS depressants. These include:

- Educating patients about the serious risks of combined use, including overdose and death, that can occur with CNS depressants even when used as prescribed, as well as when used illicitly.
- Developing strategies to manage the use of prescribed or illicit benzodiazepines or other CNS depressants when starting MAT.
- Tapering the benzodiazepine or CNS depressant to discontinuation if possible.
- Verifying the diagnosis if a patient is receiving prescribed benzodiazepines or other CNS depressants for anxiety or insomnia, and considering other treatment options for these conditions.
- Recognizing that patients may require MAT medications indefinitely and their use should continue for as long as patients are benefiting and their use contributes to the intended treatment goals.
- Coordinating care to ensure other prescribers are aware of the patient's buprenorphine or methadone treatment.
- Monitoring for illicit drug use, including urine or blood screening.

Patients taking MAT drugs should continue to take these medicines as prescribed. Patients should not stop taking other prescribed medicines without first talking to their health care professional. Before starting any new medicines, patients should tell their health care professional that they are taking MAT. Patients should not take non-prescribed benzodiazepines or other sedatives or use alcohol when taking MAT because the combined use increases the possibility of harm, including overdose and death.

In August 2016, the FDA issued a Drug Safety Communication warning about the combined use of opioid-containing pain or cough medicines with benzodiazepines or other CNS depressants. The FDA said at that time that they would continue to evaluate the evidence regarding combined use of benzodiazepines or other CNS depressants with MAT drugs.

The FDA's subsequent review of a published study and other drug use data showed that buprenorphine and benzodiazepines frequently have been prescribed for the same patient, often by the same prescriber, and these drugs are usually dispensed by the same pharmacy. An epidemiological study from Sweden found that receiving MAT with benzodiazepines or other CNS depressants such as drugs to treat insomnia appears to increase the risk of death. Based on this information, for the methadone products, information about the interaction with benzodiazepines and other CNS depressants will be added to an existing Boxed Warning about the risks of slowed or difficult breathing and death. Expanded guidance will be added to the Warnings and Precautions section on how to manage patients in methadone treatment in Opioid Treatment Programs (OTPs) who are also taking CNS depressants. For the buprenorphine products, an existing statement in the

Warnings and Precautions section will be expanded and revised to provide more detailed guidance on managing patients in buprenorphine treatment who are also taking CNS depressants.
The FDA urges patients and health care professionals to report side effects involving buprenorphine, methadone, or other medicines to the FDA MedWatch program.

Safety Announcements

FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease

[9/21/17] The FDA is warning that the liver disease medicine Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate-to-severe decreases in liver function, resulting in an increased risk of serious liver injury and death. These patients are receiving excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label for them. Ocaliva may also be associated with liver injury in some patients with mild disease who are receiving the correct dose. The recommended dosing and monitoring for patients on Ocaliva are described in the current drug label. The FDA is working with the drug manufacturer, Intercept Pharmaceuticals, to address these safety concerns.
Ocaliva is used to treat a rare, chronic liver disease known as primary biliary cholangitis (PBC). PBC causes the bile ducts in the liver to become inflamed, damaged and destroyed. This causes bile to build up in the liver. This build-up damages the liver over time, eventually causing it to lose its ability to function. Ocaliva has been shown to improve a certain blood test that measures liver problems.
Health care professionals should determine the patient's baseline liver function prior to starting Ocaliva. Patients with moderate-to-severe liver impairment (Child-Pugh B and C) should be started on the approved dosing schedule of 5mg once weekly, rather than the 5mg daily dosing used for other PBC patients, and if needed, can be increased up to a maximum approved dose of 10mg twice weekly. Health care professionals should monitor patients frequently for disease progression, and reduce the dosing frequency to once- or twice-weekly for patients who progress to moderate or severe liver impairment. All patients treated with Ocaliva should be frequently monitored for liver injury (e.g., worsened liver blood tests and adverse liver-related reactions that may be inconsistent with the patient's extent of disease). If liver injury is suspected, Ocaliva should be discontinued. After the patient has stabilized, the benefits should be weighed against the risks when deciding whether to re-initiate treatment. Patients should be educated on the symptoms of potential liver injury.
Patients should contact their health care professional if they have questions or concerns about taking Ocaliva. Patients should report new or worsening severe skin itching to their health care professional. Patients should also contact them immediately if they develop any of the following symptoms that may be signs of liver injury:

- New or worsening fatigue
- Diarrhea
- Weight loss
- Abdominal pain
- Decreased appetite
- Nausea and vomiting
- Change in behavior or confusion
- Vague symptoms such as anxiety or unease
- Abdominal swelling
- Yellow eyes or skin
- Bloody stools

In the 13 months after Ocaliva was approved in May 2016, the FDA received reports of serious liver injury or death associated with Ocaliva.* The FDA's Adverse Event Reporting System (FAERS) includes only reports submitted to FDA, so there may be additional cases about which they are unaware.
Nineteen cases of death were identified, of which eight provided information about the patient's cause of death. The cause of death was reported to be worsening of PBC disease in seven cases, with cardiovascular disease cited in the other case. Seven of these eight cases described patients with moderate-to-severe decreased liver function who received Ocaliva 5mg daily, instead of a dose no greater than 10mg twice weekly as recommended in the label prescribing information for patients with this extent of decreased liver function.
The FDA also identified 11 cases of serious liver injury with Ocaliva use. Six of the patients who had moderate or severe decreases in liver function at baseline and developed serious liver injury were receiving Ocaliva 5mg daily, instead of a dose no greater than 10mg twice weekly as recommended by the FDA in the drug label.

Three of these six patients died, which were included in the 19 death cases mentioned previously. Ocaliva was discontinued in four of six cases, which resulted in one patient experiencing symptom resolution and an improvement in a liver blood test. The remaining three cases did not report the response after discontinuation. The other five cases of serious liver injury were reported in patients with no or mild decreases in liver function prior to initiating Ocaliva. Four of these five patients received Ocaliva 5mg daily, and one did not report the dose. Ocaliva was discontinued in all five cases, which resulted in one patient experiencing symptom resolution and one patient experiencing improved liver blood tests and symptom resolution. The remaining three cases did not report the response after discontinuation.
The FDA urges health care professionals and patients to report side effects involving Ocaliva and other medicines to the FDA MedWatch program.

Current Drug Shortages Index (as of September 27th, 2017):

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

Aminocaproic Acid Injection, USP	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atenolol Tablets	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Bleomycin Sulfate for Injection	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Carbidopa and Levodopa Extended Release Tablets	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cromolyn Sodium Inhalation Solution, USP	***Currently in Shortage***
Dexrazoxane Injection	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Diazepam Injection, USP	***Currently in Shortage***
Dihydroergotamine Mesylate Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Folic Acid 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***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Mecasermin [rDNA origin] (Increlex) Injection	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methylprednisolone Sodium Succinate for Injection, USP	***Currently in Shortage***
Molindone Hydrochloride Tablets	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nitrous Oxide, Gas	***Currently in Shortage***

Pantoprazole (Protonix) Powder for Injection	***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***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Rocuronium Bromide Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine (Transderm Scop) Transdermal System Patch	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***
Tolmetin Sodium Tablets, USP	***Currently in Shortage***