Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
November 13, 2019
4:00pm

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 DUR Board Meeting – November 13, 2019

DATE: October 31, 2019

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

Enclosed are the following items related to the November meeting.
Material is arranged in order of the agenda.

Call to Order

Public Comment Forum – Appendix A

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

Action Item – 2020 Drug Utilization Review Board Meeting Dates – Appendix C

Update on Medication Coverage Authorization Unit/U.S. Food and Drug Administration (FDA) Safety Alerts – Appendix D

Action Item – Vote to Prior Authorize Harvoni® (Ledipasvir/Sofosbuvir Oral Pellets) and Sovaldi® (Sofosbuvir Oral Pellets) – Appendix E

Action Item – Vote to Prior Authorize Vyndaqel® (Tafamidis Meglumine) and Vyndamax™ (Tafamidis) – Appendix F

Action Item – Vote to Prior Authorize Recarbrio™ (Imipenem/Cilastatin/Relebactam) and Xenleta™ (Lefamulin) – Appendix G

Action Item – Vote to Prior Authorize Turalio™ (Pexidartinib) – Appendix H

Action Item – Annual Review of Skin Cancer Medications – Appendix I

30-Day Notice to Prior Authorize Elzonris® (Tagraxofusp-erzs) and Inrebic® (Fedratinib) – Appendix J

Action Item – Annual Review of Atopic Dermatitis (AD) Medications – Appendix K

Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Eticovo™ (Etanercept-ykro), Hadlima™ (Adalimumab-bwwd), Hyrimoz™ (Adalimumab-adaz), Rinvoq™ (Upadacitinib), and Skyrizi™ (Risankizumab-rzaa) – Appendix L

Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Aemcolo™ (Rifamycin), Motegrity™ (Prucalopride), Zelnorm™ (Tegaserod), and Ibsrela® (Tenapanor) – Appendix M

Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Drizalma Sprinkle™ [Duloxetine Delayed-Release (DR) Capsules], Spravato™ (Esketamine Nasal Spray), and Citalopram 20mg/10mL, Escitalopram 10mg/10mL, and Fluoxetine 20mg/5mL Unit Dose Cups – Appendix N

Annual Review of Anticoagulants and Platelet Aggregation Inhibitors and 30-Day Notice to Prior Authorize Bevyxxa® (Betrixaban) and to Update the Current Xarelto® (Rivaroxaban) Prior Authorization Criteria – Appendix O

Annual Review of Antiviral Medications and 30-Day Notice to Prior Authorize Avaclyr™ (Acyclovir 3% Ophthalmic Ointment) – Appendix P

Industry News and Updates – Appendix Q

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – November 13, 2019 @ 4:00pm

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 – See Appendix A

A. Acknowledgment of Speakers for Public Comment
B. Changes to Public Comment Procedure

Items to be presented by Dr. Muchmore, Chairman:

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

A. October 9, 2019 DUR Minutes – Vote
B. October 9, 2019 DUR Recommendations Memorandum

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

4. Action Item – 2020 Drug Utilization Review Board Meeting Dates – See Appendix C

A. 2020 DUR Board Meeting Dates – Vote

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

5. Update on Medication Coverage Authorization Unit/U.S. Food and Drug Administration (FDA) Safety Alerts – See Appendix D

A. Pharmacy Helpdesk Activity for October 2019
B. Medication Coverage Activity for October 2019
C. FDA Safety Alerts

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

6. Action Item – Vote to Prior Authorize Harvoni® (Ledipasvir/Sofosbuvir Oral Pellets) and Sovaldi® (Sofosbuvir Oral Pellets) – See Appendix E

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item –Vote to Prior Authorize Vyndaqel® (Tafamidis Meglumine) and Vyndamax™ (Tafamidis) – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Recarbrio™ (Imipenem/Cilastatin/Relebactam) and Xenleta™ (Lefamulin) – See Appendix G

A. Introduction
B. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize Turalio™ (Pexidartinib) – See Appendix H

A. Introduction

B. Recommendations

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

10. Action Item – Annual Review of Skin Cancer Medications – See Appendix I

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Skin Cancer Medications
D. Prior Authorization of Skin Cancer Medications
E. Market News and Updates
F. Recommendations
G. Utilization Details of Skin Cancer Medications

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

11. 30-Day Notice to Prior Authorize Elzonris® (Tagraxofusp-erzs) and Inrebic® (Fedratinib) – See Appendix J

A. Introduction
B. Market News and Updates
C. Elzonris® (Tagraxofusp-erzs) Product Summary
D. Inrebic® (Fedratinib) Product Summary
E. Recommendations

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

12. Action Item – Annual Review of Atopic Dermatitis (AD) Medications – See Appendix K

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

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

13. Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Eticovo™ (Etanercept-ykro), Hadlima™ (Adalimumab-bwwd), Hyrimoz™ (Adalimumab-adaz), Rinvoq™ (Upadacitinib), and Skyrizi™ (Risankizumab-rzaa) – See Appendix L

A. Current Prior Authorization Criteria
B. Utilization of Targeted Immunomodulator Agents
C. Prior Authorization of Targeted Immunomodulator Agents
D. Market News and Updates
E. Rinvoq™ (Upadacitinib) Product Summary
F. Skyrizi™ (Risankizumab-rzaa) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Targeted Immunomodulator Agents

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

14. Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Aemcolo™ (Rifamycin), Motegrity™ (Prucalopride), Zelnorm™ (Tegaserod), and Ibsrela® (Tenapanor) – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of Constipation and Diarrhea Medications
C. Prior Authorization of Constipation and Diarrhea Medications
D. Product Summaries
E. Market News and Updates
F. College of Pharmacy Recommendations
G. Utilization Details of Constipation and Diarrhea Medications

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

15. Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Drizalma Sprinkle™ [Duloxetine Delayed-Release (DR) Capsules], Spravato™ (Esketamine Nasal Spray), and Citalopram 20mg/10mL, Escitalopram 10mg/10mL, and Fluoxetine 20mg/5mL Unit Dose Cups – See Appendix N

A. Current Prior Authorization Criteria
B. Utilization of Antidepressants
C. Prior Authorization of Antidepressants
D. Market News and Updates
E. Spravato™ (Esketamine Nasal Spray) Product Summary
F. Cost Comparison
G. College of Pharmacy Recommendations
H. Utilization Details of Antidepressants

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

16. Annual Review of Anticoagulants and Platelet Aggregation Inhibitors and 30-Day Notice to Prior Authorize Bevyxxa® (Betrixaban) and to Update the Current Xarelto® (Rivaroxaban) Prior Authorization Criteria – See Appendix O

A. Current Prior Authorization Criteria
B. Utilization of Anticoagulants and Platelet Aggregation Inhibitors
C. Prior Authorization of Anticoagulants and Platelet Aggregation Inhibitors
D. Market News and Updates
E. Bevyxxa® (Betrixaban) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details Anticoagulants
H. Utilization Details of Platelet Aggregation Inhibitors

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

17. Annual Review of Antiviral Medications and 30-Day Notice to Prior Authorize Avaclyr™ (Acyclovir 3% Ophthalmic Ointment) – See Appendix P

A. Current Prior Authorization Criteria
B. Utilization of Antiviral Medications
C. Prior Authorization of Antiviral Medications
D. Market News and Updates
E. Avaclyr™ (Acyclovir 3% Ophthalmic Ointment) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Antiviral Medications

Non-Presentation; Questions Only:

18. Industry News and Updates – See Appendix Q

A. Introduction
B. News and Updates

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

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

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

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

A. Maintenance Asthma and Chronic Obstructive Pulmonary Disease (COPD) Medications
B. Thrombocytopenia Medications
C. Carbaglu® (Carglumic Acid)
D. Soliris® (Eculizumab) and Ultomiris® (Ravulizumab-cwvz)
E. Muscular Dystrophy Medications

**Future business subject to change.*

21. Adjournment

Appendix A

Changes to Public Comment Procedure

Oklahoma Health Care Authority
November 2019

Public Comment Procedure

Effective January 2020 the following procedures will apply for those who wish to provide public comment at the Oklahoma Health Care Authority (OHCA) Drug Utilization Review (DUR) Board meetings:

- Speakers who wish to sign up for public comment at the OHCA DUR Board meeting may do so in writing once the DUR Board agenda has been posted and no later than 24 hours before the meeting. This allows for a 4-day window to sign up.
- The DUR Board meeting will allow public comment and time will be limited to 40 minutes total for all speakers during the meeting. Each speaker will be given 5 minutes to speak at the public hearing. If more than 8 speakers properly request to speak, time will be divided evenly.
- Only 1 speaker per manufacturer will be allowed.
- To sign up for public comment, email DURPublicComment@okhca.org and complete the required information requested (testimony registration form will be posted prior to January 2020).

Appendix B

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF OCTOBER 9, 2019

BOARD MEMBERS:	PRESENT	ABSENT
Stephen Anderson, Pharm.D.	x	
Markita Broyles, D.Ph.; MBA	x	
Darlla D. Duniphin, MHS; PA-C		x
Theresa Garton, M.D.	x	
Ashley Huddleston, Pharm.D.; BCOP	x	
Lynn Mitchell, M.D.	x	
John Muchmore, M.D.; Ph.D.; Chairman		x
Lee Munoz, D.Ph.	x	
James Osborne, Pharm.D.		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
Thomas Ha, Pharm.D.; Clinical Pharmacist		x
Bethany Holderread, Pharm.D.; Clinical Coordinator	x	
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Grant H. Skrepnek, Ph.D.; Associate Professor	x	
Regan Smith, Pharm.D.; Clinical Pharmacist		x
Ashley Teel, Pharm.D.; Clinical Pharmacist		x
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist	x	
Tri Van, Pharm.D.; Pharmacy Resident	x	
Graduate Students: Matthew Dickson, Pharm.D.		x
Michael Nguyen, Pharm.D.	x	
Laura Tidmore, Pharm.D.		x
Corby Thompson, Pharm.D.		x
Visiting Pharmacy Student(s): Justin Wilson, Elizabeth Goetzinger, Hyshin Kwan	x	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Melody Anthony, Chief State Medicaid Director; Chief Operating Officer		x
Marlene Asmussen, R.N.; Population Care Management Director		x
Ellen Buettner; Chief of Staff		x
Kevin Corbett, C.P.A.; Chief Executive Officer		x
Susan Eads, J.D.; Director of Litigation	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
Jill Ratterman, D.Ph.; Clinical Pharmacist	x	
Kerri Wade, Pharmacy Operations Manager		x

OTHERS PRESENT:		
Trebla Grant, Kite	D.R. McCale, Akcea	Ron Cain, Pfizer
Carrie Schaack, Pfizer	Dana Koehn, Sanofi-Genzyme	Roger Grotzinger, BMS
Anthony Deleon, BMS	Michele Puyear, Gilead Sciences	Brent Hildebrand, Gilead
Frances Bauman, Novo Nordisk	Patrick Harvey, Walgreens	Gwendolyn Caldwell, PhRmA
Brian Maves, Pfizer		

PRESENT FOR PUBLIC COMMENT:	
Michele Puyear	Gilead Sciences

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. 14 MICHELE PUYEAR

ACTION: NONE REQUIRED

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

3A: SEPTEMBER 11, 2019 DUR MINUTES – VOTE

3B: SEPTEMBER 11, 2019 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Mitchell

Dr. Broyles moved to approve; seconded by Dr. Garton

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/FALL 2019 PIPELINE UPDATE

4A: PHARMACY HELPDESK ACTIVITY FOR SEPTEMBER 2019

4B: MEDICATION COVERAGE ACTIVITY FOR SEPTEMBER 2019

4C: FALL 2019 PIPELINE UPDATE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE EZALLOR™ SPRINKLE (ROSUVASTATIN CAPSULE) AND WELCHOL® (COLESEVELAM CHEWABLE BAR)

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Adams

Dr. Anderson moved to approve; seconded by Dr. Huddleston

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE SORILUX® (CALCIPOTRIENE 0.005% FOAM)

6A: INTRODUCTION

6B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

Dr. Garton moved to approve; seconded by Dr. Broyles

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE HERZUMA® (TRASTUZUMAB-PKRB), KANJINTI™ (TRASTUZUMAB-ANNS), ONTRUZANT® (TRASTUZUMAB-DTTB), PIQRAY® (ALPELISIB), TALZENNA® (TALAZOPARIB), AND TRAZIMERA™ (TRASTUZUMAB-QYYP)

7A: INTRODUCTION

7B: PRODUCT SUMMARIES

7C: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Schmidt
Dr. Huddleston moved to approve; seconded by Dr. Anderson
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE NUBEQA® (DAROLUTAMIDE)
8A: INTRODUCTION
8B: NUBEQA® (DAROLUTAMIDE) PRODUCT SUMMARY
8C: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Schmidt
Dr. Anderson moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND CHRONIC MYELOID LEUKEMIA (CML) MEDICATIONS
9A: INTRODUCTION
9B: CURRENT PRIOR AUTHORIZATION CRITERIA
9C: UTILIZATION OF ALL/CML MEDICATIONS
9D: PRIOR AUTHORIZATION OF ALL/CML MEDICATIONS
9E: MARKET NEWS AND UPDATES
9F: RECOMMENDATIONS
9G: UTILIZATION DETAILS OF ALL/CML MEDICATIONS
Materials included in agenda packet; presented by Dr. Schmidt
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: 30-DAY NOTICE TO PRIOR AUTHORIZE TURALIO™ (PEXIDARTINIB)
10A: INTRODUCTION
10B: TURALIO™ (PEXIDARTINIB) PRODUCT SUMMARY
10C: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Schmidt
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: ANNUAL REVIEW OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) MODULATORS
11A: CURRENT PRIOR AUTHORIZATION CRITERIA
11B: UTILIZATION OF CFTR MODULATORS
11C: PRIOR AUTHORIZATION OF CFTR MODULATORS
11D: MARKET NEWS AND UPDATES
11E: COLLEGE OF PHARMACY RECOMMENDATIONS
11F: UTILIZATION DETAILS OF CFTR MODULATORS
Materials included in agenda packet; presented by Dr. Nawaz
Dr. Broyles moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 12: ANNUAL REVIEW OF AMYLOIDOSIS MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE VYNDAQEL® (TAFAMIDIS MEGLUMINE) AND VYNDAMAX™ (TAFAMIDIS)
12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF AMYLOIDOSIS MEDICATIONS
12C: PRIOR AUTHORIZATION OF AMYLOIDOSIS MEDICATIONS
12D: MARKET NEWS AND UPDATES
12E: VYNDAQEL® (TAFAMIDIS MEGLUMINE) AND VYNDAMAX™ (TAFAMIDIS) PRODUCT SUMMARIES
12F: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **ANNUAL REVIEW OF VARIOUS SYSTEMIC ANTIBIOTICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE RECARBRIO™ (IMIPENEM/CILASTATIN/RELEBACTAM) AND XENLETA™ (LEFAMULIN)**

13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF VARIOUS SYSTEMIC ANTIBIOTICS
13C: PRIOR AUTHORIZATION OF VARIOUS SYSTEMIC ANTIBIOTICS
13D: MARKET NEWS AND UPDATES
13E: RECARBRIO™ (IMIPENEM/CILASTATIN/RELEBACTAM) PRODUCT SUMMARY
13F: XENLETA™ (LEFAMULIN) PRODUCT SUMMARY
13G: COLLEGE OF PHARMACY RECOMMENDATIONS
13H: UTILIZATION DETAILS OF VARIOUS SYSTEMIC ANTIBIOTICS

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

AGENDA ITEM NO. 14: **ANNUAL REVIEW OF HEPATITIS C MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE HARVONI® (LEDIPASVIR/SOFOSBUVIR ORAL PELLETS) AND SOVALDI® (SOFOSBUVIR ORAL PELLETS)**

14A: INTRODUCTION
14B: CURRENT PRIOR AUTHORIZATION CRITERIA
14C: TRENDS OF HEPATITIS C MEDICATION UTILIZATION
14D: HEPATITIS C SUMMARY STATISTICS FOR TREATED MEMBERS
14E: UTILIZATION OF HEPATITIS C MEDICATIONS
14F: PRIOR AUTHORIZATION OF HEPATITIS C MEDICATIONS
14G: MARKET NEWS AND UPDATES
14H: REGIMEN COMPARISON
14I: COLLEGE OF PHARMACY RECOMMENDATIONS
14J: UTILIZATION DETAILS OF HEPATITIS C MEDICATIONS

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

AGENDA ITEM NO. 15: **ANNUAL REVIEW OF SIGNIFOR® LAR (PASIREOTIDE)**

15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF SIGNIFOR® LAR (PASIREOTIDE)
15C: PRIOR AUTHORIZATION OF SIGNIFOR® LAR (PASIREOTIDE)
15D: MARKET NEWS AND UPDATES
15E: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: **INDUSTRY NEWS AND UPDATES**

16A: INTRODUCTION
16B: NEWS AND UPDATES

Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: **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. 18: **FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)**

18A: SKIN CANCER MEDICATIONS
18B: TARGETED IMMUNOMODULATOR AGENTS
18C: INREBIC® (FEDRATINIB)

18D: ELZONRIS® (TAGRAXOFUSP-ERZS)
18E: CONSTIPATION AND DIARRHEA MEDICATIONS
18F: ANTIDEPRESSANTS
18G: ATOPIC DERMATITIS MEDICATIONS
18H: ANTIVIRAL MEDICATIONS
18I: ANTICOAGULANTS AND PLATELET AGGREGATION INHIBITORS
**Future business subject to change.*
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: ADJOURNMENT
The meeting was adjourned at 4:52pm.

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

Memorandum

Date: October 10, 2019

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

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of October 9, 2019

Recommendation 1: Fall 2019 Pipeline Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Ezallor™ Sprinkle (Rosuvastatin Capsule) and Welchol® (Colesevelam Chewable Bar)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the placement of Ezallor™ Sprinkle (rosuvastatin capsule) and Welchol® (colesevelam chewable bar) into the Special Prior Authorization (PA) Tier of the Antihyperlipidemic Medications Product Based Prior Authorization (PBPA) category. In addition to the current Special PA criteria, the following criteria will apply (changes noted in red):

Antihyperlipidemic Medications*	
Tier-1	**Special PA**
atorvastatin (Lipitor®)	**colesevelam chewable bar (Welchol®)**
ezetimibe (Zetia®)	fluvastatin (Lescol® & Lescol® XL)
lovastatin (Mevacor®)	lovastatin ER (Altoprev®)

Antihyperlipidemic Medications*	
Tier-1	**Special PA**
pravastatin (Pravachol®)	pitavastatin calcium (Livalo®)
rosuvastatin **tablet** (Crestor®)	pitavastatin magnesium (Zypitamag™)
simvastatin (Zocor®)	**rosuvastatin capsule (Ezallor™ Sprinkle)**
	simvastatin suspension (FloLipid®)
	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.
ER = extended-release

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; and
2. Use of FloLipid® (simvastatin oral suspension) will require a patient-specific, clinically significant reason why the member cannot use simvastatin oral tablets, even when the tablets are crushed; and
3. Use of Ezallor™ Sprinkle (rosuvastatin capsule) will require a patient-specific, clinically significant reason why the member cannot use rosuvastatin oral tablets, even when the tablets are crushed; and
4. Use of Welchol® (colesevelam chewable bar) will require a patient-specific, clinically significant reason why the member cannot use other formulations of colesevelam, including oral tablets and packets for oral suspension, which are currently available without prior authorization.

Lastly, the College of Pharmacy recommends the following updates to the current PCSK9 Inhibitors Approval Criteria, based on the new FDA approved indications for Praluent® (changes noted in red):

PCSK9 Inhibitors Approval Criteria:

1. **For Repatha® (evolocumab):**
    a. An FDA approved diagnosis of homozygous familial hypercholesterolemia (HoFH) defined by the presence of at least 1 of the following:
        i. Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality via genetic testing; or
        ii. An untreated total cholesterol >500mg/dL and at least 1 of the following:
            1. Documented evidence of definite heterozygous familial hypercholesterolemia (HeFH) in both parents; or
            2. Presence of tendinous/cutaneous xanthoma prior to age 10 years; or
    b. An FDA approved diagnosis of primary hyperlipidemia (including HeFH); or
    c. An FDA approved indication to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease (CVD); and
        i. Documentation of established CVD; and
            1. Supporting diagnoses/conditions and dates of occurrence signifying established CVD; or

2. **For Praluent® (alirocumab):**
   ~~a. An FDA approved diagnosis of HeFH defined by the presence of 1 of the following criteria:~~
      ~~i. Documented functional mutation(s) in the LDL receptor (LDLR) gene or other HeFH-related genes via genetic testing; or~~
      ~~ii. Definite HeFH using either the Simon Broome Register criteria or the Dutch Lipid Network criteria; or~~
   ~~b. An FDA approved diagnosis of clinical atherosclerotic cardiovascular disease defined by the presence of 1 of the following criteria:~~
      ~~i. High cardiovascular risk confirmed by Framingham risk score; and~~
         ~~1. Supporting diagnoses/conditions signifying this risk level; or~~
      ~~ii. Documented history of Coronary Heart Disease (CHD); and~~
         ~~1. Supporting diagnoses/conditions and dates of occurrence signifying history of CHD; or~~
   c. An FDA approved diagnosis of primary hyperlipidemia (including HeFH); or
   d. An FDA approved indication to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established CVD; and
      i. Documentation of established CVD; and
         1. Supporting diagnoses/conditions and dates of occurrence signifying established CVD; and
3. Member must be 13 years of age or older for the diagnosis of HoFH or must be 18 years of age or older for all other FDA-approved diagnoses or indications; and
4. Member must be on high dose statin therapy (LDL reduction capability equivalent to rosuvastatin 40mg) or on maximally tolerated statin therapy; and
   a. Statin trials must be at least 12 weeks in duration (dosing, dates, duration of treatment, and reason for discontinuation must be provided); and
   b. LDL-cholesterol (LDL-C) levels should be included following at least 12 weeks of treatment with each statin medication; and
   c. For statin intolerance due to myalgia, creatine kinase (CK) labs verifying rhabdomyolysis must be provided; and
   d. Tier structure rules still apply; and
5. Member requires additional lowering of LDL-C (baseline, current, and goal LDL-C levels must be provided); and
6. Prescriber must verify that member has been counseled on appropriate use, storage of the medication, and administration technique; and
7. A quantity limit of 2 syringes or pens per 28 days will apply for Praluent®. A quantity limit of 2 syringes or auto-injectors per 28 days will apply for Repatha® 140mg and a quantity limit of 1 auto-injector per 28 days will apply for Repatha® 420mg. Requests for the Repatha® 420mg dose will not be approved for multiple 140mg syringes or auto-injectors but instead should use (1) 420mg auto-injector; and
8. Initial approvals will be for the duration of 3 months. Continued authorization at that time will require the prescriber to provide recent LDL-C levels to demonstrate the effectiveness of this medication, and compliance will be checked at that time and every 6 months thereafter for continued approval.

Recommendation 3: Vote to Prior Authorize Sorilux® (Calcipotriene 0.005% Foam)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Sorilux® (calcipotriene 0.005% foam) based on net cost with the following criteria:

Sorilux® (Calcipotriene 0.005% Foam) Approval Criteria:

1. An FDA approved indication for the topical treatment of plaque psoriasis of the scalp and body in patients 12 years of age and older; and
2. A patient-specific, clinically significant reason why the member cannot use the generic formulations of topical calcipotriene, which are available without a prior authorization, must be provided; and
3. A quantity limit of 120g per 30 days will apply.

Recommendation 4: Vote to Prior Authorize Herzuma® (Trastuzumab-pkrb), Kanjinti™ (Trastuzumab-anns), Ontruzant® (Trastuzumab-dttb), Piqray® (Alpelisib), Talzenna® (Talazoparib), and Trazimera™ (Trastuzumab-qyyp)

MOTION CARRIED by unanimous approval.

Halaven® (Eribulin) Approval Criteria [Recurrent or Metastatic Breast Cancer Diagnosis]:

1. Diagnosis of recurrent or metastatic breast cancer; and
2. Previously received at least 2 chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting; or
3. In combination with trastuzumab for human epidermal growth factor receptor 2 (HER2)-positive disease that is:
    a. Hormone receptor (HR)-negative; or
    b. HR-positive with or without endocrine therapy; or
4. As a single-agent for HER2-negative disease that is:
    a. HR-negative; or
    b. HR-positive with visceral crisis or endocrine therapy refractory.

Ibrance® (Palbociclib) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced, metastatic, hormone receptor positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer; and
2. In combination with:
    a. Letrozole as initial endocrine-based therapy in postmenopausal women; or
    b. Fulvestrant in women with disease progression following endocrine therapy; or
    c. An aromatase inhibitor or fulvestrant in male patients.

Kadcyla® (Ado-Trastuzumab) Approval Criteria [Early Stage or Locally Advanced Breast Cancer Diagnosis]:

1. Diagnosis of early stage or locally advanced breast cancer; and
2. Positive expression of human epidermal growth factor receptor 2 (HER2); and

3. Used as adjuvant treatment in members with residual invasive disease after neoadjuvant therapy with taxane and trastuzumab-based treatment; and
4. Maximum duration of a total of 14 cycles.

Lynparza® (Olaparib) Approval Criteria [Ovarian Cancer Diagnosis]:

1. **Treatment of Advanced Recurrent/Refractory Ovarian Cancer:**
   a. Diagnosis of deleterious or suspected deleterious germline BRCA-mutated (*gBRCAm*), advanced ovarian cancer; and
   b. Previous treatment with 3 or more prior lines of chemotherapy. Prior chemotherapy regimens should be documented on the prior authorization request; and
   c. A quantity limit based on FDA approved dosing will apply; or
2. **Maintenance Treatment of Advanced Ovarian Cancer:**
   a. Member must be in complete or partial response to first-line platinum based chemotherapy; and
      i. Diagnosis of deleterious or suspected deleterious *gBRCAm* or somatic BRCA-mutated *(sBRCAm)*, advanced ovarian cancer; or
   b. Complete or partial response to second-line or greater platinum-based based chemotherapy (no mutation required); and
   c. A quantity limit based on FDA approved dosing will apply.

Piqray® (Alpelisib) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced or metastatic breast cancer that has progressed on or after an endocrine-based regimen in men and postmenopausal women; and
2. Disease is hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative; and
3. Presence of PIK3CA-mutated disease; and
4. Must be used in combination with fulvestrant.

Talzenna® (Talazoparib) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of recurrent or metastatic breast cancer; and
2. Disease is human epidermal growth factor receptor 2 (HER2)-negative; and
3. Presence of BRCA 1/2-germline-mutated disease; and
4. Disease is hormone receptor (HR)-negative or HR-positive and endocrine therapy refractory; and
5. Member has symptomatic visceral disease; and
6. Must be used as a single-agent.

Herzuma® (Trastuzumab-pkrb), Kanjinti™ (Trastuzumab-anns), Ogivri™ (Trastuzumab-dkst), Ontruzant® (Trastuzumab-dttb), and Trazimera™ (Trastuzumab-qyyp) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of human epidermal receptor 2 (HER2)-overexpressing breast cancer; and
2. A patient-specific, clinically significant reason why the member cannot use Herceptin® (trastuzumab) must be provided.

Kanjinti™ (Trastuzumab-anns), Ogivri™ (Trastuzumab-dkst), Ontruzant® (Trastuzumab-dttb), and Trazimera™ (Trastuzumab-qyyp) Approval Criteria [Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Diagnosis]:

1. Diagnosis of human epidermal receptor 2 (HER2)-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma; and
2. A patient-specific, clinically significant reason why the member cannot use Herceptin® (trastuzumab) must be provided.

Recommendation 5: Vote to Prior Authorize Nubeqa® (Darolutamide)

MOTION CARRIED by unanimous approval.

Erleada® (Apalutamide) Approval Criteria [Castration-Resistant Prostate Cancer (CRPC) Diagnosis]:

1. Diagnosis of non-metastatic CRPC; or
2. Diagnosis of non-metastatic prostate cancer with disease progression while on androgen deprivation therapy; and
3. Prostate specific antigen doubling time of ≤10 months; and
4. Concomitant treatment with a gonadotropin-releasing hormone (GnRH) analog or prior history of bilateral orchiectomy.

Erleada® (Apalutamide) Approval Criteria [Castration-Sensitive Prostate Cancer (CSPC) Diagnosis]:

1. Diagnosis of metastatic CSPC; and
2. Concomitant treatment with a luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or prior history of bilateral orchiectomy.

Nubeqa® (Darolutamide) Approval Criteria [Castration-Resistant Prostate Cancer (CRPC) Diagnosis]:

1. Diagnosis of non-metastatic CRPC; and
2. Concomitant treatment with a gonadotropin-releasing hormone (GnRH) analog or prior history of bilateral orchiectomy.

Xtandi® (Enzalutamide) Approval Criteria [Castration-Resistant Prostate Cancer (CRPC) Diagnosis]:

1. Diagnosis of ~~metastatic,~~ CRPC.

Zytiga® (Abiraterone) Approval Criteria [Castration-Resistant Prostate Cancer (CRPC) Diagnosis]:

1. Diagnosis of metastatic CRPC; and
2. Abiraterone must be used in combination with a corticosteroid; and
3. Concomitant treatment with a gonadotropin-releasing hormone (GnRH) analog or prior history of bilateral orchiectomy.

Zytiga® (Abiraterone) Approval Criteria [Castration-Sensitive Prostate Cancer (CSPC) Diagnosis]:

1. Diagnosis of metastatic, high-risk CSPC; and
2. ~~High-risk disease defined as having at least 2 of the following risk factors:~~

~~a. Total Gleason score of ≥8; or~~
~~b. Presence of ≥3 lesions on bone scan; or~~
~~c. Evidence of measurable visceral metastases; and~~

3. Abiraterone must be used in combination with a corticosteroid.

Recommendation 6: Annual Review of Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) Medications

NO ACTION REQUIRED.

Recommendation 7: 30-Day Notice to Prior Authorize Turalio™ (Pexidartinib)

NO ACTION REQUIRED.

Recommendation 8: Annual Review of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends updating the current Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets) and Kalydeco® (ivacaftor) prior authorization criteria with the following changes noted in red:

Kalydeco® (Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) with a mutation in the CF transmembrane conductance regulator *(CFTR)* gene detected by genetic testing that is responsive to ivacaftor based on clinical and/or *in vitro* assay data; and
2. Documentation must be submitted with results of *CFTR* genetic testing; and
3. Member must be 6 months ~~1 year~~ of age or older; and
4. A quantity limit of 2 tablets or 2 granule packets per day (56 per 28 days) will apply; and
5. An age restriction of 6 months ~~1 years~~ to younger than 6 years of age will apply to Kalydeco® oral granule packets. Members 6 years of age or older will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation; and
6. Initial approval will be for the duration of 3 months, after which time compliance will be required for continued approval. After 6 months of utilization, compliance and information regarding efficacy, such as improvement in forced expiratory volume in 1 second (FEV_1), will be required for continued approval.

Symdeko® (Tezacaftor/Ivacaftor and Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in members who are homozygous for the *F508del* mutation or who have at least 1 mutation in the CF transmembrane conductance regulator *(CFTR)* gene detected by genetic testing that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence; and
2. If the member's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use; and

3. Member must be 6 ~~12~~ years of age or older; and
4. Members using Symdeko® must be supervised by a pulmonary specialist; and
5. If member is currently stabilized on Orkambi® (lumacaftor/ivacaftor) and experiencing adverse effects associated with Orkambi® use, the prescriber must indicate that information on the prior authorization request; and
6. Prescriber must verify that member has been counseled on proper administration of Symdeko® including taking with a fat-containing food; and
7. Prescriber must verify that ALT, AST, and bilirubin will be assessed prior to initiating Symdeko®, every 3 months during the first year of treatment, and annually thereafter; and
8. Member must not be taking any of the following medications concomitantly with Symdeko®: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort; and
9. A quantity limit of 2 tablets per day or 56 tablets per 28 days will apply; and
10. Initial approval will be for the duration of 3 months, after which time compliance will be required for continued approval. After 6 months of utilization, compliance and information regarding efficacy, such as improvement in forced expiratory volume in 1 second (FEV_1), will be required for continued approval. Additionally after 6 months of utilization, information regarding efficacy as previously mentioned or fewer adverse events must be provided for members who switched from Orkambi® to Symdeko®.

Recommendation 9: Annual Review of Amyloidosis Medications and 30-Day Notice to Prior Authorize Vyndaqel® (Tafamidis Meglumine) and Vyndamax™ (Tafamidis)

NO ACTION REQUIRED.

Recommendation 10: Annual Review of Various Systemic Antibiotics and 30-Day Notice to Prior Authorize Recarbrio™ (Imipenem/Cilastatin/Relebactam) and Xenleta™ (Lefamulin)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Hepatitis C Medications and 30-Day Notice to Prior Authorize Harvoni® (Ledipasvir/Sofosbuvir Oral Pellets) and Sovaldi® (Sofosbuvir Oral Pellets)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Signifor® LAR (Pasireotide)

NO ACTION REQUIRED.

Recommendation 13: Industry News and Updates

NO ACTION REQUIRED.

Recommendation 14: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

NO ACTION REQUIRED.

Recommendation 15: Future Business

NO ACTION REQUIRED.

Appendix C

2020 Drug Utilization Review Board Meeting Dates

Oklahoma Health Care Authority
November 2019

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

January 8, 2020

February 12, 2020

March 11, 2020

April 8, 2020

May 13, 2020

June 10, 2020

July 8, 2020

August 12, 2020

September 9, 2020

October 14, 2020

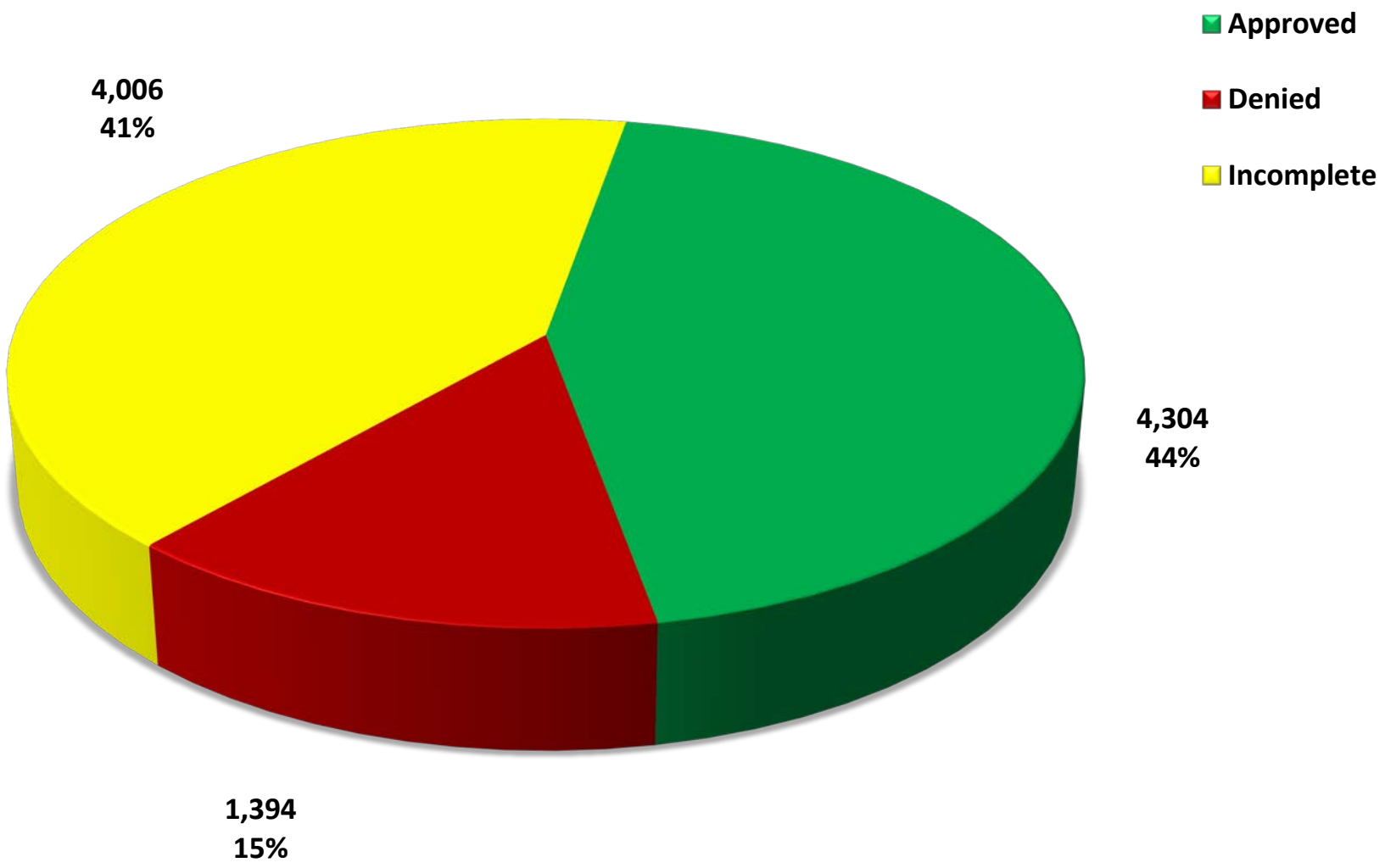
November 11, 2020**

***Meeting will need to be moved to account for Veteran's Day holiday*

December 9, 2020

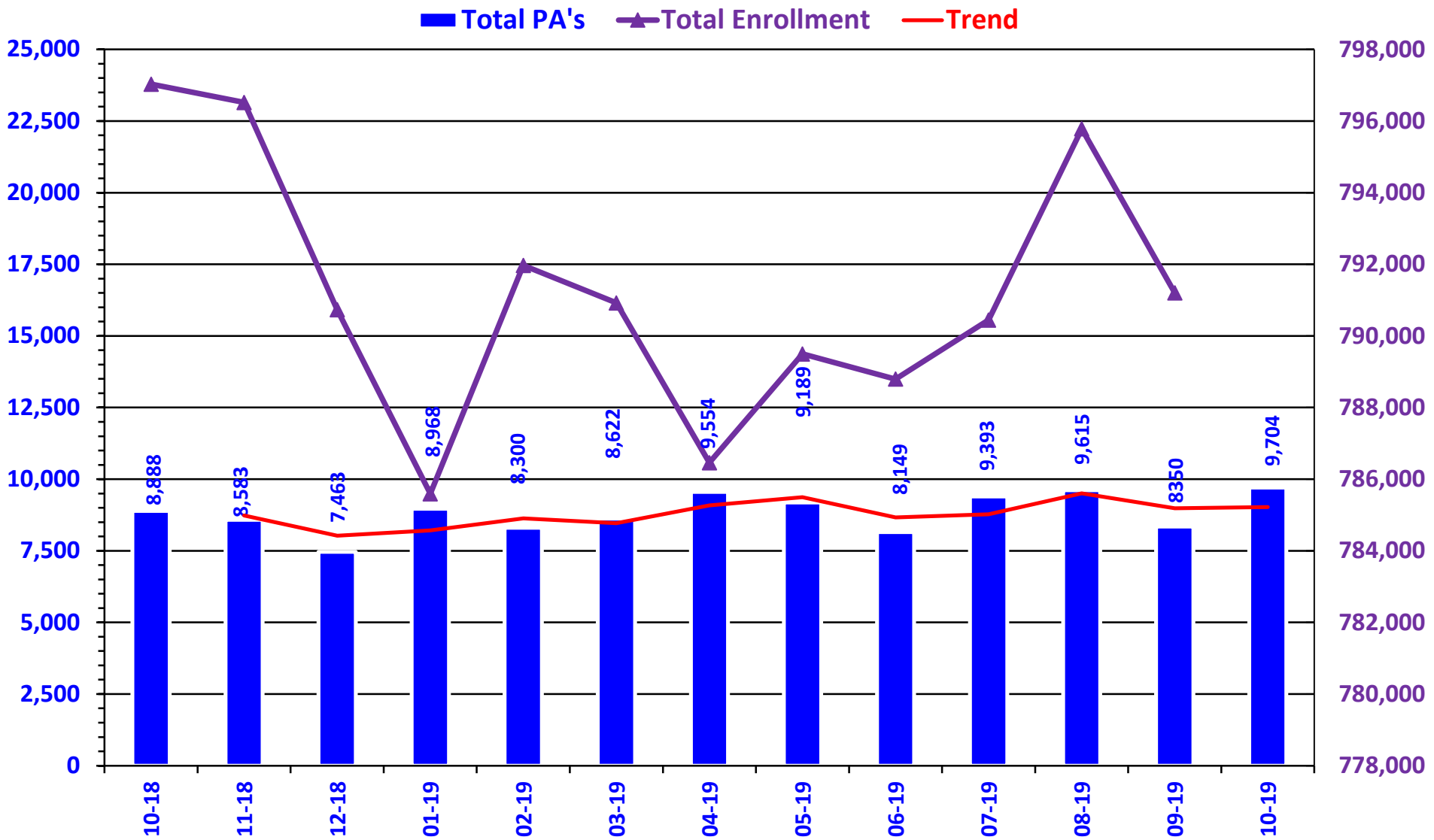
Appendix D

PRIOR AUTHORIZATION ACTIVITY REPORT: OCTOBER 2019



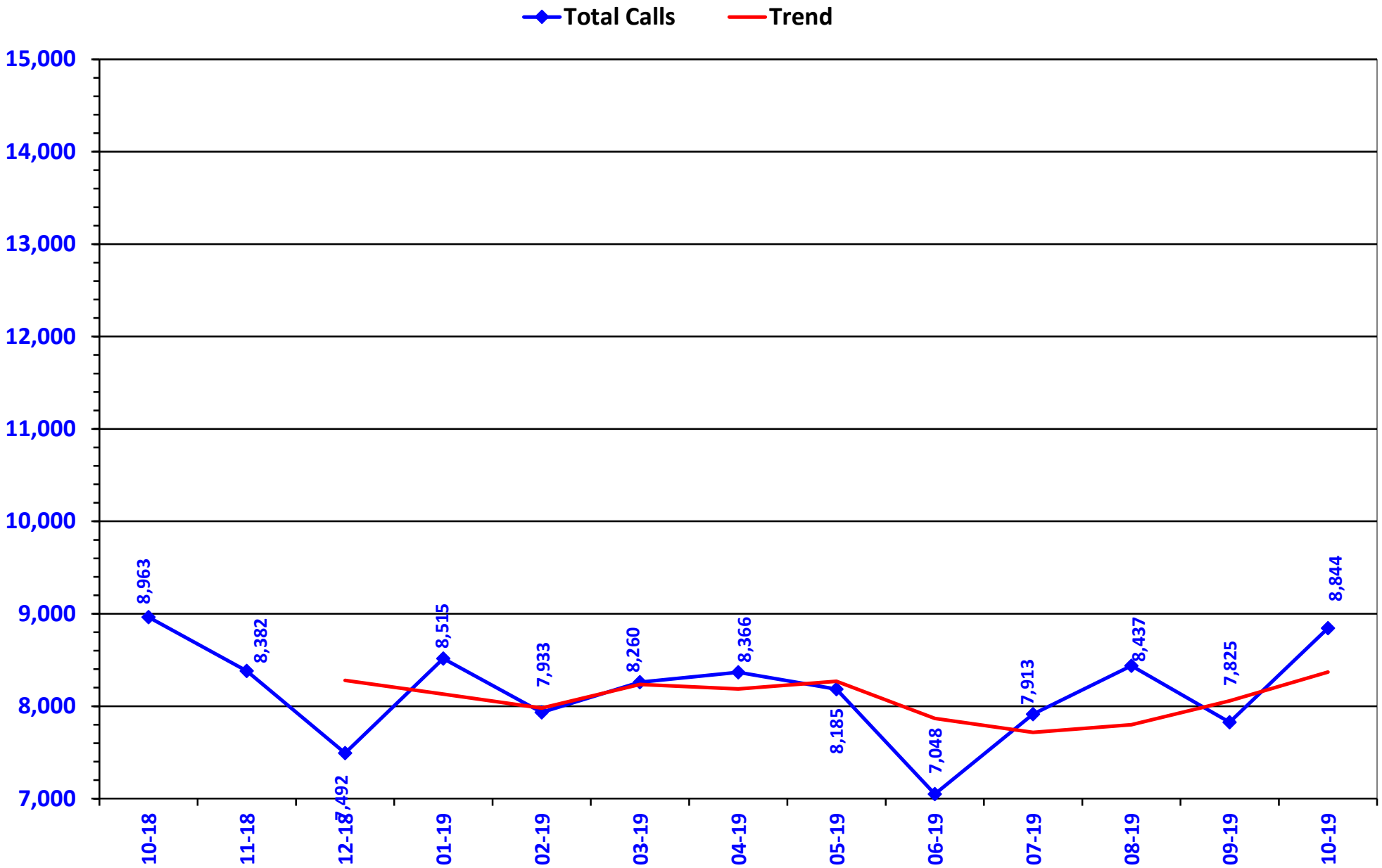
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: OCTOBER 2018 – OCTOBER 2019



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
OCTOBER 2018 – OCTOBER 2019



Prior Authorization Activity

10/1/2019 Through 10/31/2019

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	111	15	34	62	338
Analgesic - NonNarcotic	20	0	4	16	0
Analgesic - Narcotic	301	126	26	149	151
Angiotensin Receptor Antagonist	16	2	3	11	358
Antiasthma	102	22	24	56	250
Antibiotic	33	19	3	11	319
Anticonvulsant	169	79	17	73	304
Antidepressant	218	50	44	124	342
Antidiabetic	302	110	55	137	353
Antihemophilic Factor	12	7	0	5	146
Antihistamine	33	4	15	14	349
Antimigraine	151	30	46	75	122
Antineoplastic	106	63	14	29	163
Antiparasitic	20	4	8	8	16
Antiulcers	136	55	22	59	122
Anxiolytic	18	4	3	11	211
Atypical Antipsychotics	273	143	28	102	349
Biologics	198	92	28	78	280
Bladder Control	44	4	18	22	299
Blood Thinners	337	187	15	135	331
Botox	35	20	12	3	340
Buprenorphine Medications	97	14	2	81	78
Calcium Channel Blockers	11	2	4	5	104
Cardiovascular	53	22	1	30	315
Chronic Obstructive Pulmonary Disease	207	44	43	120	339
Constipation/Diarrhea Medications	176	33	50	93	180
Contraceptive	26	18	4	4	342
Corticosteroid	11	1	5	5	84
Dermatological	353	105	88	160	136
Diabetic Supplies	489	273	17	199	201
Endocrine & Metabolic Drugs	120	68	12	40	145
Erythropoietin Stimulating Agents	21	13	5	3	103
Fibric Acid Derivatives	10	0	2	8	0
Fibromyalgia	127	14	3	110	296
Fish Oils	12	0	6	6	0
Gastrointestinal Agents	117	26	25	66	189
Growth Hormones	113	78	5	30	144
Hepatitis C	196	113	21	62	8
HFA Rescue Inhalers	63	1	4	58	26
Insomnia	31	2	10	19	176
Insulin	160	60	16	84	349
Miscellaneous Antibiotics	11	3	1	7	13
Multiple Sclerosis	61	26	9	26	217
Muscle Relaxant	62	2	21	39	69
Nasal Allergy	89	8	31	50	96
Neurological Agents	131	48	23	60	214
Neuromuscular Agents	12	3	8	1	359
NSAIDs	39	2	14	23	268
Ocular Allergy	31	3	15	13	86

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Ophthalmic Anti-infectives	11	2	2	7	18
Ophthalmic Corticosteroid	11	3	2	6	47
Osteoporosis	22	10	5	7	340
Other*	371	72	80	219	240
Otic Antibiotic	20	2	3	15	6
Pediculicide	49	5	15	29	8
Respiratory Agents	23	15	0	8	246
Statins	38	7	14	17	218
Stimulant	734	333	85	316	346
Synagis	356	117	113	126	151
Testosterone	150	19	38	93	306
Topical Antifungal	18	3	4	11	40
Topical Corticosteroids	51	0	28	23	0
Vitamin	96	28	38	30	214
Pharmacotherapy	77	69	0	8	279
Emergency PAs	1	1	0	0	
Total	**7,492**	**2,704**	**1,291**	**3,497**	
Overrides					
Brand	41	19	3	19	330
Compound	20	18	0	2	90
Diabetic Supplies	16	15	1	0	125
Dosage Change	433	405	2	26	13
High Dose	2	2	0	0	193
Ingredient Duplication	6	4	0	2	8
Lost/Broken Rx	76	72	2	2	11
MAT Override	172	143	2	27	64
NDC vs Age	328	188	41	99	251
Nursing Home Issue	78	68	0	10	63
Opioid MME Limit	195	107	7	81	85
Opioid Quantity	43	34	4	5	166
Other*	63	53	0	10	14
Quantity vs. Days Supply	667	421	34	212	210
STBS/STBSM	21	15	4	2	80
Stolen	16	9	2	5	26
Third Brand Request	35	27	1	7	27
Overrides Total	**2,212**	**1,600**	**103**	**509**	
Total Regular PAs + Overrides	**9,704**	**4,304**	**1,394**	**4,006**	

Denial Reasons	
Unable to verify required trials.	3,322
Does not meet established criteria.	1,427
Lack required information to process request.	630
Other PA Activity	
Duplicate Requests	669
Letters	14,995
No Process	5
Changes to existing PAs	665
Helpdesk Initiated Prior Authorizations	791
PAs Missing Information	49

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

U.S. Food and Drug Administration (FDA) Safety Alerts

Oklahoma Health Care Authority
November 2019

Introduction[1,2,3,4,5,6,7,8]

The following are recent FDA safety alerts included for the Drug Utilization Review (DUR) Board's consideration. SoonerCare specific data may be presented where applicable. The College of Pharmacy will make recommendations as well as take recommendations from the DUR Board.

Date	Drug	Issue
02/21/2019	**Febuxostat (Uloric®)**	**Increased risk of death**
Issue Details: The FDA issued a Drug Safety Communication regarding the increased risk of death associated with febuxostat compared to allopurinol. The FDA determined the increased risk after an in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with febuxostat use. The trial was conducted in more than 6,000 patients with gout treated with either febuxostat or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and unstable angina. In patients treated with febuxostat, 15 deaths from heart-related causes were observed for every 1,000 patients treated for 1 year compared to 11 deaths from heart-related causes per 1,000 patients treated with allopurinol for 1 year. In addition, there were 26 deaths from any cause per 1,000 patients treated for 1 year with febuxostat compared to 22 deaths per 1,000 patients treated for 1 year with allopurinol. **FDA Recommendation(s):** The FDA is requiring a *Boxed Warning* be added to febuxostat labeling regarding the increased cardiovascular (CV) risks. The FDA is also limiting the approved use of febuxostat to patients who are not treated effectively or experience severe side effects with allopurinol. Prescribers should reserve febuxostat for use only in patients who have failed or do not tolerate allopurinol. Patients should be counseled about the CV risk with febuxostat and advised to seek medical attention immediately if they experience CV symptoms. **Pharmacy Claims Evaluation:** During fiscal year (FY) 2019 a total of 38 SoonerCare members had paid claims for febuxostat, accounting for 263 paid claims and an average of 6.92 paid claims per member. **SoonerCare Action:** All prior authorization requests for febuxostat require a patient-specific, clinically significant reason why allopurinol is not a viable option for the member, which is in line with current FDA recommendations that febuxostat be limited to patients who are not effectively treated with allopurinol.		

Date	Drug	Issue
02/25/2019	**Tofacitinib and Tofacitinib Extended-Release (ER) (Xeljanz®, Xeljanz® XR)**	**Increased risk of blood clots with use of higher dose**

Issue Details: The FDA issued a Drug Safety Communication regarding an increased risk of pulmonary embolism (PE) in patients using the 10mg twice daily dose of tofacitinib for the diagnosis of rheumatoid arthritis (RA). The 10mg twice daily dose is not FDA approved for RA; this dose is only approved for patients with ulcerative colitis (UC). During a recent analysis of a required on-going safety trial of RA patients with at least 1 CV risk factor, the FDA determined there was an increased risk of PE associated with the 10mg twice daily dose compared to the 5mg twice daily dose.
FDA Recommendation(s): The FDA added a *Boxed Warning* to the tofacitinib medicatoin-containing medication product labeling regarding an increased risk of PE and death with use of the 10mg twice daily dose. Additionally, the FDA limited use of tofacitinib for UC to patients who are not treated adequately or who experience severe adverse effects with other drugs.
Pharmacy Claims Evaluation: During FY 2019, a total of 4 SoonerCare members had paid claims for tofacitinib 10mg. The College of Pharmacy reviewed all authorizations for tofacitinib to ensure that no members were receiving the 10mg twice daily dose for an indication other than UC.
SoonerCare Action: Tofacitinib is currently in Tier-3 of the Targeted Immunomodulator Agent tier chart and requires use of other medications prior to approval through SoonerCare. The 10mg twice daily dose is only approved for members with a diagnosis of UC.

Date	Drug	Issue
04/9/2019	**Opioid-Containing Pain Medications**	**Risk of serious withdrawal symptoms with sudden discontinuation**

Issue Details: The FDA issued a Drug Safety Communication regarding the risk of serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide in patients who are physically dependent on opioid pain medications and who are suddenly discontinued from these therapies. Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse.
FDA Recommendation(s): The FDA is requiring changes to the prescribing information for opioid-containing medications that are intended for use in the outpatient setting. These changes will provide expanded guidance to health care professionals on how to safely decrease the dose in patients who are physically dependent on opioid pain medicines when the dose is to be decreased or the medicine is to be discontinued.
Pharmacy Claims Evaluation: During FY 2019, a total of 82,403 SoonerCare members had paid claims for an opioid-containing medication, accounting for 268,754 paid claims and an average of 3.26 claims per member.
SoonerCare Action: In January 2019, SoonerCare began implementation of morphine milligram equivalent (MME) limits for opioid-containing medications. These limits have been phased in gradually to give prescribers multiple opportunities to justify higher dosages or to

taper, where appropriate, in a cautious manner. The College of Pharmacy will continue to work with prescribers to ensure that members are not abruptly discontinued from opioid-containing medications.

Date	Drug	Issue
04/30/2019	**Insomnia Medications**	**Serious injuries caused by sleepwalking with certain insomnia medications**

Issue Details: The FDA issued a Drug Safety Communication regarding rare but serious injuries with insomnia medications because of sleep behaviors including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These behaviors appear to be more common with eszopiclone (Lunesta®), zaleplon (Sonata®), and zolpidem (Ambien®, Ambien CR®, Edluar®, Intermezzo®, Zolpimist®) than other prescription medications used for sleep.
FDA Recommendation(s): The FDA added a *Boxed Warning* to the prescribing information for medications containing eszopiclone, zaleplon, and zolpidem regarding the risk of injuries from sleep behaviors associated with the use of these medications. In addition, use of eszopiclone, zaleplon, and zolpidem is now contraindicated in patients who have previously experienced an episode of complex sleep behavior.
Pharmacy Claims Evaluation: During FY 2019, a total of 4,259 SoonerCare members had paid claims for medications containing eszopiclone, zaleplon, or zolpidem, accounting for 20,767 paid claims and an average of 4.88 claims per member.
SoonerCare Action: The College of Pharmacy provided an update regarding the new *Boxed Warning* for insomnia medications in the Fall 2019 SoonerCare Provider Newsletter.

Date	Drug	Issue
08/13/2019	**Entacapone (Comtan®) and Carbidopa/Levodopa/ Entacapone (Stalevo®)**	**No increased risk of prostate cancer with Parkinson's disease (PD) medications containing entacapone**

Issue Details: The FDA issued a Drug Safety Communication regarding a review of data finding no increased risk of prostate cancer with the use of entacapone to treat PD. The FDA conducted the additional review after an earlier trial suggested a possible increased risk of prostate cancer in patients utilizing entacapone-containing medications.
FDA Recommendation(s): The FDA recommendations for using entacapone-containing medications will remain the same as in the current prescribing information.
Pharmacy Claims Evaluation: During FY 2019, a total of 10 SoonerCare members had paid claims for medications containing entacapone, accounting for 76 paid claims and an average of 7.60 claims per member.
SoonerCare Action: The College of Pharmacy will continue to monitor the FDA recommendations.

Date	Drug	Issue
08/28/2019	**Hepatitis C Medications Containing a Protease Inhibitor**	**Risk of serious liver injury in some patients with advanced disease**

Issue Details: The FDA issued a Drug Safety Communication regarding the increased risk of rare, worsening cases of liver function or liver failure in patients with moderate-to-severe liver impairment (Child-Pugh B or C) and who utilized a hepatitis C medication containing a protease inhibitor [glecaprevir/pibrentasvir (Mavyret™), elbasvir/grazoprevir (Zepatier®), sofosbuvir/velpatasvir/voxilaprevir (Vosevi®)]. None of the hepatitis C medications that contain a protease inhibitor are indicated for use in patients with moderate-to-severe hepatic impairment. In many of the reported cases, liver failure occurred in patients who had signs and symptoms of moderate-to-severe liver impairment or other serious liver problems and should not have been treated with these medications. In most cases, liver failure or decompensation typically occurred within the first 4 weeks of starting treatment, and symptoms resolved or new onset worsening of liver function improved after stopping the medication.

FDA Recommendation(s): The FDA is recommending that prescribers continue to prescribe hepatitis C medications that contain a protease inhibitor to patients without liver impairment or with mild liver impairment as indicated in the prescribing information.

Pharmacy Claims Evaluation: During FY 2019, a total of 152 SoonerCare members had paid claims for hepatitis C medications containing a protease inhibitor, accounting for 327 paid claims and an average of 2.15 claims per member.

SoonerCare Action: Prior authorizations for hepatitis C medications that contain a protease inhibitor are not approved for members with a diagnosis of moderate-to-severe liver impairment (Child-Pugh B or C) as recommended in the prescribing information.

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[3] FDA. Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate. Available online at: https://www.fda.gov/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr. Issued 02/25/2019. Last accessed 10/28/2019.

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[5] FDA. FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering. Available online at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes. Issued 04/09/2019. Last accessed 10/28/2019.

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[8] FDA. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. Available online at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and. Issued 08/28/2019. Last accessed 10/30/2019.

Appendix E

Vote to Prior Authorize Harvoni® (Ledipasvir/Sofosbuvir Oral Pellets) and Sovaldi® (Sofosbuvir Oral Pellets)

Oklahoma Health Care Authority
November 2019

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

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

- **Mavyret™ (glecaprevir/pibrentasvir) Label Update:** In August 2018, the FDA approved updates to the Mavyret™ product labeling to include new data from the M14-730 hepatitis C virus (HCV)/human immunodeficiency virus (HIV)-1 co-infection study, and from the M13-596 liver and renal transplant study. Label updates included a revision to the *Dosage and Administration* section to state that Mavyret™ is recommended for 12 weeks in liver or kidney transplant recipients with HCV, and a 16-week treatment duration is recommended for genotype (GT) 1 HCV-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A protease inhibitor or in GT 3-infected patients who are pegylated interferon/ribavirin/sofosbuvir treatment-experienced.
- **Mavyret™ (glecaprevir/pibrentasvir) in Pediatric Patients:** In April 2019, the FDA approved Mavyret™ for the treatment of all 6 GTs of HCV in children 12 to 17 years of age. Mavyret™ was previously approved for the treatment of HCV in adults in 2017.
- **Harvoni® (ledipasvir/sofosbuvir) in Pediatric Patients:** In August 2019, the FDA approved Harvoni® for the treatment of chronic HCV in pediatric patients 3 years of age and older with GT 1, 4, 5, or 6. Harvoni® was previously approved in patients 12 years of age and older for the same indications. Along with the expanded indication, the FDA also approved a new oral pellet formulation of Harvoni® in 2 strengths: 33.75mg ledipasvir/150mg sofosbuvir or 45mg ledipasvir/200mg sofosbuvir as well as a new tablet strength: 45mg ledipasvir/200mg sofosbuvir. Previously, Harvoni® was only available as a 90mg ledipasvir/400mg sofosbuvir oral tablet. The recommended dose for patients weighing at least 35kg is 90mg/400mg per day. The recommended dose for patients weighing 17kg to <35kg is 45mg/200mg per day, and the recommended dose for patients weighing <17kg is 33.75mg/150mg per day. Launch plans for the oral pellets and new oral tablet strength are pending.
- **Sovaldi® (sofosbuvir) in Pediatric Patients:** In August 2019, the FDA approved Sovaldi® for the treatment of chronic HCV in pediatric patients 3 years of age and older with GT 2 or 3. Sovaldi® was previously approved in patients 12 years of age and older for the same indications. Along with the expanded indication, the FDA also approved a new oral pellet formulation of Sovaldi® in 2 strengths: 150mg or 200mg as well as a new tablet strength: 200mg. Previously, Sovaldi® was only available as a 400mg oral tablet. The recommended dose for patients weighing at least 35kg is 400mg per day. The recommended dose for patients weighing 17kg to <35kg is 200mg per day, and the recommended dose for patients weighing <17kg is 150mg per day. Launch plans for the oral pellets and new oral tablet strength are pending.

- **Mavyret™ (glecaprevir/pibrentasvir) 8-Week Regimen:** In September 2019, the FDA approved Mavyret™ to be used as an 8-week treatment course for the treatment of HCV in patients with compensated cirrhosis who are treatment naïve. Previously, the 8-week treatment course was only approved for treatment-naïve patients without cirrhosis; HCV-infected patients with compensated cirrhosis previously required treatment for 12 weeks. The approval applies to all 6 GTs of HCV.

Recommendations

The College of Pharmacy recommends the prior authorization of Harvoni® (ledipasvir/ sofosbuvir oral pellets) and Sovaldi® (sofosbuvir oral pellets) with criteria similar to Harvoni® (ledipasvir/sofosbuvir) and Sovaldi® (sofosbuvir) tablet formulations. Additionally, the College of Pharmacy recommends updating the Harvoni® (ledipasvir/sofosbuvir), Sovaldi® (sofosbuvir), and Mavyret™ (glecaprevir/pibrentasvir) prior authorization criteria based on new FDA approvals. The following criteria will apply (changes and additions noted in red):

Harvoni® (Ledipasvir/Sofosbuvir Tablets and Oral Pellets) Approval Criteria:

1. Member must be ~~12~~ 3 years of age or older; and
2. An FDA approved diagnosis of Chronic Hepatitis C (CHC) genotype (GT) 1, GT 4, GT 5, or GT 6; and
3. Request for the generic formulation will require a patient-specific, clinically significant reason the member cannot use the brand formulation; and***
4. Harvoni® must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated for hepatitis C treatment by a gastroenterologist, infectious disease specialist, or transplant specialist within the last 3 months; and
5. Hepatitis C Virus (HCV) GT testing must be confirmed and indicated on prior authorization request; and
6. Member has chronic HCV infection defined by:
    a. If the member has a liver fibrosis score ≥F1 (METAVIR equivalent) then only 1 detectable and quantifiable HCV RNA (>15 IU/mL) test within the last 12 months is required (must be within last 3 months if requesting 8-week regimen); or
    b. If the member has a liver fibrosis score <F1 (METAVIR equivalent) then the following must be met:
        i. Positive (i.e., reactive) HCV antibody test ~~that is at least 6 months old~~ and has a recent (within the last 3 months) detectable and quantifiable HCV RNA (>15 IU/mL) ~~test 6 months after date of positive HCV antibody test~~; or
        ii. Two detectable and quantifiable HCV RNA (>15 IU/mL) tests at least 6 months apart; and
7. The following regimens and requirements based on prior treatment experience, baseline viral load, and cirrhosis will apply:
    a. **GT-1:**
        i. Treatment-naïve without cirrhosis who have a pre-treatment HCV-RNA <6 million IU/mL: Harvoni® for 8 weeks

ii. Treatment-naïve patients who are cirrhotic or have a pre-treatment HCV-RNA >6 million IU/mL: Harvoni® for 12 weeks
iii. Treatment-experienced without cirrhosis: Harvoni® for 12 weeks
iv. Treatment-experienced with compensated cirrhosis:
    1. Harvoni® with weight-based ribavirin for 12 weeks; or
    2. Harvoni® for 24 weeks
v. Treatment-naïve or treatment-experienced with decompensated cirrhosis: Harvoni® with weight-based ribavirin for 12 weeks

b. **GT-1 or GT-4:**
    i. Treatment-naïve or treatment-experienced liver transplant recipients with or without compensated cirrhosis: Harvoni® with weight-based ribavirin for 12 weeks

c. **GT-4, GT-5, or GT-6:**
    i. Treatment-naïve or treatment-experienced with or without compensated cirrhosis: Harvoni® for 12 weeks

d. New regimens will apply as approved by the FDA; and

8. Members who are 6 years of age and older and request the oral pellet formulation of Harvoni® must provide a patient-specific, clinically significant reason for use of the oral pellet formulation in place of the tablet formulation; and
9. Member must sign and submit the Hepatitis C Intent to Treat contract; and
10. Member's pharmacy must submit the Hepatitis C Therapy Pharmacy Agreement for each member on therapy; and
11. The prescriber must verify that they will provide SoonerCare with all necessary labs to evaluate hepatitis C therapy efficacy including Sustained Virologic Response (SVR-12); and
12. Prescriber must agree to counsel members on potential harms of illicit intravenous (IV) drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
13. Must have documentation of initiation of immunization with the hepatitis A and B vaccines; and
14. Member must not have severe renal impairment [estimated Glomerular Filtration Rate (eGFR) <30mL/min/1.73m^2]; and
15. Female members must not be pregnant and must have a pregnancy test immediately prior to therapy initiation. Male and female members must be willing to use 2 forms of non-hormonal birth control while on therapy (and for 6 months after therapy completion for those on ribavirin); and
16. Member must not be taking the following medications: rifampin, rifabutin, rifapentine, carbamazepine, eslicarbazepine, phenytoin, phenobarbital, oxcarbazepine, tipranavir/ ritonavir, simeprevir, rosuvastatin, St. John's wort, or elvitegravir/cobicistat/ emtricitabine in combination with tenofovir disoproxil fumarate; and
17. All other clinically significant issues must be addressed prior to starting therapy including but not limited to the following: neutropenia, anemia, thrombocytopenia, surgery, depression, psychosis, epilepsy, obesity, weight management, severe concurrent medical diseases, such as but not limited to, retinal disease or autoimmune thyroid disease; and

18. Member must not have a limited life expectancy (<12 months) that cannot be remediated by treating hepatitis C virus (HCV), liver transplantation, or another directed therapy; and
19. Prescribing physician must verify that they will work with the member to ensure the member remains adherent to hepatitis C therapies; and
20. Member must be adherent for continued approval. Treatment gaps of therapy longer than 3 days/month will result in denial of subsequent requests for continued therapy; and
21. Approvals for treatment regimen initiation for 8 or 12 weeks of therapy will not be granted prior to the 10th of a month, and for 24 weeks of therapy prior to the 15th of a month in order to prevent prescription limit issues from affecting the member's compliance.
    ****The brand formulation of Harvoni® is preferred based on net cost after rebates, and products may be moved to non-preferred if the net cost changes in comparison to other available products.*

Sovaldi® (Sofosbuvir Tablets and Oral Pellets) Approval Criteria:

1. Member must be ~~12~~ 3 years of age or older; and
2. An FDA approved diagnosis of Chronic Hepatitis C (CHC) genotype (GT) 1, GT 2, GT 3, or GT 4; and
3. Requests for the generic formulation will require a patient-specific, clinically significant reason the member cannot use the brand formulation; and***
4. Sovaldi® must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated for hepatitis C treatment by a gastroenterologist, infectious disease specialist, or transplant specialist within the last 3 months; and
5. Sovaldi® must be used as a component of a combination regimen; and
6. Hepatitis C Virus (HCV) genotype testing must be confirmed and indicated on prior authorization request; and
7. Member has chronic HCV infection defined by:
    a. If the member has a liver fibrosis score ≥F1 (METAVIR equivalent) then only 1 detectable and quantifiable HCV RNA (>15 IU/mL) test within the last 12 months is required; or
    b. If the member has a liver fibrosis score <F1 (METAVIR equivalent) then the following must be met:
        i. Positive (i.e., reactive) HCV antibody test ~~that is at least 6 months old~~ and has a recent (within the last 3 months) detectable and quantifiable HCV RNA (>15 IU/mL) ~~test 6 months after date of positive HCV antibody test~~; or
        ii. Two detectable and quantifiable HCV RNA (>15 IU/mL) tests at least 6 months apart; and
8. The following regimens and requirements based on prior treatment experience, baseline viral load, and cirrhosis will apply:
    a. **GT-1:**
        i. Treatment-naïve or experienced, non-cirrhotic or cirrhotic: Sovaldi® with weight-based ribavirin and peginterferon alfa for 12 weeks

b. **GT-2:**
    i. Treatment-naïve, non-cirrhotic: Sovaldi® with weight-based ribavirin for 12 weeks
    ii. Treatment-naïve, cirrhotic: Sovaldi® with weight-based ribavirin for 12 or 16 weeks
    iii. Treatment-experienced, non-cirrhotic or cirrhotic:
        1. Sovaldi® with weight-based ribavirin for 12 or 16 weeks; or
        2. Sovaldi® with weight-based ribavirin and peginterferon alfa for 12 weeks
c. **GT-3:**
    i. Treatment-naïve or experienced, non-cirrhotic and cirrhotic:
        1. Sovaldi® with weight-based ribavirin and peginterferon alfa for 12 weeks; or
        2. Sovaldi® with weight-based ribavirin for 24 weeks (if interferon ineligible)
d. **GT-4:**
    i. Treatment-naïve or experienced, non-cirrhotic and cirrhotic:
        1. Sovaldi® with weight-based ribavirin and peginterferon alfa for 12 weeks
e. New regimens will apply as approved by the FDA; and

9. Members who are older than 6 years of age and request the oral pellet formulation of Sovaldi® must provide a patient-specific, clinically significant reason for use of the oral pellet formulation in place of the tablet formulation; and
10. Member must sign and submit the Hepatitis C Intent to Treat contract; and
11. Member's pharmacy must submit the Hepatitis C Therapy Pharmacy Agreement for each member on therapy; and
12. The prescriber must verify that they will provide SoonerCare with all necessary labs to evaluate hepatitis C therapy efficacy including Sustained Virologic Response (SVR-12); and
13. Prescriber must agree to counsel members on potential harms of illicit intravenous (IV) drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
14. Must have documentation of initiation of immunization with the hepatitis A and B vaccines; and
15. Member must not have decompensated cirrhosis; and
16. Female members must not be pregnant and must have a pregnancy test immediately prior to therapy initiation. Male and female members must be willing to use 2 forms of non-hormonal birth control while on therapy (and for 6 months after therapy completion for those on ribavirin); and
17. Member must not be taking the following medications: rifampin, rifabutin, rifapentine, carbamazepine, phenytoin, oxcarbazepine, tipranavir/ritonavir, didanosine, or St. John's wort; and
18. All other clinically significant issues must be addressed prior to starting therapy including but not limited to the following: neutropenia, anemia, thrombocytopenia, surgery, depression, psychosis, epilepsy, obesity, weight management, severe

concurrent medical diseases, such as but not limited to, retinal disease or autoimmune thyroid disease; and

19. Member must not have a limited life expectancy (<12 months) that cannot be remediated by treating hepatitis C virus (HCV), liver transplantation, or another directed therapy; and
20. Prescribing physician must verify that they will work with the member to ensure the member remains adherent to hepatitis C therapies; and
21. Member must be adherent for continued approval. Treatment gaps of therapy longer than 3 days/month will result in denial of subsequent requests for continued therapy.
22. Approvals for treatment regimen initiation for 12 weeks of therapy will not be granted prior to the 10th of a month, and for 24 weeks of therapy prior to the 15th of a month in order to prevent prescription limit issues from affecting the member's compliance; and
23. Additionally, due to superior SVR rates and shortened treatment durations with Harvoni®, authorization of Sovaldi® for GT-1 will require a patient-specific, clinically significant reason why Harvoni® is not an option.
    ****The brand formulation of Sovaldi® is preferred based on net cost after rebates, and products may be moved to non-preferred if the net cost changes in comparison to other available products.*

Mavyret™ (Glecaprevir/Pibrentasvir) Approval Criteria:

1. Member must be ~~18~~ 12 years of age or older or weigh at least 45kg; and
2. An FDA approved diagnosis of Chronic Hepatitis C (CHC) genotype (GT) 1, GT 2, GT 3, GT 4, GT 5, or GT 6; and
3. Mavyret™ must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated for hepatitis C treatment by a gastroenterologist, infectious disease specialist, or transplant specialist within the last 3 months; and
4. Hepatitis C Virus (HCV) genotype testing must be confirmed and indicated on the prior authorization request; and
5. Member has chronic HCV infection defined by:
    a. If the member has a liver fibrosis score ≥F1 (METAVIR equivalent) then only 1 detectable and quantifiable HCV RNA (>15 IU/mL) test within the last 12 months is required; or
    b. If the member has a liver fibrosis score <F1 (METAVIR equivalent) then the following must be met:
        i. Positive (i.e., reactive) HCV antibody test ~~that is at least 6 months old~~ and has a recent (within the last 3 months) detectable and quantifiable HCV RNA (>15 IU/mL) ~~test 6 months after date of positive HCV antibody test~~; or
        ii. Two detectable and quantifiable HCV RNA (>15 IU/mL) tests at least 6 months apart; and
6. The following regimens and requirements based on cirrhosis status, viral genotype, and treatment history will apply (new regimens will apply as approved by the FDA):

Genotype	Prior Treatment Experience	No Cirrhosis	Compensated Cirrhosis
1, 2, 3, 4, 5, or 6	Treatment-Naïve	8 weeks	~~12~~ 8 weeks
1	NS5A w/o NS3/4A PI	16 weeks	16 weeks
1	NS3/4A PI w/o NS5A	12 weeks	12 weeks
1, 2, 4, 5, or 6	PRS	8 weeks	12 weeks
3	PRS	16 weeks	16 weeks

w/o = without; PI = protease inhibitor; PRS = pegylated interferon, ribavirin, and/or sofsobuvir
Examples of NS5A inhibitors include: daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir
Examples of NS3/4A PIs include: boceprevir, glecaprevir, grazoprevir, paritaprevir, simeprevir, telaprevir, voxilaprevir
HCV/HIV-1 co-infection and patients with any degree of renal impairment follow the same dosage recommendations in the table above. Liver or Kidney Transplant Recipients: Mavyret™ is recommended for 12 weeks in adult and pediatric patients 12 years and older or weighing at least 45 kg who are liver or kidney transplant recipients. A 16-week treatment duration is recommended in GT 1-infected patients who are NS5A inhibitor-experienced without prior treatment with an NS3/4A PI or in GT 3-infected patients who are PRS treatment-experienced.

7. Member must sign and submit the Hepatitis C Intent to Treat contract; and
8. Member's pharmacy must submit the Hepatitis C Therapy Pharmacy Agreement for each member on therapy; and
9. The prescriber must verify that they will provide SoonerCare with all necessary labs to evaluate hepatitis C therapy efficacy including Sustained Virologic Response (SVR-12); and
10. Prescriber must agree to counsel members on the potential harms of illicit intravenous (IV) drug use or alcohol use and member must agree to no illicit IV drug use or alcohol use while on treatment and post-therapy; and
11. Must have documentation of initiation of immunization with the hepatitis A and B vaccines; and
12. Member must not have decompensated cirrhosis or moderate or severe hepatic impairment (Child-Pugh B or C); and
13. Member must not have a limited life expectancy (<12 months) that cannot be remediated by treating HCV, liver transplantation, or another directed therapy; and
14. Female members must not be pregnant and must have a pregnancy test immediately prior to therapy initiation. Male and female members must be willing to use 2 forms of non-hormonal birth control while on therapy; and
15. Member must not be taking the following medications: carbamazepine, rifampin, ethinyl estradiol-containing medications, St. John's wort, atazanavir, darunavir, lopinavir, ritonavir, efavirenz, atorvastatin, lovastatin, simvastatin, rosuvastatin doses greater than 10mg per day, or cyclosporine doses greater than 100mg per day; and
16. All other clinically significant issues must be addressed prior to starting therapy including but not limited to the following: neutropenia, anemia, thrombocytopenia, surgery, depression, psychosis, epilepsy, obesity, weight-management, severe concurrent medical diseases, such as but not limited to, retinal disease, or autoimmune thyroid disease; and
17. Prescribing physician must verify that they will work with the member to ensure the member remains adherent to hepatitis C therapies; and
18. Approval of the 8-week carton (in place of the 4-week carton) requires a patient-specific, clinically significant reason why the member requires the 8-week carton in place of the 4-week carton; and

19. Member must be adherent for continued approval. Treatment gaps of therapy longer than 3 days/month will result in denial of subsequent requests for continued therapy; and
20. Approvals for treatment regimen initiation for 8 or 12 weeks of therapy will not be granted prior to the 10th of a month, and for 16 weeks of therapy prior to the 15th of a month in order to prevent prescription limit issues from affecting the member's compliance.

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[1] Han DH. Mavyret Labeling Updated With Dosing for Liver, Kidney Transplant Patients. *MPR*. Available online at: https://www.empr.com/home/news/mavyret-labeling-updated-with-dosing-for-liver-kidney-transplant-patients/. Issued 08/10/2018. Last accessed 10/14/2019.

[2] FDA. FDA approves first treatment for all genotypes of hepatitis C in pediatric patients. Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-all-genotypes-hepatitis-c-pediatric-patients. Issued 04/30/2019. Last accessed 10/14/2019.

[3] OptumRx. Harvoni® (ledipasvir/sofosbuvir) – Expanded orphan indication, new formulation approval. Available online at: https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapprovals_harvoni_2019-0830.pdf. Issued 08/2019. Last accessed 10/14/2019.

[4] OptumRx. Sovaldi® (sofosbuvir) – Expanded orphan indication, new formulation approval. Available online at: https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-approvals/drugapprovals_sovaldi_2019-0830.pdf. Issued 08/2019. Last accessed 10/14/2019.

[5] FDA. FDA approves treatment for adults and children with all genotypes of hepatitis C and compensated cirrhosis that shortens duration of treatment to eight weeks. Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-treatment-adults-and-children-all-genotypes-hepatitis-c-and-compensated-cirrhosis. Issued 09/26/2019. Last accessed 10/14/2019.

Appendix F

Vote to Prior Authorize Vyndaqel® (Tafamidis Meglumine) and Vyndamax™ (Tafamidis)

Oklahoma Health Care Authority
November 2019

Introduction[1]

Vyndaqel® (tafamidis meglumine) and Vyndamax™ (tafamidis) are transthyretin (TTR) stabilizers indicated for the treatment of wild type or hereditary cardiomyopathy transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (CV) mortality and CV-related hospitalization. Vyndaqel® is supplied as a 20mg oral capsule and Vyndamax™ is supplied as a 61mg oral capsule. Vyndamax™ was developed for patient convenience and is not substitutable with Vyndaqel® on a per milligram basis. The recommended dosing is either Vyndaqel® 80mg [(4) 20mg tafamidis meglumine capsules] once daily or Vyndamax™ 61mg once daily.

Cost: The Wholesale Acquisition Cost (WAC) of Vyndaqel® (tafamidis meglumine) is $156.25 per 20mg capsule, and the WAC of Vyndamax™ (tafamidis) is $625.00 per 61mg capsule. This results in a cost per 30 days, based on recommended dosing, of $18,750.00 for either product.

Recommendations

The College of Pharmacy recommends the prior authorization of Vyndaqel® (tafamidis meglumine) and Vyndamax™ (tafamidis) with the following criteria:

Vyndaqel® (Tafamidis Meglumine) and Vyndamax™ (Tafamidis) Approval Criteria:

1. An FDA approved indication for the treatment of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (CV) mortality and CV-related hospitalization; and
2. Diagnosis confirmed by:
    a. Genetic confirmation of transthyretin (*TTR*) mutation (e.g., Val122Ile) or wild-type amyloidosis; and
    b. Cardiac imaging (including ultrasound or MRI) confirming cardiac involvement; and
3. Presence of amyloid deposits confirmed by:
    a. Nuclear scintigraphy; or
    b. Endomyocardial biopsy; and
4. Member must have medical history of heart failure (NYHA Class I to III); and
5. Prescriber must confirm light-chain amyloidosis (AL) has been ruled out; and
6. Vyndaqel® or Vyndamax™ must be prescribed by or in consultation with a cardiologist or geneticist (or an advanced care practitioner with a supervising physician who is a cardiologist or geneticist); and
7. Prescriber must verify Vyndaqel® or Vyndamax™ will not be used concomitantly with Onpattro® (patisiran) or Tegsedi™ (inotersen); and

8. Initial approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment; and
9. A quantity limit of 4 Vyndaqel® capsules or 1 Vyndamax™ capsule per day will apply.

Additionally, the College of Pharmacy recommends the following changes shown in red to the current Onpattro® and Tegsedi™ approval criteria:

Onpattro® (Patisiran) Approval Criteria:

1. An FDA approved indication for the treatment of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis; and
2. Diagnosis confirmed by the following:
    a. Tissue (fat pad) biopsy confirming amyloid deposits; and
    b. Genetic confirmation of transthyretin (*TTR*) gene mutation (e.g., Val30Met); and
3. Onpattro® must be prescribed by or in consultation with a cardiologist, geneticist, or neurologist (or an advanced care practitioner with a supervising physician who is a cardiologist, geneticist, or neurologist); and
4. Prescriber must confirm the member will take the recommended daily allowance of vitamin A; and
5. Prescriber must confirm the member will be pre-medicated with intravenous (IV) corticosteroid, oral acetaminophen, IV histamine-1 (H_1) antagonist, and IV histamine-2 (H_2) antagonist 60 minutes prior to Onpattro® administration to reduce the risk of infusion-related reaction(s); and
6. Onpattro® will not be approved for concomitant use with Tegsedi™ (inotersen), Vyndaqel® (tafamidis meglumine), or Vyndamax™ (tafamidis); and
7. 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; and
8. Onpattro® approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Tegsedi™ (Inotersen) Approval Criteria:

1. An FDA approved indication for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis; and
2. Diagnosis confirmed by the following:
    a. Tissue (fat pad) biopsy confirming amyloid deposits; and
    b. Genetic confirmation of transthyretin (*TTR*) gene mutation (e.g., Val30Met); and
3. Tegsedi™ must be prescribed by or in consultation with a cardiologist, geneticist, or neurologist (or an advanced care practitioner with a supervising physician who is a cardiologist, geneticist, or neurologist); and
4. Prescriber must confirm the member will take the recommended daily allowance of vitamin A; and
5. Prescriber must agree to monitor ALT, AST, and total bilirubin prior to initiation of Tegsedi™ and every 4 months during treatment; and
6. Prescriber must confirm the first injection of Tegsedi™ administered by the member or caregiver will be performed under the guidance of a health care professional; and

7. Prescriber must confirm the member or caregiver has been trained by a health care professional on the subcutaneous (sub-Q) administration and proper storage of Tegsedi™; and
8. Tegsedi™ will not be approved for concomitant use with Onpattro® (patisiran), Vyndaqel® (tafamidis meglumine), or Vyndamax™ (tafamidis); and
9. Prescriber, pharmacy, and member must be enrolled in the Tegsedi™ Risk Evaluation and Mitigation Strategy (REMS) program and maintain enrollment throughout therapy; and
10. Tegsedi™ approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment; and
11. A quantity limit of 4 syringes per 28 days will apply.

[1] Vyndaqel® and Vyndamax™ Prescribing Information. Pfizer. Available online at: http://labeling.pfizer.com/ShowLabeling.aspx?id=11685. Last revised 08/2019. Last accessed 10/21/2019.

Appendix G

Vote to Prior Authorize Recarbrio™ (Imipenem/Cilastatin/ Relebactam) and Xenleta™ (Lefamulin)

Oklahoma Health Care Authority
November 2019

Introduction[1,2,3,4,5,6,7,8,9,10]

- **Avycaz® (ceftazidime/avibactam)** was approved by the U.S. Food and Drug Administration (FDA) in March 2019 for a label expansion to include the treatment of pediatric patients 3 months of age and older with complicated intra-abdominal infections (cIAI), used in combination with metronidazole, or complicated urinary tract infections (cUTI), including pyelonephritis, caused by designated susceptible microorganisms. Ceftazidime/avibactam was first FDA approved in 2015 for the treatment of adult patients with the aforementioned indications and was subsequently approved in 2018 for the treatment of adult patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by designated susceptible microorganisms. Avycaz® is supplied as a 2.5g (ceftazidime/ avibactam 2g/0.5g) vial for intravenous (IV) infusion, and the recommended dosage of ceftazidime/avibactam and duration of treatment varies based on indication and patient weight (for pediatric patients). To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftazidime/avibactam and other antibacterial drugs, ceftazidime/avibactam should be used only to treat indicated infections that are proven or strongly suspected to be caused by susceptible bacteria (*refer to Avycaz® prescribing information for specific microbiology information)*.
- **Zerbaxa® (ceftolozane/tazobactam)** was approved by the FDA in June 2019 for the treatment of adult patients with HABP/VABP caused by designated susceptible gram-negative microorganisms. Ceftolozane/tazobactam was first FDA approved in 2014 for the treatment of adult patients with cIAI, used in combination with metronidazole, or cUTI, including pyelonephritis, caused by designated susceptible microorganisms. Zerbaxa® is supplied as a 1.5g (ceftolozane/tazobactam 1g/0.5g) vial for IV infusion, and the recommended dosage of ceftolozane/tazobactam and duration of treatment varies based on indication, severity and site of infection, and clinical and bacteriological progress. To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftolozane/tazobactam and other antibacterial drugs, ceftolozane/ tazobactam should be used only to treat indicated infections that are proven or strongly suspected to be caused by susceptible bacteria (*refer to Zerbaxa® prescribing information for specific microbiology information)*.
- **Recarbrio™ (imipenem/cilastatin/relebactam)** was approved by the FDA in July 2019 for use in adult patients who have limited or no alternative treatment options for the treatment of cIAI or cUTI, including pyelonephritis, caused by designated susceptible microorganisms. Recarbrio™ is supplied as a dry powder in a 1.25g (imipenem/ cilastatin/relebactam 500mg/500mg/250mg) single-dose vial (SDV) that must be

constituted and further diluted prior to IV infusion. The recommended dosage of imipenem/cilastatin/relebactam for patients with creatinine clearance (CrCl) ≥90mL/min is 1.25g administered every 6 hours by IV infusion over 30 minutes for 4 to 14 days, with the duration of treatment based on the severity and location of the infection (*refer to Recarbrio™ prescribing information for recommended dosing in patients with CrCl <90mL/min).* Cost information for Recarbrio™ is not yet available.

- **Xenleta™ (lefamulin),** a pleuromutilin antibacterial, was approved by the FDA in August 2019 for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) caused by designated susceptible microorganisms. Xenleta™ is supplied as 600mg oral tablets and as 150mg/15mL SDVs that require further dilution prior to IV infusion. The recommended dosage of lefamulin is 150mg administered every 12 hours by IV infusion over 60 minutes for 5 to 7 days, with the option to switch to oral tablets to complete the treatment course, or 600mg orally every 12 hours for 5 days (*refer to Xenleta™ prescribing information for recommended dosing in patients with severe hepatic impairment*). The Wholesale Acquisition Cost (WAC) of Xenleta™ is $137.50 per 600mg tablet or $102.45 per 150mg/15mL SDV for IV infusion, resulting in an estimated cost of lefamulin therapy of $1,375.00 for 5 days of oral therapy or $1,024.50 to $1,434.30 for 5 to 7 days of IV therapy.
- **Baxdela® (delafloxacin)** was approved by the FDA in October 2019 for the treatment of adult patients with CABP caused by designated susceptible bacteria. Delafloxacin was first FDA approved in 2017 for the treatment of adult patients with acute bacterial skin and skin structure infection (ABSSSI) caused by designated susceptible bacteria. Baxdela® is supplied as 450mg oral tablets and as 300mg SDVs that must be reconstituted and further diluted prior to IV infusion, and the recommended dosage of delafloxacin is 450mg orally or 300mg via IV infusion over 60 minutes every 12 hours for 5 to 14 days for ABSSSI or 5 to 10 days for CABP. To reduce the development of drug-resistant bacteria and maintain the effectiveness of delafloxacin and other antibacterial drugs, delafloxacin should be used only to treat indicated infections that are proven or strongly suspected to be caused by susceptible bacteria (*refer to Baxdela® prescribing information for specific microbiology information)*.

Recommendations

The College of Pharmacy recommends the prior authorization of Recarbrio™ (imipenem/ cilastatin/relebactam) and Xenleta™ (lefamulin) with the following criteria:

Recarbrio™ (Imipenem/Cilastatin/Relebactam) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following infections caused by designated susceptible microorganisms:
    a. Complicated intra-abdominal infection (cIAI); or
    b. Complicated urinary tract infection (cUTI), including pyelonephritis; and
2. Member must be 18 years of age or older; and
3. The prescriber must verify that limited or no alternative treatment options are available; and

4. A patient-specific, clinically significant reason why the member cannot use an appropriate penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenem (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s) must be provided; and
5. A quantity limit of 56 vials per 14 days will apply.

Xenleta™ (Lefamulin) Approval Criteria:

1. An FDA approved diagnosis of community-acquired bacterial pneumonia (CABP) caused by designated susceptible microorganisms; and
2. Member must be 18 years of age or older; and
3. A patient-specific, clinically significant reason why the member cannot use an appropriate beta-lactam (e.g., ceftriaxone, cefotaxime, ceftaroline, ertapenem, ampicillin/sulbactam) in combination with a macrolide (e.g., azithromycin, clarithromycin) or doxycycline, or other cost-effective therapeutic equivalent alternative(s) must be provided; and
4. Approval quantity will be based on Xenleta™ prescribing information and FDA approved dosing regimen(s).

Additionally, the College of Pharmacy recommends updating the current approval criteria for Avycaz® (ceftazidime/avibactam), Zerbaxa® (ceftolozane/tazobactam), and Baxdela® (delafloxacin) based on the new FDA approved indications (changes noted in red):

Avycaz® (Ceftazidime/Avibactam) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following infections caused by designated susceptible microorganisms:
    a. Complicated intra-abdominal infection (cIAI), used in combination with metronidazole; or
    b. Complicated urinary tract infection (cUTI), including pyelonephritis; or
    c. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP); and
2. Member must be ~~18 years~~ 3 months of age or older; and
3. For the diagnosis of cIAI, Avycaz® must be used in combination with metronidazole; and
4. A patient-specific, clinically significant reason why the member cannot use an appropriate penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenem (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s) must be provided; and
5. ~~A quantity limit of 42 vials per 14 days will apply.~~ Approval quantity will be based on Avycaz® prescribing information and FDA approved dosing regimen(s).

Zerbaxa® (Ceftolozane/Tazobactam) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following infections caused by designated susceptible microorganisms:

a. Complicated intra-abdominal infection (cIAI), used in combination with metronidazole; or
b. Complicated urinary tract infection (cUTI), including pyelonephritis; ~~and~~ or
c. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP); and

2. Member must be 18 years of age or older; and
3. For the diagnosis of cIAI, Zerbaxa® must be used in combination with metronidazole; and
4. A patient-specific, clinically significant reason why the member cannot use an appropriate penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenem (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s) must be provided; and
5. ~~A quantity limit of 42 vials per 14 days will apply.~~ Approval quantity will be based on Zerbaxa® prescribing information and FDA approved dosing regimen(s).

Baxdela® (Delafloxacin) Tablet and Vial Approval Criteria [Acute Bacterial Skin and Skin Structure Infection (ABSSSI) Diagnosis]:

1. An FDA approved diagnosis of ~~acute bacterial skin and skin structure infection (~~ABSSSI~~)~~ caused by designated susceptible bacteria; and
2. A patient-specific, clinically significant reason why the member cannot use vancomycin, linezolid, doxycycline, trimethoprim/sulfamethoxazole, or other cost-effective therapeutic equivalent alternative(s) must be provided; and
3. Approval quantity will be based on Baxdela® prescribing information and FDA approved dosing regimen(s); and
   a. For Baxdela® vials, an initial quantity limit of 6 vials for a 3-day supply will apply. Continued authorization will require a patient-specific, clinically significant reason why the member cannot switch to the oral tablets for the remainder of therapy.

Baxdela® (Delafloxacin) Tablet and Vial Approval Criteria [Community-Acquired Bacterial Pneumonia (CABP) Diagnosis]:

1. An FDA approved diagnosis of CABP caused by designated susceptible bacteria; and
2. A patient-specific, clinically significant reason why the member cannot use an appropriate beta-lactam (e.g., ceftriaxone, cefotaxime, ceftaroline, ertapenem, ampicillin/sulbactam) in combination with a macrolide (e.g., azithromycin, clarithromycin) or doxycycline, monotherapy with a respiratory fluoroquinolone (e.g., levofloxacin, moxifloxacin, gemifloxacin), or other cost-effective therapeutic equivalent alternative(s) must be provided; and
3. Approval quantity will be based on Baxdela® prescribing information and FDA approved dosing regimen(s); and
   a. For Baxdela® vials, an initial quantity limit of 6 vials for a 3-day supply will apply. Continued authorization will require a patient-specific, clinically significant reason why the member cannot switch to the oral tablets for the remainder of therapy.

Lastly, the College of Pharmacy recommends updating the current approval criteria for ciprofloxacin 100mg tablets, ciprofloxacin 500mg and 1,000mg extended-release tablets, and ofloxacin 300mg and 400mg tablets and moxifloxacin 400mg tablets, based on the current low net cost of moxifloxacin 400mg tablets (changes noted in red):

Ciprofloxacin 100mg Tablet Approval Criteria:

1. Approval requires a patient-specific, clinically significant reason why the member cannot use alternative strengths of ciprofloxacin tablets, levofloxacin tablets, moxifloxacin tablets, or other cost-effective therapeutic equivalent alternative(s).

Ciprofloxacin 500mg and 1,000mg Extended-Release (ER) Tablets Approval Criteria:

1. Approval requires a patient-specific, clinically significant reason why the member cannot use the immediate-release formulation of ciprofloxacin tablets, levofloxacin tablets, moxifloxacin tablets, or other cost-effective therapeutic equivalent alternative(s).

Ofloxacin 300mg and 400mg Tablet ~~and Moxifloxacin 400mg Tablet~~ Approval Criteria:

1. Approval requires a patient-specific, clinically significant reason why the member cannot use ciprofloxacin tablets, levofloxacin tablets, moxifloxacin tablets, or other cost-effective therapeutic equivalent alternative(s).

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[1] Allergan. Allergan Announces FDA Approval of Avycaz® (Ceftazidime and Avibactam) for Pediatric Patients. *BioSpace.* Available online at: https://www.biospace.com/article/releases/allergan-announces-fda-approval-of-avycaz-ceftazidime-and-avibactam-for-pediatric-patients/. Issued 03/18/2019. Last accessed 10/14/2019.

[2] Avycaz® (Ceftazidime/Avibactam) Prescribing Information. Allergan. Available online at: https://www.allergan.com/assets/pdf/avycaz_pi. Last revised 03/2019. Last accessed 10/14/2019.

[3] Merck. FDA Approves Merck's Zerbaxa® (Ceftolozane and Tazobactam) 3g Dose for the Treatment of Adults with Hospital-Acquired and Ventilator-Associated Bacterial Pneumonia (HABP/VABP). Available online at: https://www.mrknewsroom.com/news-release/corporate-news/fda-approves-mercks-zerbaxa-ceftolozane-and-tazobactam-3g-dose-treatment. Issued 06/03/2019. Last accessed 10/14/2019.

[4] Zerbaxa® (Ceftolozane/Tazobactam) Prescribing Information. Merck. Available online at: https://www.merck.com/product/usa/pi_circulars/z/zerbaxa/zerbaxa_pi.pdf. Last revised 06/2019. Last accessed 10/14/2019.

[5] Merck. FDA Approves Merck's Recarbrio™ (Imipenem, Cilastatin, and Relebactam) for the Treatment of Adults with Complicated Urinary Tract and Complicated Intra-Abdominal Bacterial Infections Where Limited or No Alternative Treatment Options are Available. Available online at: https://www.mrknewsroom.com/news-release/prescription-medicine-news/fda-approves-mercks-recarbrio-imipenem-cilastatin-and-releba. Issued 07/17/2019. Last accessed 10/14/2019.

[6] Recarbrio™ (Imipenem/Cilastatin/Relebactam) Prescribing Information. Merck. Available online at: https://www.merck.com/product/usa/pi_circulars/r/recarbrio/recarbrio_pi.pdf. Last revised 07/2019. Last accessed 10/14/2019.

[7] Nabriva Therapeutics. Nabriva Therapeutics Receives U.S. FDA Approval of Xenleta™ (Lefamulin) to Treat Community-Acquired Bacterial Pneumonia (CABP). Available online at: https://investors.nabriva.com/news-releases/news-release-details/nabriva-therapeutics-receives-us-fda-approval-xenleta. Issued 08/19/2019. Last accessed 10/14/2019.

[8] Xenleta™ (Lefamulin) Prescribing Information. Nabriva Therapeutics. Available online at: https://www.xenleta.com/pdf/xenleta-prescribing-information.pdf. Last revised 08/2019. Last accessed 10/14/2019.

[9] Brooks M. FDA Approves New Indication for Delafloxacin (Baxdela®) for CABP. *Medscape.* Available online at: https://www.medscape.com/viewarticle/920429?nlid=132276_3901&src=wnl_newsalrt_191025_MSCPEDIT&uac=151193DK&impID=2143722&faf=1. Issued 10/25/2019. Last accessed 10/28/2019.

[10] Baxdela® (Delafloxacin) Prescribing Information. Melinta Therapeutics. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/208610s007,208611s006lbl.pdf. Last revised 10/2019. Last accessed 10/28/2019.

Appendix H

Vote to Prior Authorize Turalio™ (Pexidartinib)

Oklahoma Health Care Authority
November 2019

Introduction[1]

Turalio™ (Pexidartinib):

- **Therapeutic Class:** Kinase inhibitor
- **Indication(s):** Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery
- **How Supplied:** 200mg capsule
- **Dose:** 400mg orally twice daily
- **Cost:** Wholesale Acquisition Cost (WAC) of $165 per 200mg capsule; resulting in a monthly cost of $19,800

Recommendations

Turalio™ (Pexidartinib) Approval Criteria [Soft Tissue Sarcoma – Pigmented Villonodular Synovitis (PVNS)/Tenosynovial Giant Cell Tumor (TGCT) Diagnosis]:

1. Member must not be a candidate for surgery; and
2. Pexidartinib must be used as a single-agent only.

[1] Turalio™ Prescribing Information. Daiichi Sankyo Company, Limited. Available online at: https://dsi.com/prescribing-information-portlet/getPIContent?productName=Turalio&inline=true. Last revised 08/2019. Last accessed 10/28/2019.

Appendix I

Fiscal Year 2019 Annual Review of Skin Cancer Medications

Oklahoma Health Care Authority
November 2019

Introduction[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16]

Skin cancers are commonly divided into 2 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 increase. 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.

According to the National Cancer Institute, in 2019, an estimated 96,480 new cases of melanoma skin cancer will be diagnosed in the United States, resulting in 7,230 deaths from the disease. 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 a very small 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 U.S. Food and Drug Administration (FDA) approval of the following agents in the last 5 years: encorafenib, binimetinib, 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. Use of these agents has also expanded into the adjuvant setting. 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.

Current Prior Authorization Criteria

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.

Braftovi® (Encorafenib) Approval Criteria [Melanoma Diagnosis]:

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
3. Used in combination with binimetinib.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
    a. Cobimetinib is not indicated for wild-type BRAF melanoma; and
3. Member meets 1 of the following:
    a. Used as first-line therapy in combination with vemurafenib; or
    b. Used as second-line therapy or subsequent therapy with vemurafenib.

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.

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

1. Diagnosis of unresectable cutaneous, subcutaneous, or nodal lesions that are recurrent after initial surgery; and
    a. Talimogene laherparepvec is not indicated in members with visceral metastases; and
2. Member is not immunocompromised or pregnant.

Keytruda® (Pembrolizumab) Approval Criteria [Cervical Cancer Diagnosis]:

1. Diagnosis of recurrent or metastatic cervical cancer; and
2. Member has had disease progression on or after chemotherapy; and
3. Tumors must express PD-L1 [Combined Positive Score (CPS) ≥1]; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Gastric or Gastroesophageal Junction Tumor Diagnosis]:

1. Diagnosis of recurrent, locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma; and
2. Tumors must express PD-L1; and
3. Disease progression on or after 2 or more prior systemic therapies (including fluoropyrimidine- and platinum-containing chemotherapy, and if appropriate, HER2/neu-targeted therapy); and
4. Member has not previously failed other PD-1 inhibitors [e.g., 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. Member has received a prior platinum-containing regimen (i.e., cisplatin, carboplatin); and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
5. Dose does not exceed 200mg every 3 weeks.

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

1. Diagnosis of relapsed or progressive HCC; and
2. Member must have been previously treated with sorafenib; and
3. Member has not previously failed other PD-1 inhibitors [e.g., 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; and
2. Pembrolizumab must be used as a single-agent; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

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

1. Member meets 1 of the following:
    a. Adjuvant treatment of members with melanoma with involvement of lymph node(s) following complete resection; or
    b. Diagnosis of unresectable or metastatic melanoma; and
2. Pembrolizumab must be used as a single-agent; and
3. Member meets 1 of the following:
    b. Pembrolizumab is being used as first-line therapy; or
    c. Pembrolizumab is being used as second-line therapy or subsequent therapy for disease progression if not previously used; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
5. For adjuvant treatment of melanoma, dose as follows:
    d. 200mg every 3 weeks; and
    e. Maximum duration of 1 year.

Keytruda® (Pembrolizumab) Approval Criteria [Merkel Cell Carcinoma (MCC) Diagnosis]:

1. Diagnosis of recurrent, locally advanced or metastatic MCC; and
2. No history of prior systemic chemotherapy; and
3. Pembrolizumab must be used as a single-agent; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

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

1. Diagnosis of metastatic NSCLC; and
2. 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. As a single-agent, first-line: ≥1%; or
    b. First-line in combination: no expression required; or
    c. As a single-agent, second-line: ≥1%; and
4. Member meets 1 of the following:
    a. Previously untreated, metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel; or
    b. Previously untreated, metastatic non-squamous NSCLC in combination with pemetrexed and carboplatin; or
    c. New diagnosis as first-line therapy (member has not received chemotherapy to treat disease) if: Tumor does not express sensitizing Epidermal Growth Factor Receptor (EGFR) mutations or Anaplastic Lymphoma Kinase (ALK) translocations; or
    d. Single-agent for disease progression on or after platinum-containing chemotherapy (i.e., cisplatin or carboplatin):
        i. Members with EGFR-mutation-positive should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations* (*examples of drugs for EGFR-mutation-positive tumors: osimertinib, erlotinib, afatinib, or gefitinib);* and
        ii. Members 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 (examples of drugs for ALK-mutation-positive tumors: crizotinib, ceritinib, or alectinib).*

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

1. Member must have 1 of the following:
    a. MSI-H or dMMR solid tumors that have progressed following prior treatment with no satisfactory alternative treatment options; or
    b. MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; and
2. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

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

1. Diagnosis of stage III NSCLC; and
2. Ineligible for surgery or definitive chemoradiation; and
3. Tumor proportion scores for PD-L1 expression ≥1%; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Primary Mediastinal Large B-cell Lymphoma (PMBCL) Diagnosis]:

1. Diagnosis of PMBCL; and
2. Member must have refractory disease or pembrolizumab must be used in members who have relapsed after 2 or more prior lines of therapy; and
3. Authorizations will not be granted for members who require urgent cytoreduction; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Renal Cell Carcinoma (RCC) Diagnosis]:

1. Newly diagnosed or recurrent stage IV clear-cell RCC; and
2. No previous systemic therapy for advanced disease; and
3. Must be used in combination with Inlyta® (axitinib); and
4. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

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

1. Member must have 1 of the following:
    a. Locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy; or
    b. Within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; or
    c. Frontline pembrolizumab for members with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy; and
        i. Cisplatin ineligibility is defined as:
            1. Baseline creatinine clearance of <60mL/min; or
            2. ECOG performance status of 2; or
            3. Class III heart failure; or
            4. Grade 2 or greater peripheral neuropathy; or
            5. Grade 2 or greater hearing loss; and
2. Member has not previously failed other PD-1 inhibitors [i.e., Opdivo® (nivolumab)].

Libtayo® (Cemiplimab-rwlc) Approval Criteria [Cutaneous Squamous Cell Carcinoma (CSCC) Diagnosis]:

1. Diagnosis of metastatic or locally advanced CSCC; and
2. Member is not eligible for curative surgery or radiation; and
3. Member has not received prior immunotherapy agent(s) [e.g., Keytruda® (pembrolizumab), Opdivo® (nivolumab), Yervoy® (ipilimumab)].

Mekinist® (Trametinib) Approval Criteria [Anaplastic Thyroid Cancer (ATC) Diagnosis]:

1. Diagnosis of ATC; and
2. Locally advanced or metastatic disease; and
3. BRAF V600E mutation; and
4. No satisfactory locoregional treatment options.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
    a. Trametinib is not indicated for wild-type BRAF melanoma; and
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; or
    c. Used as second-line therapy or subsequent therapy as a single-agent if:
        i. Member 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).

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

1. BRAF V600E or V600K mutation; and
    a. Trametinib is not indicated for wild-type BRAF NSCLC; and
2. Diagnosis of refractory or metastatic disease; and
3. Trametinib must be used in combination with dabrafenib.

Mektovi® (Binimetinib) Approval Criteria [Melanoma Diagnosis]:

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
3. Used in combination with encorafenib.

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.

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

1. Member has had complete resection of melanoma; and
2. Diagnosis of stage III B/C melanoma following complete resection; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
4. Nivolumab must be used as a single-agent; and
5. Dose as follows:
    a. Single-agent: 240mg every 2 weeks or 480mg every 4 weeks; and
    b. Maximum duration of 1 year.

Opdivo® (Nivolumab) Approval Criteria [Head and Neck Cancer Diagnosis]:

1. Diagnosis of recurrent or metastatic head and neck cancer; and
2. Squamous cell histology; and
3. Member has received prior platinum-containing regimen (i.e., cisplatin, carboplatin); and
4. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
5. Dose as follows: 240mg every 2 weeks or 480mg every 4 weeks.

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

1. Diagnosis of relapsed or progressive HCC; and
2. Member must have been previously treated with sorafenib; and
3. Member has not previously failed other PD-1 inhibitors [e.g., 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; and
2. Nivolumab must be used as a single-agent; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)].

Opdivo® (Nivolumab) Approval Criteria [Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer (mCRC) Diagnosis]:

1. Diagnosis of MSI-H or dMMR mCRC; and
2. Progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)].

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

1. Diagnosis of metastatic NSCLC; and
2. Tumor histology is 1 of the following:
    a. Adenocarcinoma; or
    b. Squamous cell; or
    c. Large cell; and
3. Disease progression on or after platinum-containing chemotherapy (i.e., cisplatin, carboplatin); and
4. Nivolumab must be used as a single-agent; and
5. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
6. Dose as follows: 240mg every 2 weeks or 480mg every 4 weeks.

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

1. For nivolumab monotherapy:
    a. Diagnosis of relapsed or surgically unresectable stage IV disease; and

b. Failed prior therapy with 1 of the following medications:
    i. Sunitinib; or
    ii. Sorafenib; or
    iii. Pazopanib; or
    iv. Axitinib; or
2. For nivolumab use in combination with ipilimumab:
    a. Diagnosis of relapsed or surgically unresectable stage IV disease in the initial treatment of members with intermediate or poor risk, previously untreated, advanced RCC; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
4. Dose as follows:
    a. Single-agent: 240mg every 2 weeks or 480mg every 4 weeks; or
    b. In combination with ipilimumab: nivolumab 3mg/kg followed by ipilimumab 1mg/kg on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240mg every 2 weeks or 480mg every 4 weeks.

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

1. One of the following criteria is met:
    a. Disease relapsed within 6 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. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)].

Opdivo® (Nivolumab) Approval Criteria [Unresectable or Metastatic 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 member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
3. Dose as follows:
    a. Single-agent: 240mg every 2 weeks or 480mg every 4 weeks; or
    b. In combination with ipilimumab: nivolumab 1mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then 240mg every 2 weeks or 480mg every 4 weeks.

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

1. A diagnosis of metastatic or unresectable locally advanced cancer; and
2. Used as second-line or greater therapy; and
3. Member has failed a platinum-containing regimen; and
4. Member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)].

Tafinlar® (Dabrafenib) Approval Criteria [Anaplastic Thyroid Cancer (ATC) Diagnosis]:

1. Diagnosis of ATC; and
2. Locally advanced or metastatic disease; and
3. BRAF V600E mutation; and
4. No satisfactory locoregional treatment options.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
    a. Dabrafenib is not indicated for wild-type BRAF melanoma; and
3. Dabrafenib must be used as a single-agent or in combination with trametinib; and
4. One of the following is met:
    a. Used as first-line therapy; or
    b. Used as second-line therapy or subsequent therapy.

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

1. Diagnosis of refractory or metastatic disease; and
2. BRAF V600E or V600K mutation; and
    a. Dabrafenib is not indicated for wild-type BRAF NSCLC; and
3. Dabrafenib must be used as a single-agent or in combination with trametinib.

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

1. Member has had complete resection of melanoma with lymphadenectomy; and
2. Member has stage III disease with regional nodes of >1mm and no in-transit metastasis; and
3. Ipilimumab must be used as a single-agent; and
4. Maximum dose of 10mg/kg will apply.

Yervoy® (Ipilimumab) Approval Criteria [Renal Cell Carcinoma (RCC) Diagnosis]:

1. Diagnosis of relapsed or surgically unresectable stage IV disease in the initial treatment of members with intermediate or poor risk, previously untreated, advanced RCC; and
2. Ipilimumab must be used in combination with nivolumab; and
3. Member has not failed previous PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
4. Dose as follows: nivolumab 3mg/kg followed by ipilimumab 1mg/kg on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240mg every 2 weeks or 480mg every 4 weeks.

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

1. One of the following criteria is met:
    a. Disease relapsed within 6 months of initial chemotherapy; or
    b. Disease is progressive on initial chemotherapy; and
2. Used in combination with nivolumab.

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 1 of the following:
   a. First-line therapy as a single course of 4 treatments; or
   b. Second-line or subsequent lines of therapy as a single course of 4 treatments; or
   c. Retreatment, consisting of a 4-dose limit, for a member who had:
      i. No significant systemic toxicity during prior ipilimumab therapy; and
      ii. Whose disease progressed after being stable >6 months following completion of a prior course of ipilimumab; and
      iii. For whom no intervening therapy has been administered; and
3. Maximum dose of 3mg/kg will apply.

Zelboraf® (Vemurafenib) Approval Criteria [Erdheim-Chester Disease (ECD) Diagnosis]:

1. Diagnosis of ECD; and
2. BRAF V600E or V600K mutation; and
3. 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).

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
   a. Vemurafenib is not indicated for wild-type BRAF melanoma; and
3. One of the following is met:
   a. Used as first-line therapy; or
   b. Used as second-line or subsequent therapy; and
4. Vemurafenib must be used as a single-agent or in combination with cobimetinib.

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

1. Diagnosis of refractory or metastatic disease; and
2. BRAF V600E or V600K mutation; and
   a. Vemurafenib is not indicated for wild-type BRAF NSCLC; and
3. Vemurafenib must be used as a single-agent.

Utilization of Skin Cancer Medications: Fiscal Year 2019

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
2018	18	117	$1,006,456.73	$8,602.19	$294.80	9,536	3,414
2019	13	110	$970,103.34	$8,819.12	$300.16	9,121	3,232
% Change	**-27.80%**	**-6.00%**	**-3.60%**	**2.50%**	**1.80%**	**-4.40%**	**-5.30%**
Change	**-5**	**-7**	**-$36,353.39**	**$216.93**	**$5.36**	**-415**	**-182**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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

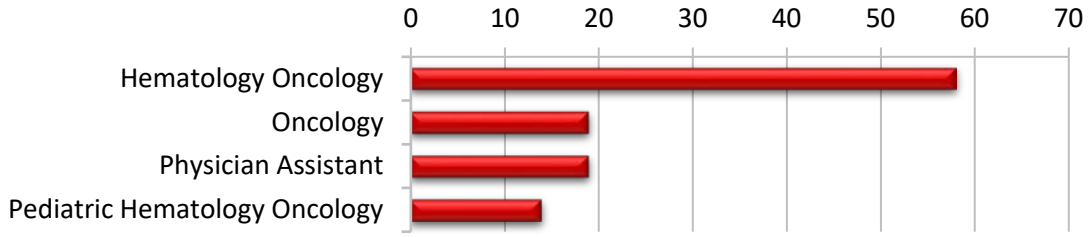
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
2018	97	519	$4,655,347.33	$8,969.84	129,439
2019	139	673	$7,409,976.85	$11,010.37	206,349
% Change	**43.30%**	**29.67%**	**59.17%**	**22.75%**	**59.42%**
Change	**42**	**154**	**$2,754,629.52**	**$2,040.53**	**76,910**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Demographics of Members Utilizing Skin Cancer Medications: Pharmacy Claims

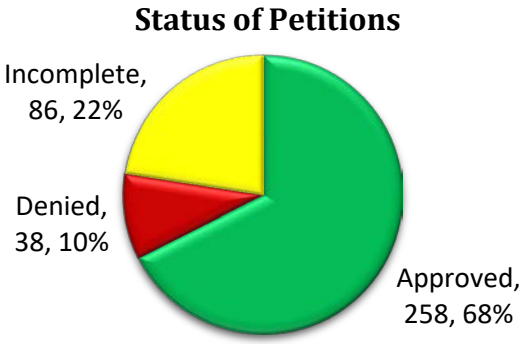
- Due to the limited number of members utilizing skin cancer medications, detailed demographic information could not be provided.

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



Prior Authorization of Skin Cancer Medications

There were 382 prior authorization requests submitted for 202 unique members for skin cancer medications during fiscal year 2019. The following chart shows the status of the submitted petitions for fiscal year 2019.



Market News and Updates[17]

New U.S. Food and Drug Administration (FDA) Approved Indication(s) and Label Update(s):

- **April 2019:** The FDA approved Keytruda® (pembrolizumab) for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) or stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation. Patients' tumors must have no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic aberrations and must express PD-L1 [Tumor Proportion Score (TPS) ≥1%]. Criteria for this new indication was approved by the Drug Utilization Review (DUR) Board in the June 2019 meeting.
- **April 2019:** The FDA approved Keytruda® (pembrolizumab) for use in combination with Inlyta® (axitinib) for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Criteria for this new indication was approved by the DUR Board in the June 2019 meeting.
- **May 2019:** The FDA approved Bavencio® (avelumab) for use in combination with Inlyta® (axitinib) for the first-line treatment of patients with advanced RCC.
- **June 2019:** The FDA approved Keytruda® (pembrolizumab) for the first-line treatment of patients with metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
- **June 2019:** The FDA approved Keytruda® (pembrolizumab) for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least 1 other prior line of therapy.
- **July 2019:** The FDA approved Keytruda® (pembrolizumab) for the treatment of patients with advanced esophageal squamous cell cancer.
- **September 2019:** The FDA approved Keytruda® (pembrolizumab) for use in combination with Lenvima® (lenvatinib) for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation.

Recommendations

- Update the prior authorization criteria to reflect new FDA approved indications; changes can be seen in the following criteria listed in red (only criteria with updates listed):

Bavencio® (Avelumab) Approval Criteria [Renal Cell Carcinoma (RCC) Diagnosis]:

1. Diagnosis of advanced RCC; and
2. Must be used as first-line treatment; and
3. Must be used in combination with axitinib.

Keytruda® (Pembrolizumab) Approval Criteria [Endometrial Cancer Diagnosis]:

1. Diagnosis of advanced endometrial cancer that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); and
2. Progressive disease following prior systemic therapy; and
3. Member is not a candidate for curative surgery or radiation; and
4. Must be used in combination with lenvatinib; and
5. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

Keytruda® (Pembrolizumab) Approval Criteria [Esophageal Cancer Diagnosis]:

1. Diagnosis of locally advanced or metastatic esophageal carcinoma; and
2. Must be used following disease progression after 1 or more prior lines of systemic therapy; and
3. Tumor must be squamous cell histology; and
4. Tumor must have positive PD-L1 expression [Combined Positive Score (CPS) ≥10]; and
5. Pembrolizumab must be used as monotherapy; and
6. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

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

1. ~~Diagnosis of recurrent or metastatic disease~~ First-line or recurrent setting; and
2. Squamous cell histology; and
3. ~~Member has received a prior platinum containing regimen (i.e., cisplatin, carboplatin); and~~
4. If used in the recurrent setting, member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
5. Dose does not exceed 200mg every 3 weeks.

Keytruda® (Pembrolizumab) Approval Criteria [Small Cell Lung Cancer (SCLC) Diagnosis]:

1. Diagnosis of metastatic SCLC; and
2. Progressed on or following a platinum-based regimen and at least 1 other regimen; and
3. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)].

Utilization Details of Skin Cancer Medications: Fiscal Year 2019

Pharmacy Claims: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
TRAMETINIB PRODUCTS					
MEKINIST TAB 0.5MG	26	4	$132,144.75	6.5	$5,082.49
MEKINIST TAB 2MG	20	4	$220,692.10	5	$11,034.61
SUBTOTAL	**46**	**8**	**$352,836.85**	**5.75**	**$7,670.37**
VEMURAFENIB PRODUCTS					

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
ZELBORAF TAB 240MG	19	2	$189,847.06	9.5	$9,991.95
SUBTOTAL	**19**	**2**	**$189,847.06**	**9.5**	**$9,991.95**
VISMODEGIB PRODUCTS					
ERIVEDGE CAP 150MG	17	3	$183,184.76	5.67	$10,775.57
SUBTOTAL	**17**	**3**	**$183,184.76**	**5.67**	**$10,775.57**
DABRAFENIB PRODUCTS					
TAFINLAR CAP 75MG	15	3	$153,076.26	5	$10,205.08
SUBTOTAL	**15**	**3**	**$153,076.26**	**5**	**$10,205.08**
COBIMETINIB PRODUCTS					
COTELLIC TAB 20MG	13	1	$91,158.41	13	$7,012.19
SUBTOTAL	**13**	**1**	**$91,158.41**	**13**	**$7,012.19**
TOTAL	**110**	**13***	**$970,103.34**	**8.46**	**$8,819.12**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Medical Claims: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM
J9299 NIVOLUMAB INJECTION	402	75	$3,891,095.50	$9,679.34
J9271 PEMBROLIZUMAB INJECTION	268	66	$2,913,462.02	$10,871.13
J9228 IPILIMUMAB INJECTION	24	12	$539,288.89	$22,470.37
J9023 AVELUMAB INJECTION	5	1	$66,130.44	$13,226.09
TOTAL	**673[+]**	**139***	**$7,409,976.85**	**$11,010.37**

[+]Total number of unduplicated claims.
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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Appendix J

30-Day Notice to Prior Authorize Elzonris® (Tagraxofusp-erzs) and Inrebic® (Fedratinib)

Oklahoma Health Care Authority
November 2019

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

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is a rare, clinically aggressive hematologic malignancy arising from precursors of myeloid-derived plasmacytoid dendritic cells (type 2 dendritic cells). The nomenclature used to describe BPDCN has evolved over the years along with the understanding of the underlying biology. The exact incidence of BPDCN is unknown due to constantly changing nomenclature and lack of precise defining criteria prior to the 2008 World Health Organization classification system. BPDCN represent 0.7% of primary cutaneous skin lymphomas; however, cutaneous lymphoma registries likely underestimate the true incidence of BPDCN because some patients present without skin lesions. BPDCN is most common in adults and the majority of patients are older adults, but it has been described in all age groups. There is a male to female ratio of approximately 2.5:1. Optimal management of BPDCN is not well defined; however, treatment suggestions are stratified by age because outcomes are generally more favorable in children than in adults. In December 2018, the U.S. Food and Drug Administration (FDA) announced the approval of Elzonris® (tagraxofusp-erzs) for the treatment of BPDCN in adults and pediatric patients 2 years of age and older. Prior to this approval, there were no FDA approved therapies for BPDCN, and treatment consisted of intensive chemotherapy followed by bone marrow transplantation.

Myelofibrosis is type of chronic leukemia. It belongs to a group of related blood cancers known as “myeloproliferative neoplasms (MPNs)” in which bone marrow cells that produce blood cells function abnormally. The result is excessive fibrous tissue formation in the bone marrow, which can lead to severe anemia, weakness, fatigue, splenomegaly, and hepatomegaly. Myelofibrosis can occur on its own (primary myelofibrosis) or as a result of another bone marrow disorder such as polycythemia vera (PV) or essential thrombocythemia (ET). Between 15 to 20% of myelofibrosis cases begin as either PV or ET. Myelofibrosis occurs in approximately 1.5 out of 100,000 individuals in the United States each year. The disease affects both men and women and is usually diagnosed in patients older than 60 years of age, but can occur at any age. In August 2019, the FDA approved Inrebic® (fedratinib) for the treatment of adult patients with certain types of myelofibrosis. Prior to this approval, Jakafi® (ruxolitinib) was the only drug that had been FDA approved for myelofibrosis; Jakafi® entered the marketplace in 2011.

Market News and Updates[6,7,8]

Anticipated Patent Expiration(s):

- Inrebic® (fedratinib): June 2028

New FDA Approval(s):

- **December 2018:** The FDA approved Elzonris® (tagraxofusp-erzs) intravenous (IV) infusion for the treatment of BPDCN in adults and pediatric patients 2 years of age and older. Prior to the approval of Elzonris®, there had been no FDA approved therapies for BPDCN. The efficacy of Elzonris® was studied in 2 cohorts of patients in a single-arm clinical trial. The first trial cohort enrolled 13 patients with untreated BPDCN and 7 patients (54%) achieved a complete remission (CR) or CR with a skin abnormality not indicative of active disease (CRc). The second cohort included 15 patients with relapsed or refractory BPDCN; 1 patient achieved CR and 1 patient achieved CRc.
- **August 2019:** The FDA approved Inrebic® (fedratinib) capsules to treat adult patients with certain types of myelofibrosis. Prior to the approval of Inrebic®, there was 1 FDA-approved drug, Jakafi® (ruxolitinib), to treat patients with myelofibrosis. The approval of Inrebic® for intermediate-2 or high-risk primary or secondary (post-PV or post-ET) myelofibrosis was based on the results of a clinical trial in 289 patients with myelofibrosis. Patients were randomized to receive 2 different doses (400mg or 500mg by mouth daily) of fedratinib or placebo. The clinical trial demonstrated that 35 of 96 patients treated with fedratinib 400mg daily experienced a significant therapeutic effect [measured by ≥35% reduction from baseline in spleen volume at the end of cycle 6 (week 24) as measured by an MRI or CT scan with a follow-up scan 4 weeks later]. As a result of treatment with fedratinib, 36 patients experienced ≥50% reduction in myelofibrosis-related symptoms, such as itching, abdominal discomfort, feeling full sooner than normal, night sweats, pain under ribs on left side, and bone or muscle pain.

Elzonris® (Tagraxofusp-erzs) Product Summary[9]

Elzonris® (Tagraxofusp-erzs):

- **Therapeutic Class:** CD123-directed cytotoxin
- **Indication(s):** Treatment of BPDCN in adults and in pediatric patients 2 years of age and older
- **Boxed Warning:** Capillary leak syndrome
- **How Supplied:** 1,000mcg/1mL single-dose vial (SDV)
- **Dose:** 12mcg/kg IV over 15 minutes once daily on days 1 to 5 of a 21-day cycle
- **Cost:** Wholesale Acquisition Cost (WAC) of $25,529.35 per 1,000mcg vial; treatment cost will vary depending on patient weight

Inrebic® (Fedratinib) Product Summary[10]

Inrebic® (Fedratinib):

- **Therapeutic Class:** Kinase inhibitor
- **Indication(s):** Treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-PV or post-ET) myelofibrosis
- **Boxed Warning:** Encephalopathy including Wernicke's
- **How Supplied:** 100mg capsule
- **Dose:** 400mg orally once daily with or without food for patients with a baseline platelet count ≥50 x 10^9/L

- **Cost:** WAC of $175.00 per 100mg capsule, resulting in a monthly cost of $21,000.00

Recommendations

Elzonris® (Tagraxofusp-erzs) Approval Criteria [Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) Diagnosis]:

1. Diagnosis of BPDCN; and
2. Member must be 2 years of age or older; and
3. Must be used as a single-agent.

Inrebic® (Fedratinib) Approval Criteria [Myelofibrosis Diagnosis]:

1. Diagnosis of myelofibrosis in adult members; and
2. Intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia).

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[9] Elzonris® (Tagraxofusp-erzs) Prescribing Information. Stemline Therapeutics, Inc. Available online at: https://www.elzonris.com/hcp/Content/documents/ELZONRIS_US_Full_Prescribing_Information.pdf. Last revised 12/2018. Last accessed 10/04/2019.

[10] Inrebic® (Fedratinib) Prescribing Information. Celgene Corporation. Available online at: https://media.celgene.com/content/uploads/inrebic-pi.pdf. Issued 08/2019. Last accessed 10/04/2019.

Appendix K

Fiscal Year 2019 Annual Review of Atopic Dermatitis (AD) Medications

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

Elidel® (Pimecrolimus Topical) and Protopic® (Tacrolimus Topical) Approval Criteria:

1. The first 90 days of a 12-month period will be covered without prior authorization; and
2. After the initial period, authorization may be granted with documentation of 1 trial at least 6 weeks in duration within the past 90 days wtih a Tier-1 topical corticosteroid; and
3. Therapy will be approved only once each 90-day period to ensure appropriate short-term and intermittent utilization as advised by the FDA; and
4. Quantities will be limited to 30 grams for use on the face, neck, and groin, and 100 grams for all other areas; and
5. Authorizations will be restricted to those members who are not immunocompromised.

Members Must Meet All of the Following Criteria for Authorization of Elidel® (Pimecrolimus Topical) or Protopic® (Tacrolimus Topical):

1. An FDA approved diagnosis:
    a. Elidel®: short-term and intermittent treatment for mild-to-moderate atopic dermatitis (eczema)
    b. Protopic®: short-term and intermittent treatment for moderate-to-severe atopic dermatitis (eczema)
2. Age Restrictions:
    a. Elidel® 1% is restricted to 2 years of age and older
    b. Protopic® 0.03% is restricted to 2 years of age and older
    c. Protopic® 0.1% is restricted to 15 years of age and older

Clinical Exceptions for Children Meeting Age Restriction for Elidel® (Pimecrolimus Topical) or Protopic® (Tacrolimus Topical):

1. Documented adverse effect, drug interaction, or contraindication to Tier-1 topical corticosteroids; or
2. Atopic dermatitis of the face or groin where prescriber does not want to use topical corticosteroids; or
3. Prescribed by a dermatologist.

Clinical Exceptions for Children Not Meeting Age Restriction for Elidel® (Pimecrolimus Topical) or Protopic® (Tacrolimus Topical): Prescribed by dermatologist.

Dupixent® (Dupilumab Injection) Approval Criteria [Atopic Dermatitis (AD) Diagnosis]:

1. An FDA approved diagnosis of moderate-to-severe AD 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 6 months for a minimum of 2 weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. 1 medium potency to very-high potency Tier-1 topical corticosteroid; and
    b. 1 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 12 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); and
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.

Dupixent® (Dupilumab Injection) Approval Criteria [Eosinophilic Phenotype Asthma Diagnosis]:

1. An FDA approved indication for add-on maintenance treatment of members with moderate-to-severe eosinophilic phenotype asthma or oral corticosteroid-dependent asthma; and
2. Member must be 12 years of age or older; and
3. Member must have a baseline blood eosinophil count of ≥150cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 asthma exacerbations requiring systemic corticosteroids within the last 12 months or require daily systemic corticosteroids despite compliant use of high-dose inhaled corticosteroid (ICS) plus at least 1 additional controller medication; and
5. Member must have failed a high-dose ICS (≥880mcg/day fluticasone propionate or equivalent daily dose or ≥440mcg/day in ages 12 to 17 years) used compliantly for at least the past 12 months (for ICS/LABA combination products, the highest FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. Prescriber must verify the member has been counseled on proper administration and storage of Dupixent®; and
8. Dupixent® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary

specialist within the last 12 months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
9. Initial approvals will be for the duration of 6 months after which time compliance will be evaluated for continued approval; and
10. Quantities approved must not exceed FDA approved dosing regimens.

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

1. An FDA approved diagnosis for the short-term (up to 8 days) management of moderate pruritus in members with atopic dermatitis or lichen simplex chronicus; and
2. Requests for use longer than 8 days will not generally be approved. Chronic use beyond 8 days may result in higher systemic levels and should be avoided.

Eucrisa® (Crisaborole Ointment) Approval Criteria:

1. An FDA approved indication for treatment of mild-to-moderate atopic dermatitis (AD; eczema); and
2. Member must be at least 2 years of age or older; and
3. Member must have a documented trial within the last 6 months for a minimum of 2 weeks that resulted in failure with a topical corticosteroid (TCS)* (or have a contraindication or documented intolerance); and
4. A quantity limit of 1 tube per 30 days will apply; and
5. Initial approvals will be for the duration of 1 month. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.
   (*The manufacturer of Eucrisa® has currently provided a supplemental rebate to require a trial with 1 TCS; however, Eucrisa® will follow the original criteria and require trials with 1 TCS and 1 topical calcineurin inhibitor if the manufacturer chooses not to participate in supplemental rebates.)

Clinical Exceptions for Children Not Meeting Age Restriction for Eucrisa® (Crisaborole Ointment):

1. Documented adverse effect, drug interaction, or contraindication to topical corticosteroids (TCSs); or
2. Atopic dermatitis (AD) of face or groin where prescriber does not want to use TCSs; or
3. Prescribed by a dermatologist.

Utilization of AD Medications: Fiscal Year 2019

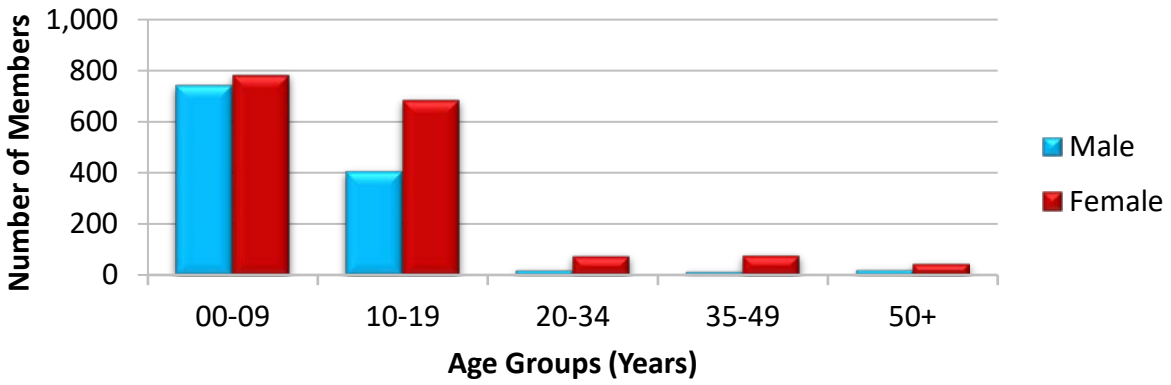
Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	2,181	3,157	$1,886,966.26	$597.71	$19.51	164,520	96,715
2019	2,872	4,717	$3,377,452.25	$716.02	$23.49	248,484	143,802
% Change	**31.70%**	**49.40%**	**79.00%**	**19.80%**	**20.40%**	**51.00%**	**48.70%**
Change	**691**	**1,560**	**$1,490,485.99**	**$118.31**	**$3.98**	**83,964**	**47,087**

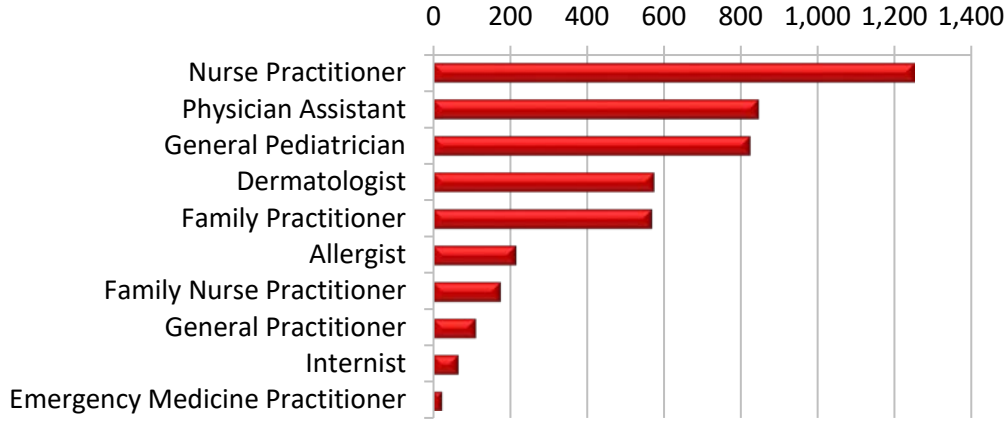
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

- The AD medications are a supplementally rebated class of medications. Supplemental rebates are not reflected in the data in this report. Costs included in this report do not reflect net costs.

Demographics of Members Utilizing AD Medications



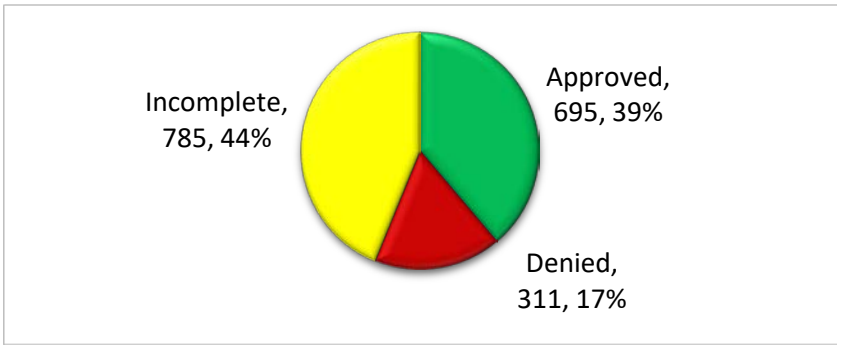
Top Prescriber Specialties of AD Medications by Number of Claims



Prior Authorization of AD Medications

There were 1,791 prior authorization requests submitted for AD medications during fiscal year 2019. The following chart shows the status of the submitted petitions for fiscal year 2019.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Eucrisa® (crisaborole): January 2030

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

- **March 2019:** The FDA approved Dupixent® (dupilumab) for adolescent patients 12 to 17 years of age with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable. Dupilumab can be used with or without topical corticosteroids (TCS). Dupixent® is also approved for the treatment of adult patients with moderate-to-severe AD that is not well controlled with topical prescription therapies, or when those therapies cannot be used; and for use with other asthma medications for the maintenance treatment of moderate-to-severe asthma in patients 12 years of age and older whose asthma is not controlled with their current asthma medications. Sanofi and Regeneron are also studying dupilumab in a broad range of clinical development programs for diseases driven by allergic and other type 2 inflammation, including pediatric (6 to 11 years of age) AD (Phase 3), pediatric (6 months to 5 years of age) AD (Phase 2/3), pediatric (6 to 11 years of age) asthma (Phase 3), eosinophilic esophagitis (Phase 2/3), and food and environmental allergies (Phase 2). A future trial is planned for chronic obstructive pulmonary disease (COPD). Dupilumab is also being studied in combination with REGN3500, which targets interleukin-33 (IL-33).
- **June 2019:** Regeneron and Sanofi announced that the FDA approved Dupixent® (dupilumab) for use with other medications to treat chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled. CRSwNP is a chronic disease of the upper airway that obstructs the sinuses and nasal passages. CRSwNP can be a debilitating condition and can lead to breathing difficulties, nasal congestion and discharge, loss of sense of smell and taste, and facial pressure. Prior to the approval of dupilumab, the standard of care included intranasal and systemic corticosteroids and sinus surgery. Many patients with CRSwNP have other type 2 inflammatory diseases like asthma, and these patients often have more severe asthma that is often more difficult to treat. In the CRSwNP trials for dupilumab, 59% of patients also had asthma. The FDA approval for CRSwNP is based on 2 pivotal trials (the 24-week SINUS-24 and 52-week SINUS-52) that are part of the Phase 3 LIBERTY clinical trial program. The trials evaluated dupilumab 300mg every 2 weeks with standard-of-care mometasone furoate nasal spray (MFNS) compared to placebo injection plus MFNS. In these trials, dupilumab significantly improved key disease measures and met all primary and secondary endpoints. At 24 weeks, patients treated with dupilumab achieved statistically significant improvements in all primary and secondary endpoints, including improvement in nasal congestion/obstruction severity, reduction in nasal polyps score, improvement in sinus opacification, and improvement in loss of smell. In a pre-specified pooled analysis of the 2 trials up to 52 weeks, dupilumab treatment resulted in significant reductions in systemic corticosteroid use and need for sinonasal surgery compared to placebo. The proportion of patients who required systemic corticosteroids was reduced by 74% with dupilumab compared to placebo and the proportion of

patients who required surgery was reduced by 83% with dupilumab compared to placebo. In the 59% of patients who also had asthma, improvements in lung function were similar to patients in the dupilumab asthma program. For patients with CRSwNP, Dupixent® (dupilumab) is supplies as a 300mg pre-filled syringe, and the recommended dose is 300mg every other week as a subcutaneous (subQ) injection. Dupixent® is intended for use under the guidance of a health care professional and can be given in a clinic or at home by self-administration after training by a health care professional.

Pipeline:

- **PAC-14028:** According to results of a Phase 2b trial published in the *British Journal of Dermatology*, adults with mild-to-moderate AD showed significant improvement after 8 weeks of treatment with a novel topical cream (PAC-14028), compared with placebo. Researchers randomized 194 adults with AD to 1 of 3 concentrations of a topical cream [containing the selective transient receptor potential vanilloid subfamily, member 1 (TRPV1) antagonist PAC-14028] or a placebo vehicle. Patients had baseline scores of 2 or 3 (mild to moderate) on the Investigator's Global Assessment (IGA) scale. After 8 weeks, treatment success (defined as a score of 0 or 1 on the IGA scale) occurred in 57% of patients given 1% cream, 38% of those given 0.3% cream, 43% of those given 0.1% cream, and 15% of those given placebo cream.
- **Bermekimab:** In December 2018, XBiotech announced that its open-label, proof-of-concept, multicenter study of bermekimab to treat patients with moderate-to-severe AD met all primary and secondary endpoints. Patients received either a low (N=10) or high (N=28) dose of bermekimab once weekly for either a 4 or 7-week treatment regimen, respectively. In the high dose group, a statistically significant improvement was seen for all efficacy endpoints and a significant dose response for the high dose compared to low dose group was observed for key endpoints.
- **Lebrikizumab:** In March 2019, Dermira, Inc. announced positive results from a Phase 2b dose-ranging study of lebrikizumab, an investigational therapy, in adult patients with moderate-to-severe AD. Lebrikizumab is an injectable, humanized monoclonal antibody designed to bind IL-13. In the study, all 3 doses of lebrikizumab met the primary endpoint, demonstrating greater improvements in the Eczema Area and Severity Index (EASI) score compared to placebo. Dermira plans to initiate a Phase 3 clinical development program for lebrikizumab by the end of 2019.
- **Tezepelumab:** According to results of a study published in *Clinical Pharmacology and Therapeutics*, tezepelumab exhibited a predictable linear pharmacokinetic profile and acceptable safety and tolerability in healthy adults and adults with AD. Tezepelumab is a fully human monoclonal antibody that targets thymic stromal lymphopoietin. Healthy adults and adults with AD were enrolled in 2 double-blind, randomized, placebo-controlled, Phase 1 studies to evaluate the pharmacokinetics, safety, and tolerability of single- and multiple-ascending doses of tezepelumab. Tezepelumab has received Breakthrough Therapy designation from the FDA in patients with severe asthma without an eosinophilic phenotype.
- **Baricitinib:** Baricitinib (Olumiant®) met primary endpoint marks in a pivotal Phase 3 trial designed to assess the therapy for the treatment of adults with moderate-to-severe AD.

Results of the trial show baricitinib plus standard-of-care TCSs significantly improved patient disease severity per validated Investigator's Global Assessment for AD (vIGA) score of "clear" or "almost clear" (vIGA 0 or 1) at 16 weeks. Baricitinib is currently approved for adults with moderately-to-severely active rheumatoid arthritis (RA).

- **Abrocitinib:** In September 2019, Pfizer, Inc. announced positive top-line results from a second Phase 3 pivotal study evaluating the efficacy and safety of its investigational oral Janus kinase 1 (JAK1) inhibitor, abrocitinib, in patients 12 years of age and older with moderate-to-severe AD. The study, JADE MONO-2, was a randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the safety and efficacy of 2 doses (100mg and 200mg once daily) of abrocitinib monotherapy over 12 weeks. Results showed that by week 12 the percentage of patients achieving each co-primary efficacy endpoint and each key secondary endpoint with either dose of abrocitinib was statistically significantly higher than placebo.
- **Tralokinumab:** According to a study published in June 2018 in *The Journal of Allergy and Clinical Immunology*, tralokinumab, a fully human immunoglobulin G4 monoclonal antibody, was shown to be safe and effective for moderate-to-severe AD in adults. The Phase 2b study randomized 204 patients to 1 of 4 treatment protocols: 45mg, 150mg, or 300mg of tralokinumab subQ, or placebo, every 2 weeks for 12 weeks, along with concomitant topical corticosteroids. At week 12, the 300mg dose of tralokinumab achieved a significant improvement of -4.94 in the EASI score compared to placebo and the difference was -4.36 for the 150mg dose. However, after pooling the data for the 300mg and 150mg doses, there was not a significant difference in the patients with an IGA response at 12 weeks in comparison to placebo (23.0% vs. 11.8%, respectively). The study found that adverse events were minimal.
- **Nemolizumab:** In March 2019, Galderma presented the final results from a Phase 2b dose-ranging study of nemolizumab, an investigational therapy in adult patients with moderate-to-severe AD. Nemolizumab is a first-in-class investigational monoclonal antibody that blocks signaling of IL-31. The study met the primary endpoint of a greater improvement in EASI scores from baseline compared with placebo. At week 24, a 73% reduction in mean EASI score was observed with nemolizumab compared with 58% for placebo. Nemolizumab was well-tolerated across all dose levels in the trial.
- **Fezakinumab:** In a randomized, double-blind, Phase 2a trial of fezakinumab, an anti-IL-22 monoclonal antibody given intravenously (IV) every 2 weeks for 10 weeks, the mean reduction in severity scoring of AD (SCORAD) was 13.8± 2.7 in the fezakinumab group versus 8.0±3.1 in the placebo group at 12 weeks. SCORAD improvement was strongest in patients with severe AD treated with fezakinumab versus placebo, measured at 12 and 20 weeks. Rates of adverse events were similar to placebo. Based on results of early clinical trials, researchers concluded that because fezakinumab targets a novel inflammatory pathway (IL-22) independent of IL-4 and IL-13, it may help patients with moderate-to-severe AD that is refractory to dupilumab therapy.
- **Upadacitinib:** According to a report presented at the 2019 World Congress of Dermatology, upadacitinib significantly improved itch in a randomized, placebo-controlled trial that enrolled patients with moderate-to-severe AD. More patients receiving upadacitinib, a selective JAK1 inhibitor, achieved an itch-free state and

maintained it over the 16 weeks of the Phase 2b trial, compared with those in the placebo group. In the trial, 167 patients with moderate-to-severe AD were randomized to upadacitinib 7.5mg, 15mg, or 30mg daily, or placebo over a 16-week, double-blind period, followed by a 72-week, blinded extension. Significant improvements in EASI were seen as early as 2 weeks and were maintained throughout the 16-week, double-blind period. By 16 weeks, the mean percentage improvement in EASI score was 74.4% for upadacitinib 30mg daily versus 23.0% for placebo ($P<0.001$). Phase 3 trials are being conducted for upadacitinib in AD, psoriatic arthritis, Crohn's disease, and ulcerative colitis. The FDA approved Rinvoq™ (upadacitinib) for the treatment of moderate-to-severe RA in August 2019.

- **Ruxolitinib:** Results from a Phase 2 study of a cream-based formulation of ruxolitinib, a JAK inhibitor, in adult patients with mild-to-moderate AD were presented at the 2019 World Congress of Dermatology. The study comprised 307 adults with mild-to-moderate AD and body surface area (BSA) involvement of 3% to 20%. Patients were randomized equally to 6 arms, including vehicle, triamcinolone cream, and ruxolitinib at dosages of 0.15%, 0.5%, 1.5% once daily, or the target dose level of 1.5% twice daily. After an 8-week double-blind period, there was a 4-week open-label period during which patients randomized to vehicle or triamcinolone were switched to ruxolitinib, and then a 4-week follow-up period during which no treatment was given. In the double-blind period, ruxolitinib 1.5% cream twice daily significantly improved EASI scores versus vehicle. The patients on the target ruxolitinib dose maintained the improvements in EASI score throughout the open-label period, with mean improvement from baseline reaching 81.4% by week 10 and 84.9% by week 12.

Other News:

- **September 2018:** Data reported at the European Academy of Dermatology and Venereology Congress showed that off-label use of biologic agents to treat refractory AD posed a significant risk of serious infection as compared with systemic nonbiologic agents. A propensity-matched analysis showed that treatment with a biologic agent doubled the risk of hospitalization for a serious bacterial or opportunistic infection as compared to high-potency TCSs or nonbiologic systemic therapy. Among the nonbiologic systemic agents, cyclosporine posed the lowest risk of infection and azathioprine and mycophenolate posed the greatest risk. The analysis did not include the newer biologic agents approved to treat AD, such as dupilumab; however, investigators intend to update the analysis with data on outcomes from the newer agents, as well as long-term outcomes with all treatments.
- **January 2019:** Recommendations for the management of severe AD were published in *The Journal of Allergy and Clinical Immunology: In Practice*. Dr. Kanwaljit Brar and colleagues developed strategies for the successful management of severe AD, including appropriate treatment strategies and diagnosis. The researchers noted that severe AD should be established based on minimum involvement of 10% BSA and individual lesions with severe features, involvement of highly visible areas or those important for function, and significantly impaired quality of life regardless of BSA. Treatment guidelines emphasize use of moisturizers in conjunction with warm baths or showers; avoiding

irritants or infections and proven triggers; and maintenance with TCSs and other therapeutic agents in a stepwise manner. During flares, TCSs and topical calcineurin inhibitors can be prescribed; wet wrap therapy is recommended in conjunction with TCSs, oral antibiotics, and other oral agents. For AD failing basic therapies, dupilumab is now being added to these guidelines.

- **January 2019:** The FDA has reversed a long-standing guidance stating that sponsors of clinical trials for AD in pediatrics do not need to start the trial first in adults. The decision was announced in October 2018 and was influenced by recommendations from its Dermatologic and Ophthalmic Drug Advisory Committee. There are some caveats to the guidance, including that upon approval applicants should disclose how to use the drug safety and effectively in pediatric patients; all pediatric groups should be studied, including children under 2 years of age, but it may be necessary to first have safety outcomes from trials conducted in older pediatric patients.
- **March 2019:** According to a study published in the *British Journal of Dermatology*, dupilumab is safe and effective when used to treat both exposed and unexposed anatomic regions in patients with moderate-to-severe AD. The investigators extracted data on a large cohort of adults with AD recruited from 4 large Phase 3 trials. Participants received dupilumab 300mg subQ every 2 weeks, dupilumab 300mg subQ every week, or placebo. Primary outcome measures were the severity and extent of AD compared with placebo using the EASI. From baseline to week 16, patients receiving dupilumab treatment showed significantly greater improvement versus placebo for all anatomic regions across all trials. Adverse events were observed at similar rates across treatment groups in all trials, and the most commonly reported adverse events included injection-site reactions and conjunctivitis.
- **July 2019:** Pfizer, Inc. announced top-line results from a Phase 4 study, which showed that Eucrisa® (crisaborole 2% ointment) was well-tolerated in children 3 months to younger than 24 months of age with mild-to-moderate AD. The trial data supports the primary study objective to examine the safety of crisaborole treatment in this patient population and are consistent with previous clinical trial experience. Crisaborole is currently FDA approved for the treatment of mild-to-moderate AD in patients 2 years of age and older.
- **August 2019:** Topline results from a Phase 3 study investigating dupilumab in the treatment of pediatric patients with severe AD showed that the therapy was safe and effective in this patient population. The double-blind, placebo-controlled trial included 367 pediatric patients 6 to 11 years of age with severe AD whose disease could not be adequately controlled with topical medications. Patients were randomized to 1 of 3 treatments for 16 weeks: dupilumab 300mg subQ every 4 weeks (with initial 600mg dose); dupilumab 100mg (<30kg) or 200mg (≥30kg) subQ every 2 weeks (with initial 200mg or 400mg dose, respectively); or placebo every 2 or 4 weeks. Each group received background treatment with moisturizers and TCS. At 16 weeks, a significantly greater proportion of patients treated with dupilumab achieved clear or almost clear skin as measured by IGA [33% for dupilumab every 4 weeks ($P<0.0001$) and 30% for dupilumab every 2 weeks ($P=0.0004$) vs. 11% for placebo]. Results from the trial are to be submitted to the FDA in the fourth quarter of 2019.

Recommendations

The College of Pharmacy recommends the following changes and additions, based on recent FDA approvals, to the prior authorization criteria for Dupixent® (dupilumab injection), as shown in red:

Dupixent® (Dupilumab Injection) Approval Criteria [Atopic Dermatitis (AD) Diagnosis]:

1. An FDA approved diagnosis of moderate-to-severe AD not adequately controlled with topical prescription therapies; and
2. Member must be ~~18~~ 12 years of age or older; and
3. Member must have documented trials within the last 6 months for a minimum of 2 weeks that resulted in failure with both of the following therapies (or have a contraindication or documented intolerance):
    a. 1 medium potency to very-high potency Tier-1 topical corticosteroid; and
    b. 1 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 12 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); and
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.

Dupixent® (Dupilumab Injection) Approval Criteria [Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) Diagnosis]:

1. An FDA approved indication for add-on maintenance treatment in adult patients with inadequately controlled CRSwNP; and
2. Member must be 18 years of age or older; and
3. Member must have a documented trial with an intranasal corticosteroid that resulted in failure (or have a contraindication or documented intolerance); and
4. Member must meet 1 of the following:
    a. Member has required prior sino-nasal surgery; or
    b. Member has previously been treated with systemic corticosteroids in the past 2 years (or has a contraindication or documented intolerance); and
5. Dupixent® must be prescribed by an otolaryngologist, allergist, immunologist, or pulmonologist or the member must have been evaluated by an otolaryngologist, allergist, immunologist, or pulmonologist within the last 12 months (or be an advanced care practitioner with a supervising physician who is an otolaryngologist, allergist, immunologist, or pulmonologist); and

6. Member has symptoms of chronic rhinosinusitis (e.g., facial pain/pressure, reduction or loss of smell, nasal blockade/obstruction/congestion, nasal discharge) for 12 weeks or longer despite attempts at medical management; and
7. Member has evidence of nasal polyposis by direct examination, sinus CT scan, or endoscopy; and
8. Member will continue to receive intranasal corticosteroid therapy, unless contraindicated; and
9. Prescriber must verify the member has been counseled on proper administration and storage of Dupixent®; and
10. 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; and
11. Initial approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment. Additionally, compliance will be evaluated for continued approval; and
12. A quantity limit of 2 syringes every 28 days will apply.

Utilization Details of AD Medications: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
EUCRISA OIN 2%	3,249	2,125	$1,925,040.67	$19.43	$592.50	57.00%
TACROLIMUS OIN 0.03%	409	303	$107,501.71	$8.60	$262.84	3.18%
DUPIXENT INJ 300/2ML	344	46	$1,026,338.04	$110.22	$2,983.54	30.39%
ELIDEL CRE 1%	274	227	$103,909.17	$11.58	$379.23	3.08%
PIMECROLIMUS CRE 1%	214	193	$53,557.09	$7.35	$250.27	1.59%
TACROLIMUS OIN 0.1%	184	122	$39,051.91	$7.00	$212.24	1.16%
DUPIXENT INJ 200/1.14ML	41	10	$121,126.84	$116.92	$2,954.31	3.59%
PROTOPIC OIN 0.03%	1	1	$546.87	$18.23	$546.87	0.02%
DOXEPIN HCL CRE 5%	1	1	$379.95	$47.49	$379.95	0.01%
TOTAL	**4,717**	**2,872***	**$3,377,452.25**	**$23.49**	**$716.02**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019
Utilization data includes Dupixent® used for all diagnoses and does not differentiate between AD diagnoses and other diagnoses, for which use may be appropriate.

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Appendix L

Fiscal Year 2019 Annual Review of Targeted Immunomodulator Agents and 30-Day Notice to Prior Authorize Eticovo™ (Etanercept-ykro), Hadlima™ (Adalimumab-bwwd), Hyrimoz™ (Adalimumab-adaz), Rinvoq™ (Upadacitinib), and Skyrizi™ (Risankizumab-rzaa)

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

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

Utilization of Targeted Immunomodulator Agents: Fiscal Year 2019

Targeted Immunomodulator Agents Fiscal Year Comparison: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	816	5,535	$30,121,658.60	$5,442.03	$184.08	62,037	163,631
2019	960	6,065	$36,223,083.04	$5,972.48	$199.59	57,881	181,486
% Change	**17.60%**	**9.60%**	**20.30%**	**9.70%**	**8.40%**	**-6.70%**	**10.90%**
Change	**144**	**530**	**$6,101,424.44**	**$530.45**	**$15.51**	**-4,156**	**17,855**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

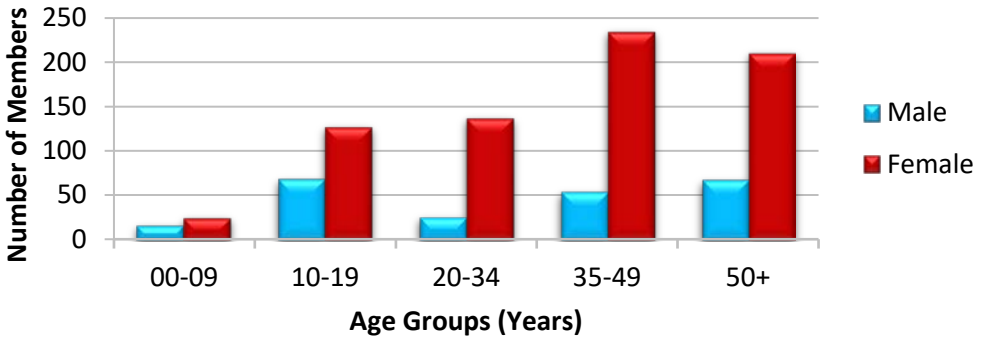
- There was a significant increase in cost while utilization remained relatively flat. This can be accounted for by price increases for some medications in the targeted immunomodulator class. The consumer price index (CPI) penalty of the federal rebate is designed to keep Medicaid net cost relatively flat despite manufacturer price increases. The cost increases in the table do not reflect the net cost increases. 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.

Targeted Immunomodulator Agents Fiscal Year Comparison: Medical Claims

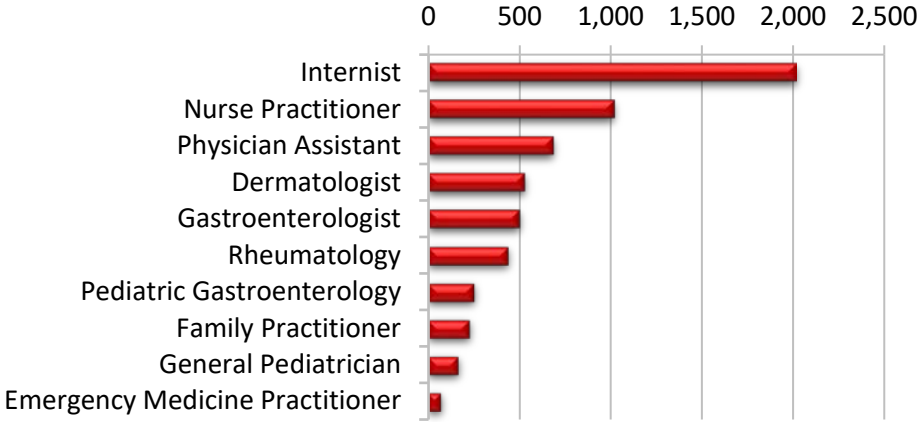
Fiscal Year	*Total Members	+Total Claims	Total Cost	Cost/Claim	Total Units
2018	198	715	$3,521,237.28	$4,924.81	98,489
2019	206	677	$3,011,845.39	$4,448.81	91,557
% Change	**8**	**-38**	**-$509,391.89**	**-$476.00**	**-6,932**
Change	**4.04%**	**-5.31%**	**-14.47%**	**-9.67%**	**-7.04%**

*Total number of unduplicated members. +Total number of unduplicated claims.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Demographics of Members Utilizing Targeted Immunomodulator Agents: Pharmacy Claims



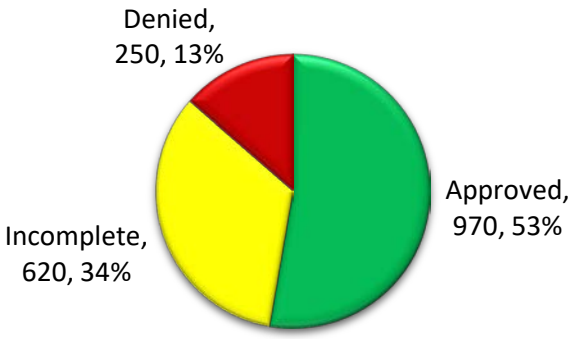
Top Prescriber Specialties of Targeted Immunomodulator Agents by Number of Claims: Pharmacy Claims



Prior Authorization of Targeted Immunomodulator Agents

There were 1,840 prior authorization requests submitted for targeted immunomodulator agents during fiscal year 2019. Computer edits are in place to detect lower tiered medications in a member's claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions for fiscal year 2019.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25]

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

- **Hyrimoz™ (adalimumab-adaz):** In October 2018, Sandoz announced the FDA approval of Hyrimoz™ (adalimumab-adaz), a biosimilar to Humira® (adalimumab), for the treatment of patients with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), or plaque psoriasis (PsO). The FDA approved Hyrimoz™ after preclinical and clinical research demonstrated that Hyrimoz™ had matching safety, efficacy, and quality to Humira®. A randomized, double-blind, 3-arm, parallel biosimilarity study confirmed the pharmacokinetics, immunogenicity, and safety of Hyrimoz™, demonstrating bioequivalence for all primary pharmacokinetic parameters. A confirmatory efficacy and safety biosimilarity study demonstrated therapeutic equivalence in patients with moderate-to-severe chronic PsO, with a similar safety and immunogenicity profile to Humira®.
- **Xeljanz® (tofacitinib):** In April 2019, Zydus Cadila announced receipt of tentative FDA approval for tofacitinib (generic Xeljanz®) oral tablets. No generic formulations of tofacitinib are currently available.
- **Eticovo™ (etanercept-ykro):** In April 2019, Samsung Bioepis announced the FDA approval of Eticovo™ (etanercept-ykro), a biosimilar to Enbrel® (etanercept), for the treatment of patients with AS, PsO, polyarticular JIA, PsA, and RA. The FDA based its approval on a 24-week, randomized, double-blind, Phase 3 trial comparing the safety and efficacy of Eticovo™ to Enbrel® in patients with moderate-to-severe RA despite treatment with methotrexate (MTX). Eticovo™ demonstrated equivalence of efficacy and comparable safety to Enbrel®. Treatment-emergent adverse events (TEAEs) were found to be similar between Eticovo™ (55.2%) and Enbrel® (58.2%); however, the incidence of antidrug antibodies at week 24 was lower in the Eticovo™ group (0.7%) compared with the Enbrel® group (13.1%).
- **Hadlima™ (adalimumab-bwwd):** In July 2019, Samsung Bioepis announced the FDA approval of Hadlima™ (adalimumab-bwwd), a biosimilar to Humira® (adalimumab), for the treatment of RA, JIA, PsA, AS, adult CD, UC, and PsO. The FDA approval was based on a randomized, double-blind, 52-week, Phase 3 study of 544 patients with moderate-to-severe RA despite MTX therapy. Patients were randomized to receive either Hadlima™ or Humira®. At week 24, the response rate was 72.4% in the Hadlima™ group versus 72.2% in the Humira® group [response rate defined as a 20% improvement in the American College of Rheumatology (ACR) composite measure of RA symptoms]. The safety profiles of the 2 products were similar.

New Molecular Entity FDA Approval(s):

- **Skyrizi™ (risankizumab-rzaa):** In April 2019, AbbVie, Inc. announced the FDA approval of Skyrizi™ (risankizumab-rzaa), an interleukin-23 (IL-23) inhibitor, for the treatment of moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy.
- **Rinvoq™ (upadacitinib):** In August 2019, AbbVie, Inc. announced the FDA approval of Rinvoq™ (upadacitinib), an oral Janus kinase (JAK) inhibitor, for the treatment of adults

with moderate-to-severe RA who have had an inadequate response or intolerance to MTX.

New FDA Approved Indication(s) and Formulations:

- **Actemra® (tocilizumab) Subcutaneous (sub-Q) for Systemic JIA (SJIA):** In September 2018, the FDA approved a sub-Q formulation of tocilizumab for the treatment of active SJIA in patients 2 years of age and older. Tocilizumab was previously FDA approved as an intravenous (IV) formulation for the same indication.
- **Humira® (adalimumab) for Pediatric Uveitis:** In October 2018, the FDA approved Humira® (adalimumab) for the treatment of uveitis in pediatric patients 2 years of age and older. Adalimumab was previously FDA approved for the treatment of adult patients with uveitis in 2016.
- **Humira® (adalimumab) for Pediatric Hidradenitis Suppurativa (HS):** In October 2018, the FDA approved Humira® (adalimumab) for the treatment of HS in pediatric patients 12 years of age and older. Adalimumab was previously FDA approved for the treatment of adult patients with HS in 2015.
- **Actemra® (tocilizumab) Autoinjector:** In November 2018, the FDA approved a single-dose, prefilled autoinjector formulation of Actemra® (tocilizumab), ACTPen™ for the treatment of RA, giant cell arteritis (GCA), and 2 forms of juvenile arthritis. Tocilizumab was previously FDA approved as a single-dose, prefilled syringe and as single-dose vials for IV infusion.
- **Tremfya® (guselkumab) Patient-Controlled Injector:** In February 2019, the FDA approved a 1-press, single-dose, patient-controlled injector formulation of Tremfya® (guselkumab) for the treatment of moderate-to-severe PsO in adults. Guselkumab was previously FDA approved as a single-dose, prefilled syringe for the same indication.
- **Cimzia® (certolizumab) for Non-Radiographic Axial Spondyloarthritis (nr-axSpA):** In March 2019, the FDA approved Cimzia® (certolizumab) for the treatment of adults with nr-axSpA with objective signs of inflammation. This is the first FDA-approved treatment for this indication. Certolizumab was previously FDA approved for the treatment of moderate-to-severe PsO, CD, RA, and active AS.
- **Benlysta® (belimumab) for Pediatric Lupus:** In April 2019, the FDA approved Benlysta® (belimumab) IV infusion for the treatment of children with systemic lupus erythematosus (SLE). This is the first time that the FDA has approved a treatment for pediatric patients with SLE. Belimumab has been FDA approved for use in adult SLE patients since 2011.
- **Otezla® (apremilast) for Behçet's Disease:** In July 2019, the FDA approved Otezla® (apremilast), an oral phosphodiesterase-4 (PDE-4) inhibitor, for the treatment of adults with oral ulcers associated with Behçet's disease. Behçet's disease affects roughly 5 in 100,000 people in the United States, with oral ulcers being the most common manifestation. Current compendia and practice guidance recommend topical corticosteroids (TCSs) applied topically to the mouth or use of oral colchicine as first-line treatments. Apremilast is the only FDA-approved treatment for oral ulcers associated with Behçet's disease. FDA approval was based on results from the RELIEF study, a randomized, placebo-controlled, double-blind Phase 3 study of 207 adults with Behçet's disease and active oral ulcers who were previously treated with at least 1 nonbiologic medication and who were candidates for systemic therapy. Treatment with apremilast

30mg twice daily led to a 42.7-point reduction from baseline in the pain of oral ulcers as measured by a visual analog scale (VAS) at week 12 compared with an 18.7-point reduction with placebo. Significantly more patients in the apremilast group were free of oral ulcers at week 12 (52.9% vs. 22.3%). The most common TEAEs associated with apremilast were diarrhea (41.3%), nausea (19.2%), headache (14.4%), and upper respiratory tract infection (11.5%). Apremilast was previously FDA approved for the treatment of patients with PsO and PsA.

- **Taltz® (ixekizumab) for AS:** In August 2019, the FDA approved Taltz® (ixekizumab) for the treatment of adults with active AS. Ixekizumab was previously FDA approved for the treatment of moderate-to-severe PsO and for the treatment of adults with active PsA.
- **Rituxan® (rituximab) for Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA):** In September 2019, the FDA approved Rituxan® (rituximab) for the treatment of GPA and MPA, rare vasculitis conditions, in patients 2 years of age and older. When used for GPA and MPA, rituximab must be used in combination with corticosteroids. Rituximab is the first FDA approved therapy for children with GPA and MPA. Characteristics of the disease include inflamed small blood vessels, which reduce the flow of blood and can ultimately damage organs such as the lungs and kidneys. The efficacy of rituximab in both GPA and MPA was evaluated in a study of 25 patients 6 to 17 years of age with an active form of the disease. Patients were treated with rituximab in an open-label, single-arm, uncontrolled assessment. A total of 14 patients reached remission at 6 months of rituximab plus corticosteroid treatment. At 18 months, all 25 patients had achieved remission. The safety profile of the therapy in pediatric patients was consistent with the known profile of rituximab in adult patients with GPA and MPA. Rituximab was previously FDA approved to treat adult patients with GPA and MPA, non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), RA, and pemphigus vulgaris (PV).
- **Stelara® (ustekinumab) for UC:** In October 2019, the FDA approved Stelara® (ustekinumab) for the treatment of adults with moderately-to-severely active UC. Ustekinumab was previously FDA approved for PsO, PsA, and CD.

News:

- **February 2019:** The American Academy of Dermatology and the National Psoriasis Foundation released updated guidelines for the management and treatment of PsO with biologics. The guidelines highlight recommended dosing and regimen considerations for anti-tumor necrosis factor (TNF) agents, IL-12/IL-23 inhibitors, IL-17 inhibitors, and IL-23 inhibitors. The guidelines also state that primary failure to respond to an anti-TNF does not preclude successful response to a different TNF inhibitor; however, subsequent TNF inhibitor use may result in reduced efficacy.
- **March 2019:** The American College of Gastroenterology (ACG) published updated recommendations to their clinical practice guidelines for the treatment and management of UC. The focus of UC management has shifted from symptom-based treatment to symptom management and mucosal healing. Recommendations for mildly active UC include: 5-aminosalicylate acid (5-ASA) as first-line therapy and oral systemic corticosteroids in patients who do not respond to 5-ASA in order to induce remission. Recommendations for moderately-to-severely active UC include: oral corticosteroids to

induce remission and anti-TNF therapy (adalimumab, golimumab, or infliximab) or vedolizumab or tofacitinib to maintain remission.

- **July 2019:** The FDA added a *Boxed Warning* to the Xeljanz® (tofacitinib) product labeling regarding an increased risk of pulmonary embolism (PE) and death with the 10mg twice daily dose, which is only indicated for patients with UC. Additionally, the FDA limited use of tofacitinib for UC to patients who are not treated adequately or who experience severe TEAEs with other drugs. Tofacitinib is currently in Tier-3 of the Targeted Immunomodulator Agent tier chart and requires use of other medications prior to approval through SoonerCare. The College of Pharmacy reviewed all authorizations for tofacitinib to ensure that no members are receiving the 10mg twice daily dose for an indication other than UC.
- **October 2019:** The Institute for Clinical and Economic Review (ICER) is planning to release an updated Draft Evidence Report assessing the comparative clinical effectiveness and value of treatments for RA. An earlier version of the Draft Evidence Report published in September 2019 was revised "to better align our economic modeling with how patients transition between these therapies." In addition, ICER indicated that clinical differentiation between therapies is uncertain over time and therefore cost-effectiveness will be analyzed over the first year instead of a patient's lifetime. ICER is seeking public comment on these revisions for its planned Evidence Report which is anticipated in late November 2019.

Pipeline Update(s):

- **Tanezumab:** In April 2019, Pfizer and Eli Lilly and Company announced top-line results from a Phase 3 clinical trial of tanezumab for the treatment of moderate-to-severe osteoarthritis (OA) of the hip or knee. Tanezumab binds to and inhibits nerve growth factor (NGF), subsequently reducing pain and inflammation. In the trial, 3,021 OA patients were randomized 1:1:1 to receive either tanezumab 2.5mg every 8 weeks, tanezumab 5mg every 8 weeks, or oral nonsteroidal anti-inflammatory drugs (NSAIDs), [i.e., naproxen 500mg, celecoxib 100mg, diclofenac extended-release (ER) 75mg]. Patients receiving the tanezumab 5mg dose showed a statistically significant improvement in pain and physical function compared to NSAIDs at 16 weeks; no difference was shown in the 2.5mg tanezumab group.
- **Mirikizumab:** In May 2019, Eli Lilly and Company announced new data for mirikizumab, an investigational IL-23 inhibitor. Mirikizumab was evaluated in a Phase 2, randomized, double-blind, placebo-controlled trial in patients with CD. Patients were randomized with a 2:1:1:2 allocation across 4 treatment arms (mirikizumab 200mg, mirikizumab 600mg, mirikizumab 1,000mg, and placebo). The primary endpoint evaluated mirikizumab versus placebo on endoscopic response, which was defined as a 50% reduction from baseline in the severity of each patient's disease, as measured by the Simple Endoscopic Score for CD (SES-CD). Rates of endoscopic response were significantly greater for patients receiving all mirikizumab doses compared to placebo: 25.8%, 37.5%, and 43.8 % of patients in the 200mg, 600mg, and 1,000mg groups, respectively, achieved response compared to 10.9% of placebo patients. The most commonly reported TEAEs were headache, weight gain, and nasopharyngitis.

Rinvoq™ (Upadacitinib) Product Summary[26]

Indication(s): Rinvoq™ (upadacitinib) is a JAK inhibitor indicated for the treatment of adults with moderately-to-severely active RA who have had an inadequate response or intolerance to MTX.

- Limitation of Use: Use of upadacitinib in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Dosing:

- Rinvoq™ is supplied as 15mg ER oral tablets.
- The recommended dose of upadacitinib is 15mg by mouth once daily. Upadacitinib tablets should be swallowed whole. Upadacitinib should not be split, crushed, or chewed.
- Upadacitinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C).

Boxed Warning: Serious Infections, Malignancy, and Thrombosis

- Serious infections leading to hospitalization or death, including tuberculosis (TB) and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving upadacitinib.
  - If a serious infection develops, upadacitinib should be interrupted until the infection is controlled.
  - Prior to starting upadacitinib, a test for latent TB should be performed; if it is positive, treatment for TB should be initiated prior to starting upadacitinib.
  - All patients should be monitored for active TB during treatment, even if the initial latent TB test is negative.
- Lymphoma and other malignancies have been observed in patients treated with upadacitinib.
- Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis have occurred in patients treated with JAK inhibitors.

Mechanism of Action: Upadacitinib is a JAK inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Upadacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs.

Contraindication(s): None.

Warnings and Precautions:

- Serious Infections: Serious and sometimes fatal infections have been reported in patients receiving upadacitinib. The most frequent serious infections reported with upadacitinib included pneumonia and cellulitis. Among opportunistic infections, TB, multidermatomal herpes zoster, oral/esophageal candidiasis, and cryptococcosis, were

reported with upadacitinib use. Use of upadacitinib should be avoided in patients with an active, serious infection, including localized infections. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with upadacitinib and treatment should be interrupted if a patient develops a serious or opportunistic infection. Patients should be screened for TB before starting upadacitinib therapy. Viral reactivation, including cases of herpes virus reactivation and hepatitis B virus reactivation, were reported in clinical studies with upadacitinib. Screening for viral hepatitis and monitoring for reactivation should be performed in accordance with clinical guidelines before starting and during therapy with upadacitinib.

- Malignancy: Malignancies were observed in clinical studies of upadacitinib. The risks and benefits of upadacitinib should be considered prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing upadacitinib in patients who develop a malignancy.
- Thrombosis: Thrombosis, including DVT, PE, and arterial thrombosis, have occurred in patients treated with JAK inhibitors, including upadacitinib. The risks and benefits of upadacitinib should be considered prior to treating patients who may be at increased risk of thrombosis. If symptoms of thrombosis occur, patients should be evaluated promptly and treated appropriately.
- Gastrointestinal (GI) Perforation: Events of GI perforation have been reported in studies with upadacitinib. In these studies, many patients with RA were receiving background therapy with NSAIDs. Upadacitinib should be used with caution in patients who may be at increased risk for GI perforation (e.g., patients with a history of diverticulitis or who are taking NSAIDs).
- Laboratory Parameters:
    - Upadacitinib should not be initiated or should be discontinued in patients with an absolute lymphocyte count <500cells/mm^3, an absolute neutrophil count (ANC) <1,000cells/mm^3, or a hemoglobin level <8g/dL.
    - Treatment with upadacitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Elevations in LDL cholesterol decreased to pre-treatment levels in response to statin therapy.
    - Treatment with upadacitinib was associated with increased incidence of liver enzyme elevation compared to placebo.
- Embryo-Fetal Toxicity: Based on findings in animal studies, upadacitinib may cause fetal harm when administered to a pregnant woman. Administration of upadacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Females of reproductive potential should be advised to use effective contraception during treatment with upadacitinib and for 4 weeks following completion of therapy.
- Vaccinations: Use of live, attenuated vaccines during, or immediately prior to, upadacitinib therapy is not recommended.

Efficacy: The efficacy and safety of upadacitinib 15mg once daily were assessed in 5 Phase 3 randomized, double-blind, multicenter studies in adult patients with moderately-to-severely active RA.

- Study RA-I was a 24-week monotherapy trial in 947 RA patients who were naïve to MTX. Patients received upadacitinib 15mg once daily or MTX as monotherapy. The primary endpoint was the proportion of patients who achieved a 50% improvement in the ACR composite measure of RA symptoms (ACR50) at week 12.
- Study RA-II was a 14-week monotherapy trial in 648 RA patients who had an inadequate response to MTX. Patients received upadacitinib 15mg once daily monotherapy or continued their stable dose of MTX monotherapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 14.
- Study RA-III was a 12-week trial in 661 RA patients who had an inadequate response to conventional DMARDs (cDMARDs). Patients received upadacitinib 15mg once daily or placebo added to background cDMARD therapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12 versus placebo.
- Study RA-IV was a 48-week trial in 1,629 RA patients who had an inadequate response to MTX. Patients received upadacitinib 15mg once daily, active comparator, or placebo added to background MTX. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12 versus placebo.
- Study RA-V was a 12-week trial in 499 RA patients who had an inadequate response or intolerance to biologic DMARDs (bDMARDs). Patients received upadacitinib 15mg once daily or placebo added to background cDMARD therapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 12 versus placebo.

Table 1: Proportion of Patients Who Achieved ACR20 at Week 12 or 14

Study RA-I MTX-Naïve		Study RA-II MTX-IR		Study RA-III cDMARD-IR		Study RA-IV MTX-IR		Study RA-V bDMARD-IR	
MTX N=314	UPA N=317	MTX N=216	UPA N=217	PBO N=221	UPA N=221	PBO N=651	UPA N=651	PBO N=169	UPA N=164
ACR20									
54	76	41	68	36	64	36	71	28	65

MTX = methotrexate; IR = inadequate responder; cDMARD = conventional disease-modifying anti-rheumatic drug; bDMARD = biologic disease-modifying anti-rheumatic drug; UPA = upadacitinib; PBO = placebo; N = number; ACR20 = American College of Rheumatology ≥20% improvement

Cost Comparison:

Medication	Cost Per Unit	Cost for 24 Weeks of Therapy
Rinvoq™ (upadacitinib) 15mg tablet	**$163.89**	**$27,553.52**
Enbrel® (etanercept) 50mg/mL SureClick® autoinjector	$1,293.52*	$31,044.48*
Humira® (adalimumab) 40mg/0.8mL pen	$2,521.08*	$30,252.96*
Olumiant® (baricitinib) 2mg tablet	$71.23	$11,966.64
Xeljanz® (tofacitinib) 5mg tablet	$72.67	$24,417.12

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.
Unit = tablet, autoinjector, or pen
*Supplementally rebated products.
Dosing based on recommended treatment doses for RA in a 75kg adult patient.
Cost for 24 weeks of therapy based on maintenance treatment dosing after initial dosing is complete.

Skyrizi™ (Risankizumab-rzaa) Product Summary[27]

Indication(s): Skyrizi™ (risankizumab-rzaa) is an IL-23 antagonist indicated for the treatment of moderate-to-severe PsO in adults who are candidates for systemic therapy or phototherapy.

Dosing:

- Skyrizi™ is supplied as 75mg/0.83mL single-dose, prefilled syringes. The syringes must be refrigerated and removed from refrigeration 30 minutes prior to injection.
- The recommended dose of risankizumab is 150mg [(2) 75mg injections] administered by sub-Q injection at week 0, week 4, and every 12 weeks thereafter.
- Risankizumab is intended for use under the guidance and supervision of a health care professional. Patients may self-inject risankizumab after training in sub-Q injection technique.
- Risankizumab may be administered via sub-Q injection into the thighs or abdomen. Administration of risankizumab in the upper, outer arm should only be performed by a health care professional or caregiver.

Mechanism of Action: Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that selectively binds to the p19 subunit of human IL-23 cytokine and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Risankizumab inhibits the release of pro-inflammatory cytokines and chemokines.

Contraindication(s): None.

Warnings and Precautions:

- Infections: Risankizumab may increase the risk of infections. In clinical studies, infections occurred in 22.1% of the risankizumab-group compared to 14.7% of the placebo group through 16 weeks of treatment. The rate of serious infections for the risankizumab group and the placebo group was ≤0.4%. Treatment with risankizumab 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 risankizumab. Across the Phase 3 PsO clinical studies, of the 72 subjects with latent TB who were concurrently treated with risankizumab and appropriate TB prophylaxis during the studies, none developed active TB during the mean follow-up of 61 weeks. Anti-TB therapy should be considered prior to initiating risankizumab in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Risankizumab should not be administered to patients with active TB.
- Vaccinations: Prior to initiating therapy with risankizumab, consider completion of all age-appropriate immunizations according to current immunization guidelines. Use of live vaccines should be avoided in patients treated with risankizumab.

Efficacy: The efficacy and safety of risankizumab was assessed in 3 randomized, double-blind, studies including 2,109 adult patients with moderate-to-severe PsO. Eligible patients had a minimum body surface area (BSA) involvement of 10%, a static Physician's Global Assessment

(sPGA) score ≥3 ("moderate") in the overall assessment (plaque thickness/induration, erythema, and scaling) of PsO on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12. Across all studies, 38% of subjects had received prior phototherapy, 48% had received prior non-biologic systemic therapy, and 42% had received prior biologic therapy for the treatment of PsO.

- In ULTIMMA-1 and ULTIMMA-2, 997 patients were enrolled (598 randomized to the risankizumab 150mg group, 200 randomized to the placebo group, and 199 to the biologic active control group). Patients received treatment at weeks 0, 4, and every 12 weeks thereafter. Both studies assessed the responses at week 16 compared to placebo for the 2 co-primary endpoints: the proportion of patients who achieved a sPGA score of 0 ("clear") or 1 ("almost clear"); the proportion of patients who achieved at least a 90% reduction from baseline PASI (PASI 90).

Table 2: Proportion of Patients With sPGA of 0 or 1 or PASI 90 or 100 at Week 16

	ULTIMMA-1		ULTIMMA-2	
	Risankizumab (N=304) n (%)	**Placebo (N=102) n (%)**	**Risankizumab (N=294) n (%)**	**Placebo (N=98) n (%)**
sPGA 0 or 1	267 (88)	8 (8)	246 (84)	5 (5)
PASI 90	229 (75)	5 (5)	220 (75)	2 (2)
sPGA 0	112 (37)	2 (2)	150 (51)	3 (3)
PASI 100	109 (36)	0 (0)	149 (51)	2 (2)

N = number; % = percentage; sPGA = static Physician's Global Assessment score; 0 = clear; 1 = almost clear; PASI = Psoriasis Area and Severity Index score; PASI 90 = proportion of subjects who achieved at least a 90% reduction from baseline PASI; PASI 100 = proportion of patients who achieved a 100% reduction from baseline PASI

- MMHANCE enrolled 507 patients (407 randomized to risankizumab 150mg and 100 to placebo). Patients received treatment at weeks 0, 4, and every 12 weeks thereafter. At week 16, risankizumab was superior to placebo on the co-primary endpoints of sPGA 0 or 1 (84% risankizumab vs. 7% placebo) and PASI 90 (73% risankizumab vs. 2% placebo). The respective response rates for risankizumab and placebo at week 16 were: sPGA 0 (46% risankizumab vs. 1% placebo); PASI 100 (47% risankizumab vs. 1% placebo); and PASI 75 (89% risankizumab and 8% placebo).

Cost Comparison:

Medication	Cost Per Unit	Cost for 24 Weeks of Therapy
Skyrizi™ (risankizumab-rzaa) 75mg/0.83mL syringe	**$7,375.00**	**$29,500.00**
Enbrel® (etanercept) 50mg/mL SureClick® autoinjector	$1,293.52*	$31,044.48*
Humira® (adalimumab) 40mg/0.8mL pen	$2,521.08*	$30,252.96*
Ilumya™ (tildrakizumab-asmn) 100mg/mL syringe	$13,648.90	$27,297.80

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.
Unit = pen, syringe, or autoinjector
*Supplementally rebated products.
Dosing based on recommended treatment doses for PsO in a 75kg adult patient.
Cost for 24 weeks of therapy based on maintenance treatment dosing after initial dosing is complete.

Recommendations

The College of Pharmacy recommends the addition of Eticovo™ (etanercept-ykro), Hadlima™ (adalimumab-bwwd), Hyrimoz™ (adalimumab-adaz), Rinvoq™ (upadacitinib) and Skyrizi™ (risankizumab-rzza) to Tier-3 of the Targeted Immunomodulator Agents Product Based Prior Authorization (PBPA) category. Current Tier-3 approval criteria for this category will apply.

Targeted Immunomodulator Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and
2. A trial of at least 1 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 1 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 1 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.

Additionally, the College of Pharmacy recommends the following criteria for Otezla® (apremilast) for the treatment of ulcers associated with Behçet's Disease (BD) and Rituxan® (rituximab) for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA):

Otezla® (Apremilast) Approval Criteria [Behçet's Disease (BD) Diagnosis]:

1. An FDA approved indication for the treatment of oral ulcers associated with BD; and
2. Member must have had oral ulcers at least 3 times in the last 12 month period; and
3. Member must have had a 2 week trial of the following that resulted in inadequate efficacy or intolerable adverse effects (or be contraindicated for the member):
    a. Topical corticosteroids (applied topically to the mouth); and
    b. Colchicine; and
4. Quantity limits according to package labeling will apply.

Rituxan® (Rituximab) Approval Criteria [Granulomatosis With Polyangiitis (GPA, Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) Diagnosis]:

1. An FDA approved diagnosis of GPA or MPA in adult and pediatric patients 2 years of age and older; and
2. Rituxan® must be used in combination with corticosteroids; and
3. Approval quantity will be based on Rituxan® prescribing information and FDA approved dosing regimen(s).

Lastly the College of Pharmacy recommends updating the prior authorization criteria for Humira® (adalimumab) when used for uveitis and Benlysta® (belimumab) based on new FDA approvals. The following criteria will apply (changes and additions noted in red):

Benlysta® (Belimumab) Approval Criteria:

1. The intravenous (IV) formulation will be covered as a medical claim only benefit while the subcutaneous (sub-Q) formulation will be covered as a pharmacy only benefit; and
2. An FDA approved indication for the treatment of ~~adults~~ members 5 years of age and older with active, autoantibody-positive, systemic lupus erythematosus (SLE) already receiving standard therapy; and
3. Documented inadequate response to at least 2 of the following medications:
    a. High-dose oral corticosteroids; or
    b. Methotrexate; or
    c. Azathioprine; or
    d. Mycophenolate; or
    e. Cyclophosphamide; and
4. Member must not have severe active lupus nephritis or severe active central nervous system lupus; and
5. Benlysta® will not be approved for combination use with biologic therapies or IV cyclophosphamide.

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~~ members 2 years of age and older; and
2. A failed trial with a corticosteroid injection or systemic corticosteroid in which member has had an inadequate response; or
3. A patient-specific, clinically significant reason a trial of corticosteroid treatment is inappropriate for the member must be provided.
4. Hyrimoz™ (adalimumab-adaz),

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-adaz (Hyrimoz™)**
leflunomide		adalimumab-atto (Amjevita™)
mesalamine		**adalimumab-bwwd (Hadlima™)**
methotrexate		alefacept (Amevive®)
minocycline		anakinra (Kineret®)
NSAIDs		apremilast (Otezla®)β
oral corticosteroids		baricitinib (Olumiant®)
		brodalumab (Siliq™)
		canakinumab (Ilaris®)¥
		certolizumab pegol (Cimzia®)

Targeted Immunomodulator Agents*±		
Tier-1 (DMARDs appropriate to disease state)	**Tier-2***	**Tier-3**
		etanercept-szzs (Erelzi™)
		etanercept-ykro (Eticovo™)
		golimumab (Simponi® & Simponi® Aria™)
		guselkumab (Tremfya™)
		infliximab (Remicade®)
		infliximab-abda (Renflexis™)
		infliximab-dyyb (Inflectra™)
		ixekizumab (Taltz®)
		risankizumab-rzza (Skyrizi™)
		rituximab (Rituxan®)~
		sarilumab (Kevzara®)
		secukinumab (Cosentyx®)Ω
		tildrakizumab-asmn (Ilumya™)
		tocilizumab (Actemra®)π
		tofacitinib (Xeljanz® & Xeljanz® XR)
		upadacitinib (Rinvoq™)
		ustekinumab (Stelara®)
		vedolizumab (Entyvio™)

DMARDs = disease modifying anti-rheumatic drugs, NSAIDs = nonsteroidal anti-inflammatory drugs

*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.

±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.

+Unique criteria applies for a diagnosis of hidradenitis suppurativa (HS) and noninfectious intermediate and posterior uveitis and panuveitis.

βUnique criteria applies for a diagnosis of Behçet's disease (BD).

¥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).

~Unique criteria applies for a diagnosis of pemphigus vulgaris (PV). Unique criteria applies for a diagnosis of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

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 (GCA) and chimeric antigen receptor (CAR) T-cell-induced cytokine release syndrome (CRS).

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

1. An FDA approved diagnosis of 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 corticosteroids for a minimum of 4 weeks or a reason why this is not appropriate; and
5. Actemra® will be taken in combination with tapering course of a corticosteroids 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 members 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(s).

Actemra® (Tocilizumab) Approval Criteria [Chimeric Antigen Receptor (CAR) T-Cell-Induced Cytokine Release Syndrome (CRS) Diagnosis]:

1. An FDA approved diagnosis of CAR T-cell-induced CRS.

Humira® (Adalimumab) Approval Criteria [Hidradenitis Suppurativa (HS) Diagnosis]:

1. A diagnosis of moderate-to-severe HS; and
2. Hurley Stage II or III disease; and
3. Member must have at least 3 abscesses or inflammatory nodules; and
4. Previous failure of at least 2 of the following: topical or systemic antibiotics, oral or intralesional corticosteroids, dapsone, cyclosporine, antiandrogens (spironolactone or oral contraceptives), finasteride, or surgery.

Ilaris® (Canakinumab) Approval Criteria [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 TRAPS with chronic or recurrent disease activity defined as 6 flares per year; or
2. A diagnosis of HIDS/MKD; or
3. A diagnosis of 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 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. 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 members 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 >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 1 year.

Rituxan® (Rituximab) Approval Criteria [Pemphigus Vulgaris (PV) Diagnosis]:

1. A diagnosis of moderate-to-severe PV; and
2. Rituxan® must be used in combination with a tapering course of corticosteroids; and
3. Initial approvals will be for (2) 1,000mg intravenous (IV) infusions separated by 2 weeks and a 500mg infusion at month 12. Subsequent approvals may be authorized based on 6 month evaluations or upon relapse no sooner than 16 weeks after the previous infusion.

Utilization Details of Targeted Immunomodulator Agents: Fiscal Year 2019

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	1,417	266	$8,770,317.94	5.33	$6,189.36
HUMIRA PEN INJ 40MG/0.4ML	815	185	$4,568,749.73	4.41	$5,605.83
HUMIRA INJ 40MG/0.4ML	260	64	$1,429,245.54	4.06	$5,497.10
HUMIRA KIT 40MG/0.8ML	231	55	$1,294,316.67	4.2	$5,603.10
HUMIRA INJ 20MG/0.2ML	64	11	$320,961.75	5.82	$5,015.03
HUMIRA PEN KIT CD/UC/HS	48	45	$704,311.97	1.07	$14,673.17
HUMIRA PEN INJ CD/UC/HS	29	28	$418,399.69	1.04	$14,427.58
HUMIRA PEN KIT PS/UV	21	21	$215,212.91	1	$10,248.23
HUMIRA PEN INJ PS/UV	17	17	$164,108.01	1	$9,653.41
HUMIRA INJ 10MG/0.1ML	10	2	$50,640.40	5	$5,064.04
HUMIRA PED INJ CD	9	8	$121,577.47	1.13	$13,508.61
HUMIRA KIT 20MG/0.4ML	6	2	$29,064.59	3	$4,844.10
HUMIRA PED INJ CD	5	5	$38,407.05	1	$7,681.41
SUBTOTAL	**2,932**	**508**	**$18,125,313.72**	**5.77**	**$6,181.89**
ETANERCEPT PRODUCTS					
ENBREL SRCLK INJ 50MG/ML	974	186	$4,930,993.83	5.24	$5,062.62
ENBREL INJ SYG 50MG/ML	232	52	$1,169,893.72	4.46	$5,042.65
ENBREL MINI INJ 50MG/ML	98	23	$475,903.24	4.26	$4,856.16
ENBREL INJ SYG 25MG/0.5ML	88	14	$262,626.94	6.29	$2,984.40
ENBREL INJ 25MG	76	13	$206,758.15	5.85	$2,720.50
SUBTOTAL	**1,468**	**268**	**$7,046,175.88**	**5.48**	**$4,799.85**
TIER-2 SUBTOTAL	**4,400**	**718***	**$25,171,489.60**	**6.13**	**$5,720.79**
TIER-3 PRODUCTS					
INFLIXIMAB PRODUCTS					
REMICADE INJ 100MG	311	41	$2,058,117.68	7.59	$6,617.74
SUBTOTAL	**311**	**41**	**$2,058,117.68**	**7.59**	**$6,617.74**
SECUKINUMAB PRODUCTS					
COSENTYX PEN INJ 300MG DOSE	163	23	$866,936.01	7.09	$5,318.63
COSENTYX PEN INJ 150MG/ML	47	13	$397,922.37	3.62	$8,466.43
COSENTYX INJ 300MG DOSE	33	8	$223,787.97	4.13	$6,781.45
COSENTYX INJ 150MG/ML	2	1	$9,438.18	2	$4,719.09
SUBTOTAL	**245**	**42**	**$1,498,084.53**	**5.83**	**$6,114.63**
ABATACEPT PRODUCTS					
ORENCIA INJ 125MG/ML	148	24	$592,368.85	6.17	$4,002.49

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
ORENCIA CLCK INJ 125MG/ML	28	8	$103,254.62	3.5	$3,687.67
ORENCIA INJ 250MG	8	1	$34,538.48	8	$4,317.31
ORENCIA INJ 87.5MG/0.7ML	5	1	$9,178.78	5	$1,835.76
SUBTOTAL	**189**	**33**	**$739,340.73**	**5.73**	**$3,911.86**
TOFACITINIB PRODUCTS					
XELJANZ TAB 5MG	119	37	$500,768.16	3.22	$4,208.14
XELJANZ XR TAB 11MG	41	8	$170,142.22	5.13	$4,149.81
XELJANZ TAB 10MG	12	4	$53,487.84	3	$4,457.32
SUBTOTAL	**172**	**46**	**$724,398.22**	**3.74**	**$4,211.62**
USTEKINUMAB PRODUCTS					
STELARA INJ SYG 90MG/ML	73	17	$1,508,311.93	4.29	$20,661.81
STELARA INJ SYG 45MG/0.5ML	55	22	$585,084.39	2.5	$10,637.90
STELARA INJ 45MG/0.5ML	6	2	$64,658.44	3	$10,776.41
SUBTOTAL	**134**	**41**	**$2,158,054.76**	**3.27**	**$16,104.89**
TOCILIZUMAB PRODUCTS					
ACTEMRA INJ 162MG/0.9ML	69	12	$244,424.25	5.75	$3,542.38
ACTEMRA INJ 400MG/20ML	31	3	$99,081.59	10.33	$3,196.18
ACTEMRA INJ 200MG/10ML	17	3	$39,078.68	5.67	$2,298.75
ACTEMRA INJ 80MG/4ML	14	2	$11,071.15	7	$790.80
SUBTOTAL	**131**	**18**	**$393,655.67**	**7.28**	**$3,005.01**
APREMILAST PRODUCTS					
OTEZLA TAB 30MG	91	22	$275,481.99	4.14	$3,027.27
OTEZLA TAB 10MG/20MG/30MG	14	14	$46,892.30	1	$3,349.45
SUBTOTAL	**105**	**26**	**$322,374.29**	**4.04**	**$3,070.23**
CANAKINUMAB PRODUCTS					
ILARIS INJ 150MG/ML	96	18	$1,611,218.94	5.33	$16,783.53
SUBTOTAL	**96**	**18**	**$1,611,218.94**	**5.33**	**$16,783.53**
CERTOLIZUMAB PRODUCTS					
CIMZIA PREFL KIT 200MG/ML	83	14	$337,042.37	5.93	$4,060.75
CIMZIA KIT STARTER	4	4	$47,110.31	1	$11,777.58
SUBTOTAL	**87**	**16**	**$384,152.68**	**5.44**	**$4,415.55**
GOLIMUMAB PRODUCTS					
SIMPONI INJ 50MG/0.5ML	52	9	$234,529.41	5.78	$4,510.18
SIMPONI INJ 100MG/ML	6	1	$32,582.30	6	$5,430.38
SIMPONI INJ SYG 50MG/0.5ML	3	1	$13,122.90	3	$4,374.30
SUBTOTAL	**61**	**10**	**$280,234.61**	**6.1**	**$4,594.01**
IXEKIZUMAB PRODUCTS					
TALTZ INJ 80MG/ML	42	9	$328,001.20	4.67	$7,809.55
SUBTOTAL	**42**	**9**	**$328,001.20**	**4.67**	**$7,809.55**
SARILUMAB PRODUCTS					
KEVZARA INJ 200MG/1.14ML	22	4	$69,713.06	5.5	$3,168.78
KEVZARA INJ 200MG/1.14ML	7	2	$22,982.44	3.5	$3,283.21
SUBTOTAL	**29**	**5**	**$92,695.50**	**5.8**	**$3,196.40**
GUSELKUMAB PRODUCTS					
TREMFYA INJ 100MG/ML	24	6	$272,698.08	4	$11,362.42
SUBTOTAL	**24**	**6**	**$272,698.08**	**4**	**$11,362.42**
VEDOLIZUMAB PRODUCTS					
ENTYVIO INJ 300MG	19	4	$112,606.67	4.75	$5,926.67

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
SUBTOTAL	**19**	**4**	**$112,606.67**	**4.75**	**$5,926.67**
ANAKINRA PRODUCTS					
KINERET INJ 100MG/0.67ML	18	4	$71,668.34	4.5	$3,981.57
SUBTOTAL	**18**	**4**	**$71,668.34**	**4.5**	**$3,981.57**
BARICITINIB PRODUCTS					
OLUMIANT TAB 2MG	2	1	$4,291.54	2	$2,145.77
SUBTOTAL	**2**	**1**	**$4,291.54**	**2**	**$2,145.77**
TIER-3 SUBTOTAL	**1,665**	**296***	**$11,051,593.44**	**5.63**	**$6,637.59**
TOTAL	**6,065**	**960***	**$36,223,083.04**	**6.32**	**$5,972.48**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Above 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.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	TOTAL UNITS	COST/ CLAIM
REMICADE INJ J1745	221	52	$748,060.68	11,016	$3,384.89
RITUXAN INJ J9310	158	84	$1,137,451.75	1,247	$7,199.06
ACTEMRA INJ J3262	103	18	$228,005.54	47,979	$2,213.65
SIMPONI ARIA INJ J1602	75	27	$299,056.26	14,045	$3,987.42
ORENCIA INJ J0129	74	20	$285,168.18	5,748	$3,853.62
ENTYVIO INJ J3380	34	9	$201,228.00	10,200	$5,918.47
STELARA INJ J3357	8	3	$105,502.90	800	$13,187.86
INFLECTRA INJ Q5103	4	2	$2,469.24	118	$617.31
CIMZIA INJ J0717	1	1	$3,256.00	400	$3,256.00
ENBREL INJ J1438	1	1	$1,646.84	4	$1,646.84
TOTAL	**677+**	**206***	**$3,011,845.39**	**91,557**	**$4,448.81**

+Total number of unduplicated claims.
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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Appendix M

Fiscal Year 2019 Annual Review of Constipation and Diarrhea Medications and 30-Day Notice to Prior Authorize Aemcolo™ (Rifamycin), Motegrity™ (Prucalopride), Zelnorm™ (Tegaserod), and Ibsrela® (Tenapanor)

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

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

1. An FDA approved diagnosis of CIC in members 18 years of age or older, or 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 3 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 3 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; and
6. A quantity limit of 60 capsules per 30 days will apply.

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

1. An FDA approved diagnosis of 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 3 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 3 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; and
6. Amitiza® must be discontinued if treatment with the opioid pain medication is also discontinued; and
7. A quantity limit of 60 capsules per 30 days 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 3 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 3 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; and
6. A quantity limit of 30 capsules per 30 days 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.

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 3 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 3 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; and
7. Movantik® must be discontinued if treatment with the opioid pain medication is also discontinued; and
8. A quantity limit of 30 tablets per 30 days 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 3 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 3 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), Movantik® (naloxegol), or Symproic® (naldemedine) 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; and
8. Relistor® must be discontinued if treatment with the opioid pain medication is also discontinued; and
9. A quantity limit of 90 tablets per 30 days will apply.

Relistor® (Methylnaltrexone) Injection Approval Criteria [Opioid-Induced Constipation (OIC) in Chronic Non-Cancer Pain Diagnosis]:

1. An FDA approved diagnosis of OIC in members 18 years of age or older 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
2. Documentation of the underlying cause of chronic pain, or reason why member is on chronic opioid therapy; and
3. Member must have current use of opioid medications; 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 3 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 3 trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
6. Member must not have known or suspected gastrointestinal obstruction; and
7. A patient-specific, clinically significant reason why member cannot use Amitiza® (lubiprostone), Movantik® (naloxegol), or Symproic® (naldemedine) must be provided; and
8. A patient-specific, clinically significant reason why member cannot use the tablet formulation of Relistor® must be provided; and
9. 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; and
10. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment; and
11. Relistor® must be discontinued if treatment with the opioid pain medication is also discontinued; and
12. A quantity limit of 30 units per 30 days will apply.

Relistor® (Methylnaltrexone) Injection Approval Criteria [Opioid-Induced Constipation (OIC) in Terminal Disease Diagnosis Receiving Palliative Care]:

1. An FDA approved diagnosis of OIC in patients with severe terminal disease who are receiving only palliative care (life expectancy less than 6 months); and
2. Current use of opioid medications; and
3. Documentation of hydration attempts and trials of at least 3 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 3 trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
4. Member must not have known or suspected gastrointestinal obstruction; and
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; 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; and

7. Relistor® must be discontinued if treatment with the opioid pain medication is also discontinued; and
8. A quantity limit of 30 units per 30 days 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 3 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 3 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; and
7. Symproic® must be discontinued if treatment with the opioid pain medication is also discontinued; and
8. A quantity limit of 30 tablets per 30 days will apply.

Trulance® (Plecanatide) 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 3 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 3 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; and
6. A quantity limit of 30 tablets per 30 days 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 2 of the following 3 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
5. Approval will initially be for 12 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment; and
6. A quantity limit of 60 tablets per 30 days 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 3 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; and
6. A quantity limit of 90 tablets per 30 days 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 quantity limit of 9 tablets per 3 days will apply.

Xifaxan® (Rifaximin) 550mg Approval Criteria:

1. An FDA approved indication for the reduction in risk of overt hepatic encephalopathy (HE) recurrence; and
    a. Xifaxan® 550mg will not require a prior authorization and claims will pay at the point of sale if the member has a reported diagnosis of hepatic encephalopathy or hepatic failure within the past 12 months of claims history; or
    b. If the member does not have a reported diagnosis, a manual prior authorization will be required for coverage consideration; 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 2 of the following 3 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; and

3. A quantity limit of 60 tablets per 30 days 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 2 times with the same dosage regimen (550mg three times daily for 14 days).

Utilization of Constipation and Diarrhea Medications: Fiscal Year 2019

Comparison of Fiscal Years: Constipation and Diarrhea Medications

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	165	889	$348,875.40	$392.44	$13.11	34,531	26,621
2019	188	880	$355,719.83	$404.23	$13.64	33,588	26,084
% Change	**13.90%**	**-1.00%**	**2.00%**	**3.00%**	**4.00%**	**-2.70%**	**-2.00%**
Change	**23**	**-9**	**$6,844.43**	**$11.79**	**$0.53**	**-943**	**-537**

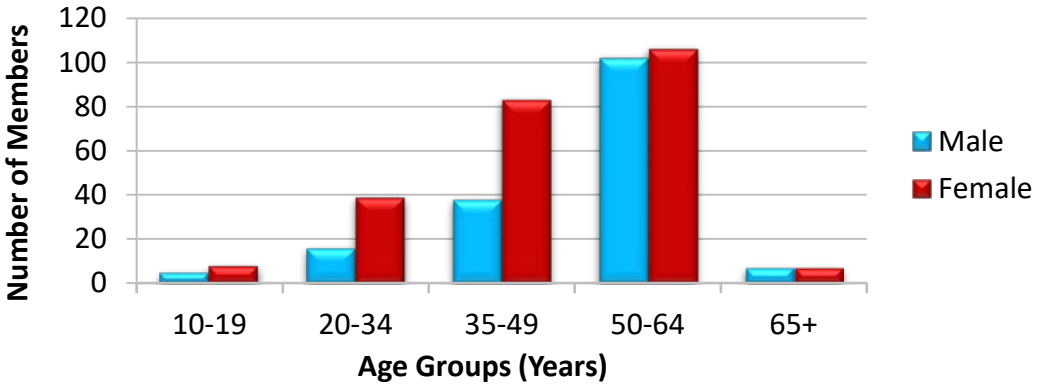
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Please note, the above data does not include Xifaxan® (rifaximin).
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Comparison of Fiscal Years: Xifaxan® (Rifaximin)

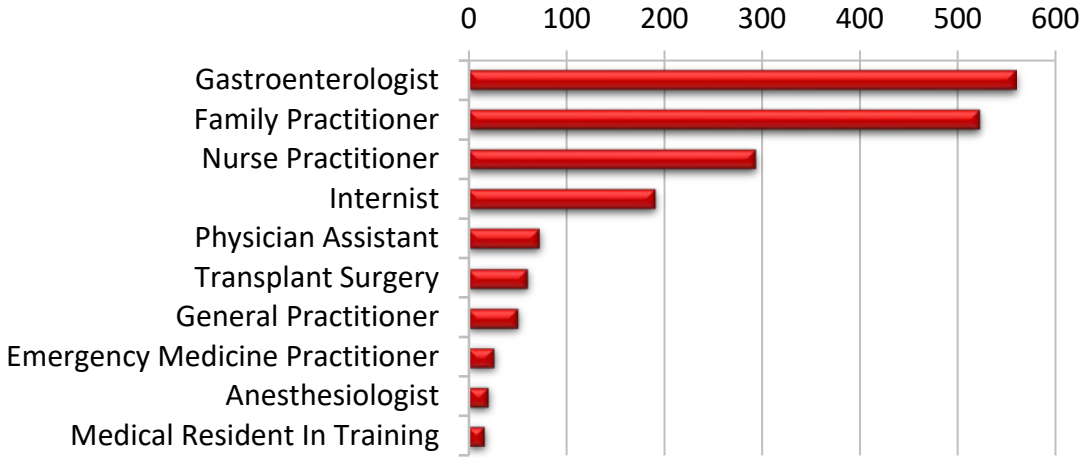
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	246	1,175	$2,150,664.84	$1,830.35	$66.04	64,941	32,565
2019	224	1,022	$2,047,953.41	$2,003.87	$71.48	57,209	28,651
% Change	**-8.90%**	**-13.00%**	**-4.80%**	**9.50%**	**8.20%**	**-11.90%**	**-12.00%**
Change	**-22**	**-153**	**-$102,711.43**	**$173.52**	**$5.44**	**-7,732**	**-3,914**

*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.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Demographics of Members Utilizing Constipation and Diarrhea Medications



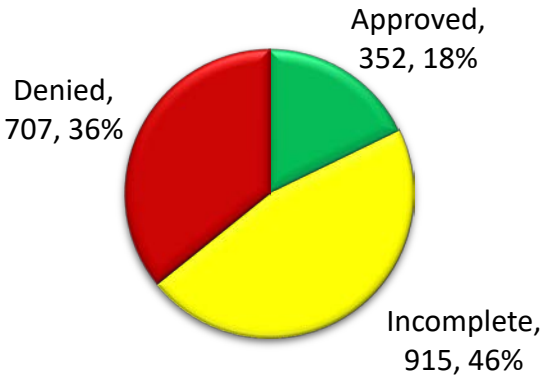
Top Prescriber Specialties of Constipation and Diarrhea Medications by Number of Claims



Prior Authorization of Constipation and Diarrhea Medications

There were 1,974 prior authorization requests submitted for constipation and diarrhea medications during fiscal year 2019. The following chart shows the status of the submitted petitions for fiscal year 2019.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Aemcolo™ [rifamycin delayed-release (DR) tablet]: May 2025
- Amitiza® (lubiprostone capsule): October 2027
- Xifaxan® (rifaximin tablet): March 2030
- Relistor® [methylnaltrexone subcutaneous (sub-Q) injection]: December 2030
- Xermelo® (telotristat tablet): February 2031
- Relistor® (methylnaltrexone tablet): March 2031
- Symproic® (naldemedine tablet): November 2031
- Movantik® (naloxegol tablet): April 2032
- Viberzi® (eluxadoline tablet): March 2033
- Linzess® (linaclotide capsule): August 2033
- Trulance® (plecanatide tablet): June 2034

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

- **November 2018:** The FDA approved Aemcolo™ (rifamycin) for the treatment of adult patients with travelers' diarrhea caused by non-invasive strains of *Escherichia coli* (*E. coli*). Aemcolo™ is an orally administered, minimally absorbed antibiotic that is engineered with Cosmo Pharmaceuticals' Multi Matrix Technology (MMX®), which allows for delayed release to the colon.
- **December 2018:** The FDA approved Motegrity™ (prucalopride) for the treatment of adult patients with chronic idiopathic constipation (CIC). Prucalopride is a once-daily, oral selective serotonin-4 (5-HT_4) receptor agonist that improves bowel motility by stimulating colonic peristalsis.
- **March 2019:** The FDA approved a supplemental New Drug Application (sNDA) for Zelnorm™ (tegaserod), a selective 5-HT_4 receptor agonist, for the treatment of irritable bowel syndrome with constipation (IBS-C) in adult women younger than 65 years of age. Zelnorm™ was originally FDA approved in 2002 for the treatment of IBS-C in women but was voluntarily withdrawn from the United States market in 2007 due to a potential safety signal regarding ischemic events including angina and stroke; however, Zelnorm™ has remained available in the United States through an expanded access program authorized by the FDA.
- **September 2019:** The FDA approved Ibsrela® (tenapanor) for the treatment of adult patients with IBS-C. Tenapanor is an oral, minimally-absorbed small molecule that acts locally in the gastrointestinal (GI) tract to inhibit the sodium/hydrogen exchanger 3 (NHE3), which reduces the absorption of sodium from the small intestine and colon, resulting in an increase in water secretion into the intestinal lumen, thereby accelerating intestinal transit time and resulting in a softer stool consistency.
- **September 2019:** In an ongoing effort to stem misuse and abuse of loperamide, the FDA approved changes to the packaging for brand-name, over-the-counter (OTC) tablet and capsule formulations of the opioid-based antidiarrheal medication. The changes to Imodium® A-D, Imodium® Multi-Symptom Relief, and Be Health® Loperamide HCl capsules limit each carton to no more than 48mg of loperamide and require the tablets and capsules to be packaged in individual (unit-dose) blister packs. The maximum

approved daily dose for adults is 8mg/day for OTC use and 16mg/day for prescription use. According to the FDA, abuse and misuse of loperamide is an ongoing problem in the United States, with some individuals taking higher than recommended doses of loperamide to treat symptoms of opioid withdrawal or to achieve euphoric effects of opioid use, and evidence suggests that package size limits and unit-dose packaging may reduce medication overdose and death. In 2018, the FDA asked manufacturers and packagers of OTC loperamide products to make these changes and is now formally notifying the public of these approved changes.

News:

- **Opioid-Induced Constipation (OIC) Guidelines:** In January 2019, the American Gastroenterological Association (AGA) released a clinical guideline on the medical management of OIC. OIC by definition is a condition associated with opioid use; therefore, one of the first steps to managing patients with OIC is to ensure that the indication for opioid therapy is appropriate, that patients are participating in a pain management program, and that they are taking the minimum necessary opioid dose. Other potential causes or contributors to constipation should be explored and excluded, and lifestyle modifications (e.g., increasing one's fluid intake, regular moderate exercise as tolerated, toileting as soon as possible in response to the urge to defecate) are appropriate first steps for all patients with constipation. Some key recommendations from the guideline include:
  - **Traditional laxatives [e.g., osmotic (polyethylene glycol {PEG}, lactulose, magnesium citrate, magnesium hydroxide), stimulant (bisacodyl, sodium picosulfate, senna), detergent/surfactant stool softeners (docusate), lubricant (mineral oil)]:**
    - In patients with OIC, the AGA recommends the use of traditional laxatives as first-line agents (*Strong Recommendation; Quality of Evidence: Moderate*)
  - **Peripherally acting μ-opioid receptor antagonists (PAMORAs):**
    - In patients with laxative refractory OIC, the AGA recommends naldemedine over no treatment (*Strong Recommendation; Quality of Evidence: High*)
    - In patients with laxative refractory OIC, the AGA recommends naloxegol over no treatment (*Strong Recommendation; Quality of Evidence: Moderate*)
    - In patients with laxative refractory OIC, the AGA suggests methylnaltrexone over no treatment (*Conditional Recommendation; Quality of Evidence: Low*)
  - **Intestinal secretagogues:**
    - In patients with OIC, the AGA makes no recommendation for the use of lubiprostone (*No Recommendation; Quality of Evidence: Evidence Gap*)
  - **Selective 5-HT agonists:**
    - In patients with OIC, the AGA makes no recommendation for the use of prucalopride (*No Recommendation; Quality of Evidence: Evidence Gap)*
- **Meta-Analysis of CIC Therapies:** A systematic review and network meta-analysis of 33 recent, randomized, placebo-controlled trials was completed to determine the relative efficacy and safety of medications available for CIC at 4 weeks and at 12 weeks. Medications evaluated included prucalopride, linaclotide, tegaserod, plecanatide,

elobixibat, lubiprostone, stimulant laxatives, osmotic laxatives, and velusetrag. For the more stringent measure of ≥3 complete, spontaneous bowel movements (CSBMs) per week over baseline, the stimulants bisacodyl and sodium picosulfate, both diphenyl methane stimulants, were most effective at 4 weeks of treatment, while prucalopride was most effective at 12 weeks of treatment. Almost all drugs studied in the trials and all those with current FDA approval proved superior to placebo. For safety, bisacodyl was ranked last, for the total number of adverse events and abdominal pain. There were some study limitations, including that very few trials reported whether patients had been previously unresponsive to or dissatisfied with laxatives, there were no eligible head-to-head trials of 1 active drug versus another, estimates of relative efficacy were based on indirect comparisons, and there was no standardized reporting of adverse events which may have rendered safety comparisons between treatments less valid.

Aemcolo™ (Rifamycin) Product Summary[9]

Indication(s): Aemcolo™ (rifamycin) is a rifamycin antibacterial indicated for the treatment of travelers' diarrhea caused by non-invasive strains of *E. coli* in adult patients.

- Limitations of Use: Aemcolo™ is not recommended for use in patients with diarrhea complicated by fever and/or bloody stool or due to pathogens other than non-invasive strains of *E. coli*.
- To reduce the development of drug-resistant bacteria and maintain the effectiveness of rifamycin and other antibacterial drugs, rifamycin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria.

Dosing:

- Aemcolo™ is supplied as 194mg DR tablets.
- The recommended dosage of Aemcolo™ is 388mg (2 tablets) orally twice daily (in the morning and evening) for 3 days. Each dose should be taken with 6 to 8 ounces of liquid and can be taken with or without food.
- Aemcolo™ should be taken whole, and DR tablets should not be crushed, broken, or chewed.
- Aemcolo™ should not be taken concomitantly with alcohol.
- Aemcolo™ is contraindicated in patients with a known hypersensitivity to rifamycin, any of the other rifamycin class antimicrobial agents (e.g., rifaximin), or any of the components in Aemcolo™.
- The safety and effectiveness of Aemcolo™ have not been established in pediatric patients younger than 18 years of age with travelers' diarrhea.

Mechanism of Action: Aemcolo™ DR tablets are enteric coated with a pH-resistant polymer film which breaks down above pH 7; the tablet core contains rifamycin. Rifamycin is an antibacterial drug that acts by inhibiting the beta-subunit of the bacterial DNA-dependent RNA polymerase, blocking 1 of the steps in DNA transcription; this results in inhibition of bacterial synthesis and consequently, the growth of bacteria. Rifamycin has been shown to be active

against most isolates of *E. coli* (enterotoxigenic and enteroaggregative isolates) both *in vitro* and in clinical studies of travelers' diarrhea.

Efficacy: The efficacy of Aemcolo™ dosed orally (338mg twice daily for 3 days) was evaluated in 1 multi-center, randomized, double-blind, placebo-controlled trial in adults with travelers' diarrhea; Trial 1 was conducted at clinical sites in Guatemala and Mexico and provides the primary evidence for the efficacy of Aemcolo™. A second active-controlled trial (Trial 2) conducted in India, Guatemala, and Ecuador provided supportive evidence for the efficacy of Aemcolo™. Although patients with fever and/or bloody stool at baseline were to be excluded from both trials, 18 patients treated with Aemcolo™ had fever and bloody diarrhea at enrollment in Trial 2. Stool specimens were collected before treatment and 1 to 2 days following the end of treatment to identify enteric pathogens; the predominant pathogen in both trials was *E. coli.* The clinical efficacy of Aemcolo™ was assessed using an endpoint of time to last unformed (watery or soft) stool (TLUS) before achieving clinical cure. The endpoint of clinical cure was defined as 2 or fewer soft stools and minimal enteric symptoms at the beginning of a 24-hour period or no unformed stools at the beginning of a 48-hour period. In Trial 1, Aemcolo™ significantly reduced the TLUS compared to placebo (P=0.0008), and more patients treated with Aemcolo™ were classified as clinical cures than were those in the placebo group. The following table (Table 1) summarizes the clinical response in Trial 1. The results of Trial 2 supported the results presented for Trial 1; in addition, Trial 2 provided evidence that Aemcolo™-treated patients with fever and/or bloody diarrhea at baseline had prolonged TLUS.

Table 1. Clinical Response in Trial 1 (ITT Population)

	Aemcolo™ (N=199)	Placebo (N=65)	Treatment Difference*	P Value
Median TLUS (hours)	46	68	-22	P=0.0008[a]
Clinical Cure, n (%)	162 (81.4)	37 (56.9)	24.5%	P=0.0001[b]

ITT = intent-to-treat; TLUS = time to last unformed stool (in hours); N = number of patients in the ITT population; n = number of patients achieving clinical cure; % = percentage
*Treatment difference = Aemcolo™ – placebo
[a]log-rank test
[b]chi-square test

Cost: The Wholesale Acquisition Cost (WAC) of Aemcolo™ is $12.00 per 194mg DR tablet, resulting in a cost per 3-day treatment of $144.00 based on the recommended dosing of 388mg twice daily for 3 days.

Motegrity™ (Prucalopride) Product Summary[10]

Indication(s): Motegrity™ (prucalopride) is a 5-HT_4 receptor agonist indicated for the treatment of CIC in adult patients.

Dosing:

- Motegrity™ is supplied as 1mg and 2mg oral tablets.

- The recommended dosage of prucalopride is 2mg once daily, taken with or without food. For patients with severe renal impairment [creatinine clearance (CrCl) <30mL/min], the recommended dosage of prucalopride is 1mg once daily.
- Prucalopride is contraindicated in patients with a history of hypersensitivity to prucalopride and in patients with intestinal perforation or obstruction due to structural or functional disorder of the gut wall, obstructive ileus, or severe inflammatory conditions of the intestinal tract (e.g., Crohn's disease, ulcerative colitis, toxic megacolon/megarectum).
- In clinical trials of prucalopride, suicides, suicide attempts, and suicidal ideation have been reported; however, a causal association between treatment with prucalopride and an increased risk of suicidal ideation and behavior has not been established. All patients treated with prucalopride should be monitored for persistent worsening of depression or the emergence of suicidal thoughts and behaviors.
- The safety and effectiveness of prucalopride have not been established in pediatric patients younger than 18 years of age.

Mechanism of Action: Prucalopride, a selective 5-HT_4 receptor agonist, is a GI prokinetic agent that stimulates colonic peristalsis [high-amplitude propagating contractions (HAPCs)], which increases bowel motility.

Efficacy: The efficacy of prucalopride for the treatment of CIC was evaluated in 6 double-blind, placebo-controlled, randomized, multicenter clinical trials in 2,484 adult patients (Studies 1 to 6). Studies 1 through 5 were 12 weeks in treatment duration, and Study 6 included 24 weeks of treatment. The mean adult age was 47±16 years (range 17 to 95 years) and the mean duration of constipation was 16±15 years, with 28% of patients having CIC for at least 20 years. Eligible patients required a history of CIC defined as having fewer than 3 spontaneous bowel movements (SBMs) per week that resulted in a feeling of complete evacuation (CSBM) and 1 or more of the following symptoms for >25% of bowel movements (BMs) in the preceding 3 months, with symptoms onset >6 months prior to screening: lumpy or hard stools, sensation of incomplete evacuation, or straining at defecation. In all studies, patients were excluded if constipation was due to secondary causes or suspected to be drug-induced. Efficacy was assessed using information provided by patients in a daily diary. For the primary efficacy endpoint, a responder was defined as a patient with an average of ≥3 CSBMs per week, over the 12-week treatment period. In the Intent-to-Treat (ITT) population in 6 studies, 1,237 patients received prucalopride 1mg or 2mg and 1,247 patients received placebo. In all studies, improvement in the frequency of CSBMs/week was seen as early as week 1 and was maintained through week 12. The following table (Table 2) summarizes the efficacy responder rates in the 6 studies.

Table 2. Efficacy Responder Rates in Prucalopride Studies of CIC (ITT Population)

	Prucalopride 1mg or 2mg QD n/N (%)	Placebo n/N (%)	Treatment Difference* (95% CI)	P Value
Study 1	83/249 (33)	26/252 (10)	23 (16, 30)	P<0.001
Study 2	67/177 (38)	32/181 (18)	20 (11, 29)	P<0.001
Study 3	46/236 (19)	23/240 (10)	10 (4, 16)	P=0.002
Study 4	55/190 (29)	25/193 (13)	16 (8, 24)	P<0.001
Study 5	50/214 (24)	25/212 (12)	12 (4, 19)	P<0.001
Study 6	43/171 (25)	34/169 (20)	5 (-4, 14)	P=0.341

CIC= chronic idiopathic constipation; ITT = intent-to-treat; QD = once daily; n = number of responders; N = number of patients per treatment group; % = percentage; CI = confidence interval
*Treatment difference = % prucalopride – % placebo

Cost: The National Average Drug Acquisition Cost (NADAC) of Motegrity™ is $13.66 per 2mg tablet, resulting in a monthly cost of $409.80.

Zelnorm™ (Tegaserod) Product Summary[11]

Indication(s): Zelnorm™ (tegaserod) is a 5-HT_4 receptor agonist indicated for the treatment of IBS-C in adult women younger than 65 years of age.

- Limitations of Use: The safety and effectiveness of tegaserod in men with IBS-C have not been established.
- Tegaserod is not recommended for the treatment of IBS-C in women 65 years of age and older.

Dosing:

- Zelnorm™ is supplied as 6mg oral tablets.
- The recommended dosage of tegaserod is 6mg twice daily, taken at least 30 minutes before meals.
- Tegaserod should be discontinued in patients who have not had adequate control of symptoms after 4 to 6 weeks of treatment.
- Tegaserod is contraindicated in patients with a history of myocardial infarction (MI), stroke, transient ischemic attack (TIA), or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment [estimated glomerular filtration rate (eGFR) <15mL/min/1.73m^2] or end-stage renal disease (ESRD); moderate or severe hepatic impairment (Child-Pugh B or C); a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; or hypersensitivity to tegaserod.
- Stroke, MI, and cardiovascular (CV) death [major adverse CV events (MACE)] have been reported in adults taking tegaserod who had an increased risk of developing an adverse CV event based on their medical history.
- Suicide, suicidal attempt ideation, and self-injurious behavior have been reported in clinical trials of IBS-C and other GI motility disorders. The frequency of suicidal ideation or attempts with tegaserod treatment was higher than placebo. All patients treated with

tegaserod should be monitored for clinical worsening of depression and the emergence of suicidal thoughts and behaviors, especially during the first few months of treatment.

- The safety and effectiveness of tegaserod have not been established in pediatric patients younger than 18 years of age.

Mechanism of Action: Tegaserod, a selective 5-HT_4 receptor agonist, is a GI prokinetic agent that stimulates colonic peristalsis (HAPCs), which increases bowel motility.

CV Safety: A retrospective analysis was conducted of the pooled clinical trial database data of 29 placebo-controlled trials of IBS-C and other GI motility disorders (involving 18,645 patients, both male and female) of at least 4 weeks duration, and an external adjudication of the reported CV ischemic (CVI) events identified an imbalance in patients taking tegaserod (13 events, 0.1%) compared to placebo (1 event, 0.01%). A second external adjudication was conducted with additional patient-level information and used a comprehensive pre-specified methodology regarding both case selection and assessment; this adjudication confirmed 7 CVI events (0.06%) with tegaserod compared to 1 event (0.01%) with placebo. An imbalance in MACE events (defined as CV death, non-fatal MI, or non-fatal stroke) was observed in patients taking tegaserod compared to placebo, as reported in both external adjudications. All events occurred in male and female patients with a history of CVI disease (defined as prior MI, stroke, TIA, or angina) and/or more than 1 CV risk factor [defined as active smoking, current hypertension (HTN)/history of antihypertensive treatment, current hyperlipidemia/history of lipid lowering medication, history of diabetes mellitus (DM), age ≥55 years, or obesity (body mass index {BMI} >30kg/m^2)]. The rate of MACE events for tegaserod-treated patients ranged from 0.03% to 0.06% in the overall population and 0.01% to 0.03% in the female population younger than 65 years of age without a history of CVI disease, compared to no MACE events in the placebo-treated group.

Efficacy: The efficacy of tegaserod for the treatment of IBS-C in women younger than 65 years of age was evaluated in 3 multicenter, double-blind, placebo-controlled clinical trials in 2,470 female patients [mean age 43 years (range 17 to 89 years)] with at least a 3-month history of IBS-C symptoms prior to the baseline period that included abdominal pain, bloating, and constipation. Following a 4-week baseline period, patients received either tegaserod 6mg twice daily or placebo for 12 weeks. In all patients, constipation was characterized by at least 2 of the following 3 symptoms, each occurring >25% of the time over a 3-month period: <3 BMs/week, hard or lumpy stools, or straining with a BM. Each week of the 4-week baseline period and the 12-week double-blind treatment period, patients were asked the question, “Please consider how you felt this past week in regard to your IBS, in particular your overall well-being, and symptoms of abdominal discomfort, pain, and altered bowel habit. Compared to the way you usually felt before entering the trial, how would you rate your relief of symptoms during the past week?” The response variable consisted of the following 5 categories: (1) completely relieved, (2) considerably relieved, (3) somewhat relieved, (4) unchanged, or (5) worse. Patients were classified as responders within a month if they were (1) completely relieved or (2) considerably relieved for at least 2 of the 4 weeks or if they were at least (3) somewhat relieved for each of the 4 weeks. The following table (Table 3) summarizes the efficacy responder rates in the 3 trials. In a subgroup of female patients younger than 65 years of age, the treatment

differences were generally similar at both month 1 and month 3 to the overall results shown in Table 3.

Table 3. Efficacy Responder Rates in Tegaserod Studies of IBS-C

	Proportion of Responders (Female) Month 1			Proportion of Responders (Female) Month 3¥		
	Tegaserod 6mg BID n/N (%)	Placebo n/N (%)	Treatment Difference* (95% CI)	Tegaserod 6mg BID n/N (%)	Placebo n/N (%)	Treatment Difference* (95% CI)
Study 1	76/244 (31%)	42/240 (17%)	14 (6, 21)	95/244 (39%)	66/240 (28%)	11 (3, 20)
Study 2	265/767 (35%)	164/752 (22%)	13 (8, 17)	334/767 (44%)	292/752 (39%)	5 (0, 10)
Study 3	80/233 (34%)	47/234 (20%)	14 (6, 22)	100/233 (43%)	88/234 (38%)	5 (-4, 14)

IBS-C = irritable bowel syndrome with constipation; BID = twice daily; n = number of responders; N = number of patients per treatment group; % = percentage; CI = confidence interval
*Treatment difference = % tegaserod – % placebo
¥Primary efficacy assessment

Cost: The WAC of Zelnorm™ is $6.48 per 6mg tablet, resulting in a monthly cost of $388.80.

Ibsrela® (Tenapanor) Product Summary[12]

Indication(s): Ibsrela® (tenapanor) is a NHE3 inhibitor indicated for the treatment of IBS-C in adult patients.

Dosing:

- Ibsrela® is supplied as 50mg oral tablets.
- The recommended dosage of tenapanor is 50mg twice daily. Tenapanor should be taken immediately prior to breakfast or the first meal of the day and immediately prior to dinner. If a dose of tenapanor is missed, the patient should skip the missed dose and take the next dose at the regular time. Patients should not take 2 doses of tenapanor at the same time.
- Tenapanor is contraindicated in patients younger than 6 years of age due to the risk of serious dehydration (*refer to the following Boxed Warning*) and in patients with known or suspected mechanical GI obstruction.

Boxed Warning: Risk of Serious Dehydration in Pediatric Patients

- Tenapanor is contraindicated in patients younger than 6 years of age; in nonclinical studies in young juvenile rats, administration of tenapanor caused deaths presumed to be due to dehydration.
- Use of tenapanor should be avoided in patients 6 years to younger than 12 years of age.
- The safety and effectiveness of tenapanor have not been established in pediatric patients younger than 18 years of age.

Mechanism of Action: Tenapanor is a locally acting inhibitor of NHE3, an antiporter expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium. By inhibiting NHE3 on the apical surface of the enterocytes, tenapanor reduces absorption of sodium from the small intestine and colon, resulting in an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency.

Efficacy: The efficacy of tenapanor for the treatment of IBS-C was established in 2 double-blind, placebo-controlled, randomized, multicenter clinical trials in adult patients (Trial 1 and Trial 2). The ITT analysis population included 620 patients in Trial 1 and 606 patients in Trial 2 with a mean age of 46 years (range 18 to 75 years). To enter the trials, all patients met Rome III criteria for IBS-C and were required to meet the following clinical criteria during the 2-week baseline run-in period: a mean abdominal pain score of at least 3 on a 0-to-10 point numeric rating scale (0 = no pain; 10 = very severe pain), <3 CSBMs per week, and ≤5 SBMs per week (SBM defined as a BM occurring in the absence of laxative use). The trial designs were identical through the first 12 weeks of treatment, and thereafter differed in that Trial 1 continued for an additional 14 weeks of treatment (26 weeks double-blind treatment), whereas Trial 2 included a 4-week randomization withdrawal period. Efficacy of tenapanor was assessed using responder analyses based on daily diary entries. In both trials, the primary endpoint was the proportion of responders, where a responder was defined as a patient achieving both the stool frequency and abdominal pain intensity responder criteria in the same week for at least 6 of the first 12 weeks of treatment. The stool frequency (CSBM) responder was defined as a patient who experienced an increase of at least 1 CSBM in weekly average from baseline, and the abdominal pain responder was defined as a patient who experienced at least a 30% reduction in the weekly average of abdominal pain score compared with baseline. The following table (Table 4) summarizes the responder rates for the primary endpoint and components of the primary endpoint (CSBM and abdominal pain) in the 2 trials. In both trials, improvements from baseline in average weekly CSBMs and abdominal pain were observed by week 1, with improvement maintained through the end of treatment.

Table 4. Efficacy Responder Rates in Tenapanor Studies of IBS-C (ITT Population)

	Trial 1			Trial 2		
	Tenapanor N=293	**Placebo N=300**	**Treatment Difference* (95% CI)**	**Tenapanor N=307**	**Placebo N=299**	**Treatment Difference* (95% CI)**
Responder¥	37%	24%	13 (6, 20)	27%	19%	8 (2, 15)
CSBM Responder+	47%	33%	-	34%	29%	-
Abdominal Pain Responder+	50%	38%	-	44%	33%	-

IBS-C = irritable bowel syndrome with constipation; ITT = intent-to-treat; N = number of patients per treatment group; CI = confidence interval; CSBM = complete spontaneous bowel movement

*Treatment difference = % tenapanor – % placebo

¥Primary endpoint

+Components of the primary endpoint

Cost: Cost information for Ibsrela® is not yet available.

Cost Comparison: Constipation Medications

Medication	Recommended Dose	Cost/Month*
Chronic Idiopathic Constipation (CIC) Indication		
Amitiza® (lubiprostone) 24mcg cap	24mcg PO BID	$355.80
Linzess® (linaclotide) 145mcg cap	72mcg or 145mcg PO QDay	$406.20
Motegrity™ (prucalopride) 2mg tab	2mg PO QDay	$409.80
Trulance® (plecanatide) 3mg tab	3mg PO QDay	$395.40
Irritable Bowel Syndrome with Constipation (IBS-C) Indication		
Amitiza® (lubiprostone) 8mcg cap	8mcg PO BID	$354.60
Ibsrela® (tenapanor) 50mg tab	50mg PO BID	n/a
Linzess® (linaclotide) 290mcg cap	290mcg PO QDay	$406.80
Trulance® (plecanatide) 3mg tab	3mg PO QDay	$395.40
Zelnorm™ (tegaserod) 6mg tab	6mg PO QDay	$388.80
Opioid-Induced Constipation (OIC) Indication[+]		
Amitiza® (lubiprostone) 24mcg cap	24mcg PO BID	$355.80
Movantik® (naloxegol) 25mg tab	12.5mg or 25mg PO QDay	$340.80
Relistor® (methylnaltrexone) 150mg tab	450mg PO QDay	$1,659.60
Relistor® (methylnaltrexone) 12mg/0.6mL inj[¥]	12mg sub-Q QDay	$3,327.12[α]
Symproic® (naldemedine) 0.2mg tab	0.2mg PO QDay	$344.70

cap = capsule; tab = tablet; inj = injection; PO = by mouth; BID = twice daily; QDay = once daily; sub-Q = subcutaneous; n/a = not available

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

[+]Medications included in the table 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.

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

[α]Cost/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 Aemcolo™ (rifamycin), Motegrity™ (prucalopride), Zelnorm™ (tegaserod), and Ibsrela® (tenapanor) with the following criteria:

Aemcolo™ (Rifamycin) Approval Criteria:

1. An FDA approved diagnosis of travelers' diarrhea; and
2. Member must be 18 years of age or older; and
3. Travelers' diarrhea must be due to non-invasive strains of *Escherichia coli*; and
4. A patient-specific, clinically significant reason why the member cannot use Xifaxan® (rifaximin) oral tablets must be provided; and
5. A quantity limit of 12 tablets per 3 days will apply.

Motegrity™ (Prucalopride) 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 3 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 3 trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
5. A patient-specific, clinically significant reason why member cannot use Linzess® (linaclotide), Amitiza® (lubiprostone), or Trulance® (plecanatide) must be provided; 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; and
7. A quantity limit of 30 tablets per 30 days will apply.

Zelnorm™ (Tegaserod) Approval Criteria:

1. An FDA approved diagnosis of irritable bowel syndrome with constipation (IBS-C) in female members 18 to 64 years of age; and
2. Member must be female for authorization of Zelnorm™ (the safety and effectiveness of Zelnorm™ in men with IBS-C have not been established); and
3. Member must not have any of the contraindications for use of Zelnorm™ [e.g., history of myocardial infarction (MI), stroke, transient ischemic attack (TIA), or angina; history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment (estimated glomerular filtration rate {eGFR} <15mL/min/1.73m^2) or end stage renal disease (ESRD); moderate or severe hepatic impairment (Child-Pugh B or C); history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; hypersensitivity to tegaserod); and
4. Documentation that constipation-causing therapies for other disease states have been discontinued (excluding opioid pain medications for cancer patients); 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 3 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 3 trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
7. A patient-specific, clinically significant reason why member cannot use Amitiza® (lubiprostone), Linzess® (linaclotide), or Trulance® (plecanatide) must be provided; and

8. Approval will initially be for 6 weeks of therapy. Further approval may be granted if prescriber documents member is responding well to treatment. Zelnorm™ should be discontinued in patients who have not had adequate control of symptoms after 4 to 6 weeks of treatment; and
9. A quantity limit of 60 tablets per 30 days will apply.

Ibsrela® (Tenapanor) Approval Criteria:

1. An FDA approved diagnosis of 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 3 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 3 trials must be polyethylene glycol 3350 (PEG-3350); and
    b. Members with an oncology-related diagnosis are exempt from the trial requirements; and
5. A patient-specific, clinically significant reason why member cannot use Amitiza® (lubiprostone), Linzess® (linaclotide), or Trulance® (plecanatide) must be provided; 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; and
7. A quantity limit of 60 tablets per 30 days will apply.

Additionally, the College of Pharmacy recommends updating the current approval criteria for Symproic® (naldemedine) based on net costs (changes noted in red):

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 3 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 3 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; and
8. Symproic® must be discontinued if treatment with the opioid pain medication is also discontinued; and
9. A quantity limit of 30 tablets per 30 days will apply.

Utilization Details of Constipation and Diarrhea Medications: Fiscal Year 2019

Constipation and Diarrhea Medications

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
LINACLOTIDE PRODUCTS						
LINZESS CAP 290MCG	240	43	$92,222.79	$384.26	5.6	25.93%
LINZESS CAP 145MCG	215	50	$83,433.12	$388.06	4.3	23.45%
LINZESS CAP 72MCG	56	18	$22,499.82	$401.78	3.1	6.33%
SUBTOTAL	**511**	**111**	**$198,155.73**	**$387.78**	**4.6**	**55.71%**
LUBIPROSTONE PRODUCTS						
AMITIZA CAP 24MCG	183	43	$65,638.16	$358.68	4.3	18.45%
AMITIZA CAP 8MCG	43	11	$16,223.39	$377.29	3.9	4.56%
SUBTOTAL	**226**	**54**	**$81,861.55**	**$362.22**	**4.2**	**23.01%**
NALOXEGOL PRODUCTS						
MOVANTIK TAB 25MG	78	19	$21,768.40	$279.08	4.1	6.12%
MOVANTIK TAB 12.5MG	5	3	$1,743.35	$348.67	1.7	0.49%
SUBTOTAL	**83**	**22**	**$23,511.75**	**$283.27**	**3.8**	**6.61%**
ELUXADOLINE PRODUCTS						
VIBERZI TAB 100MG	22	4	$25,474.90	$1,157.95	5.5	7.16%
VIBERZI TAB 75MG	12	2	$13,949.98	$1,162.50	6	3.92%
SUBTOTAL	**34**	**6**	**$39,424.88**	**$1,159.56**	**5.7**	**11.08%**
PLECANATIDE PRODUCTS						
TRULANCE TAB 3MG	12	6	$4,781.97	$398.50	2	1.34%
SUBTOTAL	**12**	**6**	**$4,781.97**	**$398.50**	**2**	**1.34%**
NALDEMEDINE PRODUCTS						
SYMPROIC TAB 0.2MG	10	4	$2,912.82	$291.28	2.5	0.82%
SUBTOTAL	**10**	**4**	**$2,912.82**	**$291.28**	**2.5**	**0.82%**
METHYLNALTREXONE PRODUCTS						
RELISTOR INJ 12MG/0.6ML	3	2	$3,495.08	$1,165.03	1.5	0.98%
RELISTOR TAB 150MG	1	1	$1,576.05	$1,576.05	1	0.44%
SUBTOTAL	**4**	**3**	**$5,071.13**	**$1,267.78**	**1.3**	**1.43%**
TOTAL	**880**	**188***	**$355,719.83**	**$404.23**	**4.7**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Please note, the above data does not include Xifaxan® (rifaximin).
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Xifaxan® (Rifaximin)

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
RIFAXIMIN PRODUCTS						
XIFAXAN TAB 550MG	999	223	$2,026,573.12	$2,028.60	4.5	98.96%
XIFAXAN TAB 200MG	23	2	$21,380.29	$929.58	11.5	1.04%
TOTAL	**1,022**	**224***	**$2,047,953.41**	**$2,003.87**	**4.6**	**100%**

*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.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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Appendix N

Fiscal Year 2019 Annual Review of Antidepressants and 30-Day Notice to Prior Authorize Drizalma Sprinkle™ [Duloxetine Delayed-Release (DR) Capsules], Spravato™ (Esketamine Nasal Spray), and Citalopram 20mg/10mL, Escitalopram 10mg/10mL, and Fluoxetine 20mg/5mL Unit Dose Cups

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
citalopram (Celexa®)			fluoxetine tabs
escitalopram (Lexapro®)			fluoxetine DR (Prozac® Weekly™)
fluoxetine caps (Prozac®)			fluvoxamine CR (Luvox CR®)
fluvoxamine (Luvox®)			paroxetine CR (Paxil CR®)
paroxetine (Paxil®)			paroxetine (Pexeva®)
sertraline (Zoloft®)			
Dual-Acting Antidepressants			
bupropion (Wellbutrin®, Wellbutrin SR®, XL®)	desvenlafaxine (Pristiq®)	desvenlafaxine (Khedezla®)	bupropion ER (Aplenzin®)
duloxetine (Cymbalta®)		levomilnacipran (Fetzima®)	bupropion ER (Forfivo XL®)
mirtazapine (Remeron®, Remeron® SolTab™)		nefazodone (Serzone®)	duloxetine 40mg (Irenka™)
trazodone 50mg, 100mg, & 150mg tabs (Desyrel®)		Vilazodone (Viibryd®)	trazodone 300mg tabs (Desyrel®)
venlafaxine (Effexor®, Effexor XR® capsules)			venlafaxine ER tabs (Effexor XR® tabs)
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.
PA = prior authorization; CR = controlled-release; DR = delayed-release; ER = extended-release; tabs = tablets; caps = capsules

Antidepressant Tier-2 Approval Criteria:

1. Member must have a documented, recent (within 6 months) trial of 2 Tier-1 medications at least 4 weeks in duration each and titrated to recommended dosing, that did not provide an adequate response. Tier-1 selection must include at least 1 medication from the SSRI category and 1 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 Tier-3 Approval Criteria:

1. Member must have a documented, recent (within 6 months) trial with 2 Tier-1 medications (1 medication from the SSRI category and 1 trial with duloxetine) and a trial of a Tier-2 medication at least 4 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 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; and
3. Tier structure rules still apply.
4. **Irenka™ (Duloxetine 40mg) Approval Criteria [Non-Depression Diagnosis]:**
    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 2 duloxetine 20mg capsules in place of Irenka™ 40mg capsules; and
    c. A quantity limit of 30 capsules per 30 days will apply; and
    d. Tier structure rules still 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 2 trazodone 150mg tablets or 3 trazodone 100mg tablets to achieve a 300mg dose.
7. **Fluoxetine Tablets Approval Criteria:**
    a. Fluoxetine capsules are available without a prior authorization. The tablet formulation will require prior authorization and reasoning why the tablet formulation is required in place of the capsule formulation.

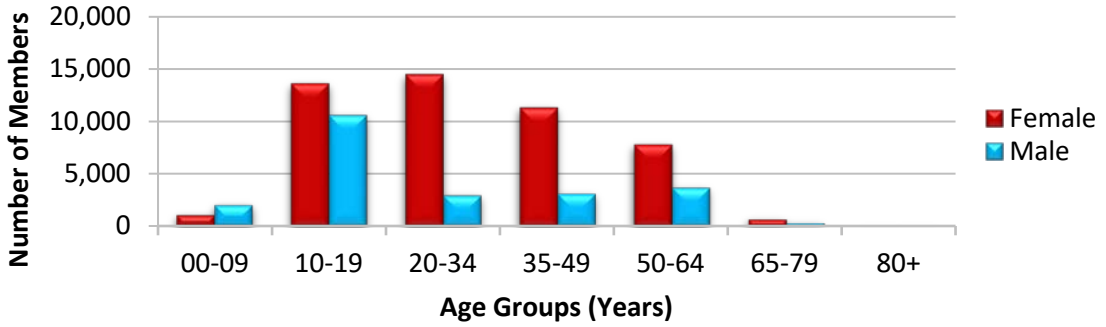
Utilization of Antidepressants: Fiscal Year 2019

Comparison of Fiscal Years

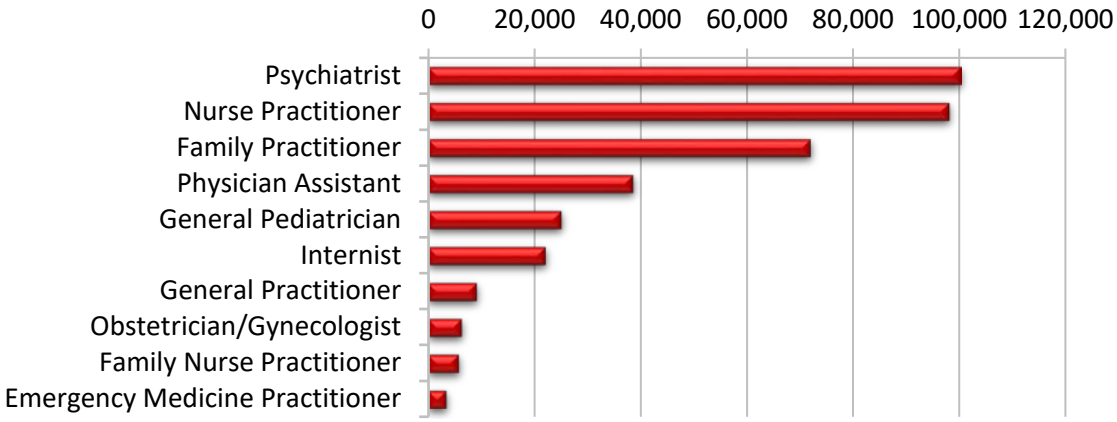
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	72,106	401,928	$6,544,477.48	$16.28	$0.48	15,810,203	13,660,934
2019	71,661	394,431	$6,171,599.87	$15.65	$0.45	15,867,909	13,692,475
% Change	**-0.60%**	**-1.90%**	**-5.70%**	**-3.90%**	**-6.20%**	**0.40%**	**0.20%**
Change	**-445**	**-7,497**	**-$372,877.61**	**-$0.63**	**-$0.03**	**57,706**	**31,541**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Demographics of Members Utilizing Antidepressants

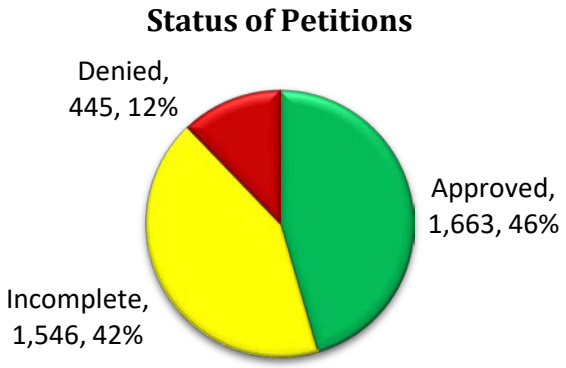


Top Prescriber Specialties of Antidepressants by Number of Claims



Prior Authorization of Antidepressants

There were 3,654 prior authorization requests submitted for antidepressants during fiscal year 2019. Computer edits are in place to detect lower tiered medications in the 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 2019.



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

Anticipated Patent Expiration(s):

- Pexeva® (paroxetine tablets): May 2025
- Aplenzin® [bupropion extended-release (ER) tablets]: June 2026
- Forfivo XL® (bupropion ER tablets): June 2027
- Trintellix® (vortioxetine tablets): June 2031
- Spravato™ (esketamine nasal spray): July 2031
- Fetzima® (levomilnacipran ER capsules): May 2032
- Drizalma Sprinkle™ (duloxetine DR capsules): April 2037

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

- **March 2019:** The FDA approved Spravato™ (esketamine), a Schedule III controlled substance (CIII) nasal spray, for use in conjunction with an oral antidepressant in adults with treatment-resistant depression (TRD).
- **March 2019:** The FDA approved Zulresso™ (brexanolone) injection for the treatment of postpartum depression (PPD). Brexanolone is an allosteric modulator of both synaptic and extrasynaptic gamma-aminobutyric acid A ($GABA_A$) receptors. The FDA approval of brexanolone is based on findings from 3 multicenter, randomized, double-blind, parallel-group, placebo-controlled trials designed to evaluate the safety and effectiveness of brexanolone in women with moderate and severe PPD between 18 and 45 years of age who were ≤6 months postpartum at screening and who had onset of symptoms no earlier than the third trimester and no later than the first 4 weeks following delivery. In all trials at all doses, brexanolone achieved the primary endpoint, a significant mean reduction from baseline in the Hamilton Rating Scale for Depression (HAM-D) total score at 60 hours compared to placebo. Brexanolone is administered as a continuous intravenous (IV) infusion lasting a total of 60 hours (2.5 days).

- **July 2019:** The FDA approved Drizalma Sprinkle™ (duloxetine DR capsules), a serotonin and norepinephrine reuptake inhibitor (SNRI) for the treatment of major depressive disorder (MDD) in adults, generalized anxiety disorder (GAD) in adults and pediatric patients 7 to 17 years of age, diabetic peripheral neuropathic pain in adults, and chronic musculoskeletal pain in adults. Drizalma Sprinkle™ is available in the following dosage strengths: 20mg, 30mg, 40mg, and 60mg. The recommended dosing range is from 30mg/day to 120mg/day depending on diagnosis. Drizalma Sprinkle™ may be swallowed whole or opened and the contents sprinkled over applesauce and swallowed immediately. Additionally, Drizalma Sprinkle™ may be opened and mixed with water for nasogastric (NG) tube administration. Further information on dosage and administration can be found in the Drizalma Sprinkle™ prescribing information. Drizalma Sprinkle™ carries a *Boxed Warning* for suicidal thoughts and behaviors. In October 2019, Sun Pharma launched Drizalma Sprinkle™ in the United States. The Wholesale Acquisition Cost (WAC) is $5.85 per capsule regardless of strength, resulting in a monthly cost of $175.50 for once daily dosing; dosing may vary based on diagnosis. For comparison, duloxetine 60mg DR capsules (generic Cymbalta®) has a National Average Drug Acquisition Cost (NADAC) of $0.16 per capsule, resulting in monthly cost of $4.80 at a dose of 60mg once daily.

News:

- **June 2019:** The Institute for Clinical and Economic Review (ICER) released a Final Evidence Report and Report-at-a-Glance assessing the comparative clinical effectiveness and value of esketamine nasal spray (Spravato™). Spravato™ was approved by the FDA in March 2019 as a therapy for TRD. ICER's report was reviewed at the May 2019 public meeting of the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC). During the meeting, the CEPAC found that the evidence demonstrated esketamine plus background antidepressant to be clinically superior to background antidepressant alone. The panel acknowledged that esketamine is intended to treat patients with a condition of high severity and a high lifetime burden of illness, and that esketamine offers a novel mechanism of action compared to other approved treatments for TRD, which may allow the successful treatment of many patients for whom other available treatments have failed. Nevertheless, a majority of the panel felt that there is uncertainty about the long-term benefits and risks of esketamine, citing the lack of long-term trial evidence. ICER's evaluation of long-term cost-effectiveness found that the fair value-based price benchmark for esketamine is between $17,700 and $25,200 per year, a range that would require a 25 to 52% discount from the announced list price of $32,400. Consistent with ICER's value-assessment framework, esketamine is deemed to deliver a "low value for money" because the treatment's incremental cost-effectiveness ratio, using the current list price, exceeds $175,000 per quality-adjusted life year (QALY) gained. Given that the clinical goal for uptake would exceed the potential budget impact threshold at the national level, ICER is issuing an Affordability and Access Alert as part of its final report on esketamine. At esketamine's current list price, only 16% of eligible Americans with TRD could receive the treatment before crossing ICER's potential budget threshold of $819 million per year. Even if esketamine's price was lowered to ICER's

value-based price benchmark range for long-term cost-effectiveness, only 20 to 30% of all eligible patients with TRD could be treated with esketamine before exceeding the potential budget impact threshold.

- **October 2019:** The FDA approved Teva's vilazodone hydrochloride tablets (10mg, 20mg, and 40mg) for treatment of MDD. This is the first generic FDA approved for Allergan's Viibryd®, which was originally approved by the FDA in 2011.

Pipeline:

- **Lumateperone:** Intra-Cellular Therapies announced top-line data from 2 Phase 3 clinical trials, Study 401 and Study 404, of lumateperone as a monotherapy to treat major depressive (MD) episodes in patients with bipolar I or bipolar II disorder. Lumateperone selectively and simultaneously regulates the serotonin, dopamine, and glutamate neurotransmitter pathways. In Study 401, a 28mg and 42mg dose was compared to placebo in a total of 554 patients. The investigational drug failed to meet the primary endpoint of statistical separation from placebo on the Montgomery-Asberg Depression Rating Scale (MADRS) total score. However, in Study 404, which included 381 patients, the drug's 42mg dose succeeded in meeting the primary endpoint by demonstrating statistically significant greater improvement at week 6 compared to placebo. Intra-Cellular Therapies chairman and Chief Executive Officer (CEO) Dr. Sharon Mates said: "The distinct pharmacological profile of lumateperone and positive clinical results in schizophrenia and bipolar depression further support the potential for benefits in a broad range of neuropsychiatric conditions, including major depressive disorder."
- **SAGE-217 (zuranolone):** Sage Therapeutics reported top-line results from the Phase 3 ROBIN Study of zuranolone, a $GABA_A$ receptor agonist being studied for the treatment of depressive symptoms in women with PPD. After 2 weeks of outpatient treatment, patients treated with zuranolone had a statistically significant improvement of 17.8 points in the HAM-D score, compared to 13.6 for placebo (primary endpoint, P=0.0029), with statistically significant reductions in HAM-D compared to placebo maintained through the end of the 4-week follow-up. Remission was achieved in 45% of patients treated with zuranolone for 2 weeks as measured by the HAM-D compared with 23% of patients receiving placebo (P=0.0122). Zuranolone is a next generation positive allosteric modulator that has been optimized for selectivity to synaptic and extrasynaptic $GABA_A$ receptors and a pharmacokinetic profile intended for daily oral dosing.

Spravato™ (Esketamine Nasal Spray) Product Summary[10,11,12]

Indication(s): Spravato™ (esketamine nasal spray) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of TRD in adults.

Dosing:

- Spravato™ is available as a nasal spray of esketamine hydrochloride in a stoppered glass vial within a nasal spray device. Each nasal spray device delivers 2 sprays, 1 for each nostril, containing a total of 28mg of esketamine.

- Spravato™ is supplied as a 56mg dose kit containing (2) 28mg nasal spray devices or an 84mg dose kit containing (3) 28mg nasal spray devices.
- Spravato™ is self-administered by the patient under the direct supervision of a health care provider. A treatment session consists of nasal administration of Spravato™ and post-administration observation.
- The patient must wait 5 minutes after delivery of medication from each device to allow the medication to absorb.
- It is recommended to assess the patient's blood pressure (BP) before and after administration.
- The recommended dosing for the induction phase is twice per week during weeks 1 to 4. The day 1 starting dose is 56mg with subsequent doses of 56mg or 84mg. Dosage adjustments should be made based on efficacy and tolerability.
- Evidence of therapeutic benefit should be evaluated at the end of the induction phase to determine need for continued treatment.
- The recommended dosing for the maintenance phase is once weekly dosed at 56mg or 84mg for weeks 5 to 8. For week 9 and after, the recommended dosing is 56mg or 84mg every 2 weeks or once weekly. Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Boxed Warning: Sedation, Dissociation, Abuse and Misuse, and Suicidal Thoughts and Behaviors

- Patients are at risk for sedation and dissociative or perceptual changes after administration of esketamine.
- Because of the risks of sedation and dissociation, it is recommended that patients be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the health care setting.
- Esketamine has the potential to be abused and misused. It is recommended to consider the risks and benefits of prescribing esketamine prior to use in patients at higher risk of abuse. Patients should be monitored for signs and symptoms of abuse and misuse.
- Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. All esketamine-treated patients should be closely monitored for clinical worsening and for emergence of suicidal thoughts and behaviors. Esketamine is not approved for use in pediatric patients.

Spravato™ REMS program

- Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, esketamine is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Spravato™ REMS program.

Contraindications:

- Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation

- History of intracerebral hemorrhage
- Hypersensitivity to esketamine, ketamine, or any of the excipients

Warnings and Precautions:

- Increase in BP: Esketamine causes increases in systolic and/or diastolic BP at all recommended doses. Increases in BP peak approximately 40 minutes after esketamine administration and last approximately 4 hours. A substantial increase in BP could occur after any dose administered even if smaller BP effects were observed with previous administrations. BP should be assessed prior to administration of esketamine. In patients whose BP is elevated prior to esketamine administration (>140/90mmHg) a decision to delay esketamine therapy should take into account the balance of benefit and risk in individual patients. BP should be monitored for at least 2 hours after esketamine administration. BP should be taken around 40 minutes post-dose and subsequently as clinically warranted until values decline. If BP remains high, the patient should receive prompt medical assistance. BP should be closely monitored in patients using esketamine with psychostimulants or monoamine oxidase inhibitors (MAOIs).
- Cognitive Impairment: In a study of healthy volunteers, esketamine-treated patients required greater effort to complete cognitive tests at 40 minutes post-dose compared to placebo-treated patients. Cognitive performance and mental effort were comparable between esketamine and placebo at 2 hours post-dose. Sleepiness was comparable between esketamine and placebo at 4 hours post-dose. Long-term cognitive and memory impairment have been reported with repeated ketamine misuse or abuse. No adverse effects of esketamine nasal spray on cognitive functioning were observed in a 1-year open-label safety study; however, the long-term cognitive effects of esketamine have not been evaluated beyond 1 year.
- Impaired Ability to Drive and Operate Machinery: Two placebo-controlled studies were conducted to assess the effects of esketamine on the ability to drive. The effects of esketamine 84mg were comparable to placebo at 6 hours and 18 hours post-dose; however, 2 esketamine-treated subjects in 1 of the studies discontinued the driving test at 8 hours post-dose because of esketamine-related adverse reactions. Before esketamine administration, patients should be instructed not to engage in potentially hazardous activities requiring complete mental alertness and motor coordination, such as driving a motor vehicle or operating machinery, until the next day following a restful sleep.
- Ulcerative or Interstitial Cystitis: Cases of ulcerative or interstitial cystitis have been reported in individuals with long-term, off-label use or misuse/abuse of ketamine. In clinical studies with esketamine nasal spray, there was a higher rate of lower urinary tract symptoms (pollakiuria, dysuria, micturition urgency, nocturia, and cystitis) in esketamine-treated patients than in placebo-treated patients. No cases of esketamine-related interstitial cystitis were observed in any of the studies, which included treatment for up to 1 year.

Adverse Reactions: The most commonly observed adverse reactions in TRD patients treated with esketamine plus an oral antidepressant (incidence ≥5% and at least twice that of placebo

nasal spray plus an oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased BP, vomiting, and feeling drunk.

Use in Specific Populations:

- Pregnancy: Esketamine is not recommended during pregnancy. There are insufficient data on esketamine use in pregnant women to draw conclusions about any drug associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Based on published findings from pregnant animals treated with ketamine, the racemic mixture of arketamine and esketamine, esketamine may cause fetal harm when administered to pregnant women. If a woman becomes pregnant while being treated with esketamine, treatment should be discontinued and the patient should be counseled about the potential risk to the fetus. Published studies in pregnant primates demonstrated that the administration of drugs that block NMDA receptors during the period of peak brain development increased neuronal apoptosis in the developing brain of the offspring.
- Lactation: Esketamine is present in human milk. There are no data on the effects of esketamine on the breastfed infant or on milk production. Published studies in juvenile animals report neurotoxicity. Because of the potential for neurotoxicity, breast-feeding is not recommended during treatment with esketamine.
- Females of Reproductive Potential: Based on published animal reproduction studies, esketamine may cause embryo-fetal harm when administered to a pregnant woman. Consider pregnancy planning and prevention for females of reproductive potential during treatment with esketamine.
- Pediatric Use: The safety and effectiveness of esketamine in pediatric patients have not been established.
- Geriatric Use: Of the total number of patients (N=1,601) in Phase 3 clinical studies exposed to esketamine, 194 (12%) were 65 years of age and older, and 25 (2%) were 75 years of age and older. No overall differences in the safety profile were observed between patients 65 years of age and older and patients younger than 65 years of age.
- Hepatic Impairment: The mean esketamine area under the curve (AUC) and terminal half-life ($t_{1/2}$) values were higher in patients with moderate hepatic impairment compared to those with normal hepatic function. Esketamine-treated patients with moderate hepatic impairment may need to be monitored for adverse reactions for a longer period of time than patients with normal hepatic function. Esketamine has not been studied in patients with severe hepatic impairment (Child-Pugh class C). Use in this population is not recommended.

Efficacy:

- Study 1: Esketamine was evaluated in a randomized, placebo-controlled, double-blind, multicenter, short-term (4-week), Phase 3 study in 223 adult patients 18 to <65 years of age with TRD. Patients met DSM-5 criteria for MDD and in the current depressive episode, had not responded adequately to at least 2 different antidepressants of adequate dose and duration. After discontinuing prior antidepressant treatments, patients were randomized to receive twice weekly doses of intranasal esketamine

(flexible dose of 56mg or 84mg) or intranasal placebo. All patients also received open-label concomitant treatment with a newly initiated daily oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine ER as determined by the investigator based on the patient's prior treatment history). Esketamine could be titrated up to 84mg starting with the second dose. The primary efficacy measure was change from baseline in the MADRS total score at the end of the 4-week double-blind induction phase. The MADRS is a 10-item, clinician rated scale used to assess severity of depressive symptoms. Scores on the MADRS range from 0 to 60, with higher scores indicating more severe depression. Esketamine plus a newly initiated oral antidepressant demonstrated statistical superiority [difference of least square means: −4.0; 95% confidence interval (CI): −7.31, −0.64; P=0.020] on the primary efficacy measure compared to placebo nasal spray plus a newly initiated oral antidepressant. In a post hoc analysis, 70 of 101 patients (69.3%) in the esketamine plus antidepressant arm and 52 of 100 patients (52.0%) in the antidepressant plus placebo arm were responders (≥50% reduction from baseline MADRS score) at day 28. The proportion of patients with ≥50% decrease in MADRS score by day 2 (24 hours after a single dose) who also maintained this magnitude of reduction to day 28 (the first key secondary endpoint) was higher for the esketamine plus antidepressant arm compared with the antidepressant plus placebo arm [9 of 114 patients (7.9%) compared with 5 of 109 patients (4.6%)], although the difference was not statistically significant (P=0.321).

- Study 2: Study 2 was a long-term, randomized, double-blind, parallel-group, multicenter maintenance-of-effect study in adults 18 to <65 years of age who were known remitters and responders to esketamine. Patients were previous responders in 1 of 2 short-term controlled trials (Study 1 and another 4-week study) or in an open-label direct-enrollment study in which they received flexibly-dosed esketamine (56mg or 84mg twice weekly) plus daily oral antidepressants in an initial 4-week phase. Stable remission was defined as a MADRS total score ≤12 for at least 3 of the last 4 weeks. Stable response was defined as a MADRS total score reduction ≥50% for the last 2 weeks of optimization and not in remission. After at least 16 initial weeks of treatment with esketamine and an oral antidepressant, stable remitters and stable responders were randomized separately to continue intranasal treatment with esketamine or switch to placebo nasal spray, in both cases with continuation of their oral antidepressant. The primary study endpoint was time to relapse in the stable remitter group. Relapse was defined as a MADRS total score ≥22 for 2 consecutive weeks or hospitalization for worsening depression or any other clinically relevant event indicative of relapse. Patients in stable remission who continued treatment with esketamine plus oral antidepressant experienced a statistically significantly longer time to relapse of depressive symptoms than did patients on placebo nasal spray plus an oral antidepressant (P=0.003). Time to relapse was also significantly delayed in the stable responder population (P<0.001).

Cost Comparison:

Medication	Cost Per Unit	Cost Per Dose	Cost Per Month*
Spravato™ (esketamine nasal spray) 56mg kit	**$295.00**	**$590.00**	**$2,360.00**
Spravato™ (esketamine nasal spray) 84mg kit	**$295.00**	**$885.00**	**$3,540.00**
duloxetine 60mg capsule	$0.16	$0.16	$4.80
escitalopram 20mg tablet	$0.07	$0.07	$2.10

Unit = nasal spray device, capsule, or tablet.
*Cost per month for duloxetine and escitalopram based on maximum FDA recommended maintenance dosing for major depressive disorder. Cost per month for Spravato™ based on once weekly dosing (4 doses).
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 Comparison

The use of liquid formulation antidepressants serve a purpose in special populations who have an FDA approved indication for these medications, but are unable to take solid oral dosage formulations. The selective serotonin reuptake inhibitors (SSRIs) currently available as liquid formulations supplied in bulk stock bottles include: citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Of these options citalopram, escitalopram, and fluoxetine also have liquid formulations available in unit dose cups. While this option may provide convenience, it comes at a considerably higher cost than those available in bulk stock bottles.

Cost Comparison:

Medication	Cost Per mL (Unit Dose)	Cost Per 30 days* (Unit Dose)	Cost Per mL (Bulk)	Cost Per 30 Days* (Bulk)
citalopram 20mg/10mL	**$1.12**	**$336.00**	$0.16	$48.00
escitalopram 10mg/10mL	**$0.72**	**$216.00**	$0.33	$99.00
fluoxetine 20mg/5mL	**$1.11**	**$166.50**	$0.49	$73.50

*Cost per 30 days based on FDA recommended dosing for major depressive disorder. Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendations

The College of Pharmacy recommends the placement of Drizalma Sprinkle™ [duloxetine delayed-release (DR) capsules] into the Special Prior Authorization (PA) Tier of the Antidepressants Product Based Prior Authorization (PBPA) category. Current Special PA criteria will apply. When Drizalma Sprinkle™ (duloxetine DR capsule) is being requested for non-depression/anxiety-related diagnoses, the criteria below will apply:

Drizalma Sprinkle™ (Duloxetine Delayed-Release Capsule) Approval Criteria [Diabetic Peripheral Neuropathic Pain/Chronic Musculoskeletal Pain Diagnosis]:

1. An FDA approved diagnosis of diabetic peripheral neuropathy or chronic musculoskeletal pain; and

2. A patient-specific, clinically significant reason why the member cannot use generic duloxetine 20mg, 30mg, or 60mg capsules, which are available without prior authorization, in place of Drizalma Sprinkle™ must be provided; and
3. A quantity limit of 30 capsules per 30 days will apply.

Additionally, the College of Pharmacy recommends the placement of Spravato™ (esketamine nasal spray) into the Special PA Tier of the Antidepressants PBPA category with the following criteria:

Spravato™ (Esketamine Nasal Spray) Approval Criteria:

1. An FDA approved indication of treatment-resistant depression in adults; and
2. Member must be 18 years of age or older; and
3. Spravato™ must be used in conjunction with an oral antidepressant; and
4. Member must have had an inadequate response to at least 2 different antidepressants from different classes at least 4 weeks in duration each and titrated to recommended dosing during the current depressive episode, unless contraindicated or clinically significant adverse effects; and
5. Prescriber must agree that member will be monitored by a health care provider for at least 2 hours after each administration; and
6. Prescriber must agree that member's blood pressure will be monitored prior to and after administration of Spravato™ in accordance with the prescribing information; and
7. Member must not have any contraindications to therapy [e.g., aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial, and peripheral arterial vessels) or arteriovenous malformation; intracerebral hemorrhage; hypersensitivity to esketamine, ketamine, or any of the excipients]; and
8. Member must not have severe hepatic impairment (Child Pugh C); and
9. Prescriber must verify that female members are not currently pregnant and will use effective contraception while receiving treatment with Spravato™; and
10. Prescriber must verify member is not breastfeeding; and
11. Pharmacy and health care setting must be certified in the Spravato™ Risk Evaluation and Mitigation Strategy (REMS) program; and
12. Member must be enrolled in the Spravato™ REMS program; and
13. Spravato™ must be administered under the direct observation of a health care provider in a REMS certified health care setting; and
14. Initial approvals will be for the duration of the induction phase. For continued authorization, prescriber must verify member demonstrated an adequate response during the induction phase and member is using Spravato™ in combination with an oral antidepressant; and
15. A quantity limit of 4 kits per 28 days will apply. A quantity limit override will be approved for induction of therapy upon meeting Spravato™ approval criteria.

Finally, the College of Pharmacy recommends the placement of citalopram 20mg/10mL, escitalopram 10mg/10mL, and fluoxetine 20mg/5mL unit dose cups into the Special PA Tier of the Antidepressants PBPA category based on Wholesale Acquisition Cost (WAC) with the following criteria:

Citalopram 20mg/10mL Solution, Escitalopram 10mg/10mL Solution, and Fluoxetine 20mg/5mL Solution Unit Dose Cups Approval Criteria:

1. An FDA approved indication; and
2. A patient-specific, clinically significant reason why the member cannot use the bulk medication must be provided.

Antidepressants*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Selective Serotonin Reuptake Inhibitors (SSRIs)			
citalopram (Celexa®)			**citalopram 20mg/10mL soln (unit dose cups)**
escitalopram (Lexapro®)			**escitalopram 10mg/10mL soln (unit dose cups)**
fluoxetine caps (Prozac®)			**fluoxetine 20mg/5mL soln (unit dose cups)**
fluvoxamine (Luvox®)			fluoxetine tabs
paroxetine (Paxil®)			fluoxetine DR (Prozac® Weekly™)
sertraline (Zoloft®)			fluvoxamine CR (Luvox CR®)
			paroxetine CR (Paxil CR®)
			paroxetine (Pexeva®)
Dual-Acting Antidepressants			
bupropion (Wellbutrin®, Wellbutrin SR®, Wellbutrin XL®)	desvenlafaxine (Pristiq®)	desvenlafaxine (Khedezla®)	bupropion ER (Aplenzin®)
Duloxetine (Cymbalta®)		levomilnacipran (Fetzima®)	bupropion ER (Forfivo XL®)
mirtazapine (Remeron®, Remeron® SolTab™)		nefazodone (Serzone®)	duloxetine 40mg (Irenka™)
trazodone 50mg, 100mg, & 150mg tabs (Desyrel®)		vilazodone (Viibryd®)	**duloxetine (Drizalma Sprinkle™)**
venlafaxine (Effexor®, Effexor XR® caps)			trazodone 300mg tabs (Desyrel®)
			venlafaxine ER tabs (Effexor XR® tabs)
Monoamine Oxidase Inhibitors (MAOIs)			
		phenelzine (Nardil®)	isocarboxazid (Marplan®)
		selegiline (Emsam®)	
		tranylcypromine (Parnate®)	
Unique Mechanisms of Action			
		vortioxetine (Trintellix®)	**esketamine nasal spray (Spravato™)**

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. PA = prior authorization; CR = controlled-release; DR = delayed-release; ER = extended-release; tabs = tablets; caps = capsules; soln = solution

Utilization Details of Antidepressants: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
TIER-1 MEDICATIONS					
SERTRALINE PRODUCTS					
SERTRALINE TAB 100MG	29,762	7,031	$352,039.10	$0.34	$11.83
SERTRALINE TAB 50MG	28,978	10,505	$340,052.87	$0.33	$11.73
SERTRALINE TAB 25MG	15,649	5,862	$185,475.45	$0.36	$11.85
SERTRALINE CON 20MG/ML	637	183	$43,916.81	$2.03	$68.94
SUBTOTAL	**75,026**	**23,581**	**$921,484.23**	**$0.36**	**$12.28**
FLUOXETINE PRODUCTS					
FLUOXETINE CAP 20MG	29,663	9,079	$301,632.24	$0.30	$10.17
FLUOXETINE CAP 10MG	16,265	5,564	$179,902.14	$0.34	$11.06
FLUOXETINE CAP 40MG	15,297	3,989	$185,843.46	$0.34	$12.15
FLUOXETINE SOL 20MG/5ML	1,592	374	$24,453.73	$0.52	$15.36
PROZAC CAP 20MG	22	3	$25,110.89	$36.93	$1,141.40
PROZAC CAP 40MG	17	2	$17,915.80	$35.13	$1,053.87
PROZAC CAP 10MG	1	1	$444.28	$14.81	$444.28
SUBTOTAL	**62,857**	**19,012**	**$735,302.54**	**$0.35**	**$11.70**
TRAZODONE PRODUCTS					
TRAZODONE TAB 50MG	28,101	8,413	$300,601.40	$0.33	$10.70
TRAZODONE TAB 100MG	21,566	5,723	$256,526.14	$0.36	$11.89
TRAZODONE TAB 150MG	12,429	3,072	$175,749.43	$0.42	$14.14
SUBTOTAL	**62,096**	**17,208**	**$732,876.97**	**$0.36**	**$11.80**
ESCITALOPRAM PRODUCTS					
ESCITALOPRAM TAB 20MG	18,190	4,427	$223,839.68	$0.34	$12.31
ESCITALOPRAM TAB 10MG	17,834	6,475	$209,652.33	$0.34	$11.76
ESCITALOPRAM TAB 5MG	3,025	1,269	$37,138.82	$0.36	$12.28
ESCITALOPRAM 5MG/5ML	222	54	$21,908.99	$3.55	$98.69
LEXAPRO TAB 20MG	25	4	$11,239.55	$11.18	$449.58
SUBTOTAL	**39,296**	**12,229**	**$503,779.37**	**$0.36**	**$12.82**
CITALOPRAM PRODUCTS					
CITALOPRAM TAB 20MG	15,578	5,291	$150,014.54	$0.26	$9.63
CITALOPRAM TAB 40MG	8,553	2,419	$81,115.98	$0.23	$9.48
CITALOPRAM TAB 10MG	7,499	2,674	$76,453.71	$0.30	$10.20
CITALOPRAM 10MG/5ML	272	58	$10,907.20	$1.35	$40.10
SUBTOTAL	**31,902**	**10,442**	**$318,491.43**	**$0.27**	**$9.98**
DULOXETINE PRODUCTS					
DULOXETINE CAP 60MG	17,673	4,370	$290,351.90	$0.44	$16.43
DULOXETINE CAP 30MG	10,527	3,956	$171,678.03	$0.47	$16.31
DULOXETINE CAP 20MG	1,929	796	$34,661.59	$0.56	$17.97
CYMBALTA CAP 60MG	9	1	$2,136.40	$7.91	$237.38
SUBTOTAL	**30,138**	**9,123**	**$498,827.92**	**$0.46**	**$16.55**
BUPROPION PRODUCTS					

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
BUPROPN TAB 150MG XL	9,230	3,401	$178,013.95	$0.53	$19.29
BUPROPN TAB 300MG XL	7,315	1,939	$154,724.10	$0.55	$21.15
BUPROPION TAB 150MG SR	6,565	2,269	$105,840.65	$0.51	$16.12
BUPROPION TAB 100MG SR	2,473	942	$39,993.71	$0.51	$16.17
BUPROPION TAB 75MG	1,704	606	$32,843.44	$0.62	$19.27
BUPROPION TAB 100MG	1,312	461	$28,857.01	$0.70	$21.99
BUPROPION TAB 200MG SR	1,212	326	$23,785.96	$0.61	$19.63
WELLBUTRIN TAB XL 150MG	26	2	$62,478.20	$83.75	$2,403.01
WELLBUTRIN TAB XL 300MG	4	1	$13,303.28	$55.43	$3,325.82
SUBTOTAL	**29,841**	**9,947**	**$639,840.30**	**$0.61**	**$21.44**
MIRTAZAPINE PRODUCTS					
MIRTAZAPINE TAB 15MG	11,301	3,343	$136,326.42	$0.37	$12.06
MIRTAZAPINE TAB 30MG	6,099	1,677	$78,716.92	$0.38	$12.91
MIRTAZAPINE TAB 45MG	2,704	611	$41,945.46	$0.43	$15.51
MIRTAZAPINE TAB 7.5MG	1,268	433	$55,975.71	$1.41	$44.14
MIRTAZAPINE 15MG ODT	253	84	$7,244.25	$0.88	$28.63
MIRTAZAPINE 30MG ODT	141	47	$4,561.45	$0.92	$32.35
MIRTAZAPINE 45MG ODT	117	34	$3,799.83	$1.05	$32.48
SUBTOTAL	**21,883**	**6,229**	**$328,570.04**	**$0.45**	**$15.01**
VENLAFAXINE PRODUCTS					
VENLAFAXINE CAP 150MG ER	8,221	1,973	$127,699.31	$0.41	$15.53
VENLAFAXINE CAP 75MG ER	6,673	2,410	$91,859.55	$0.37	$13.77
VENLAFAXINE CAP 37.5MG ER	2,977	1,464	$39,590.27	$0.41	$13.30
VENLAFAXINE TAB 75MG	1,775	503	$31,481.31	$0.53	$17.74
VENLAFAXINE TAB 37.5MG	520	263	$8,628.30	$0.52	$16.59
VENLAFAXINE TAB 100MG	438	103	$9,290.99	$0.66	$21.21
VENLAFAXINE TAB 50MG	212	70	$4,185.37	$0.60	$19.74
VENLAFAXINE TAB 25MG	154	69	$2,752.64	$0.60	$17.87
EFFEXOR XR CAP 75MG	14	2	$16,407.70	$39.07	$1,171.98
EFFEXOR XR CAP 150MG	9	2	$4,165.87	$15.43	$462.87
EFFEXOR XR CAP 37.5MG	1	1	$366.37	$12.21	$366.37
SUBTOTAL	**20,994**	**6,860**	**$336,427.68**	**$0.45**	**$16.02**
PAROXETINE PRODUCTS					
PAROXETINE TAB 20MG	4,832	1,910	$51,321.02	$0.28	$10.62
PAROXETINE TAB 40MG	3,398	920	$45,702.12	$0.33	$13.45
PAROXETINE TAB 10MG	2,265	955	$26,290.31	$0.32	$11.61
PAROXETINE TAB 30MG	1,500	445	$18,392.30	$0.33	$12.26
PAXIL SUS 10MG/5ML	88	18	$21,926.93	$8.66	$249.17
PAXIL TAB 40MG	1	1	$608.69	$6.76	$608.69
SUBTOTAL	**12,084**	**4,249**	**$164,241.37**	**$0.35**	**$13.59**
FLUVOXAMINE PRODUCTS					
FLUVOXAMINE TAB 100MG	1,587	259	$39,398.32	$0.82	$24.83
FLUVOXAMINE TAB 50MG	1,154	293	$22,584.61	$0.62	$19.57

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
FLUVOXAMINE TAB 25MG	366	118	$6,787.81	$0.59	$18.55
SUBTOTAL	**3,107**	**670**	**$68,770.74**	**$0.71**	**$22.13**
TIER-1 SUBTOTAL	**389,224**	**71,287***	**$5,248,612.59**	**$0.39**	**$13.48**
TIER-2 MEDICATIONS					
DESVENLAFAXINE PRODUCTS					
DESVENLAFAX 50MG ER	850	297	$31,996.99	$1.05	$37.64
DESVENLAFAX 100MG ER	592	155	$24,109.35	$1.05	$40.73
DESVENLAFAX 25MG ER	186	90	$6,930.89	$1.15	$37.26
PRISTIQ TAB 100MG	13	2	$5,609.02	$12.46	$431.46
PRISTIQ TAB 50MG	3	1	$1,127.58	$12.53	$375.86
SUBTOTAL	**1,644**	**545**	**$69,773.83**	**$1.16**	**$42.44**
TIER-2 SUBTOTAL	**1,644**	**430***	**$69,773.83**	**$1.16**	**$42.44**
TIER-3 MEDICATIONS					
VORTIOXETINE PRODUCTS					
TRINTELLIX TAB 20MG	503	109	$187,281.12	$12.43	$372.33
TRINTELLIX TAB 10MG	465	138	$200,295.10	$12.94	$430.74
TRINTELLIX TAB 5MG	76	27	$27,949.07	$12.41	$367.75
SUBTOTAL	**1,044**	**274**	**$415,525.29**	**$12.67**	**$398.01**
VILAZODONE PRODUCTS					
VIIBRYD TAB 40MG	632	104	$162,406.41	$8.51	$256.97
VIIBRYD TAB 20MG	234	57	$58,956.28	$8.43	$251.95
VIIBRYD TAB 10MG	43	17	$10,617.21	$8.71	$246.91
SUBTOTAL	**909**	**178**	**$231,979.90**	**$8.50**	**$255.20**
LEVOMILNACIPRAN PRODUCTS					
FETZIMA CAP 80MG	42	6	$15,555.97	$12.35	$370.38
FETZIMA CAP 40MG	32	8	$11,647.52	$12.13	$363.99
FETZIMA CAP 120MG	32	4	$11,764.05	$12.25	$367.63
FETZIMA CAP 20MG	3	1	$1,049.76	$11.66	$349.92
SUBTOTAL	**109**	**19**	**$40,017.30**	**$12.24**	**$367.13**
NEFAZODONE PRODUCTS					
NEFAZODONE TAB 100MG	32	7	$2,268.36	$2.36	$70.89
NEFAZODONE TAB 200MG	30	4	$2,362.19	$2.47	$78.74
NEFAZODONE TAB 150MG	7	2	$868.37	$4.34	$124.05
NEFAZODONE TAB 250MG	7	1	$1,017.29	$2.91	$145.33
NEFAZODONE TAB 50MG	2	2	$157.05	$2.62	$78.53
SUBTOTAL	**78**	**16**	**$6,673.26**	**$2.64**	**$85.55**
DESVENLAFAXINE PRODUCTS					
DESVENLAFAXINE 50MG ER	7	2	$1,051.26	$5.01	$150.18
DESVENLAFAXINE 100MG ER	1	1	$358.55	$3.98	$358.55
SUBTOTAL	**8**	**3**	**$1,409.81**	**$4.70**	**$176.23**
SELEGILINE PRODUCTS					
EMSAM DIS 6MG/24HR	2	2	$2,950.72	$49.18	$1,475.36
EMSAM DIS 9MG/24HR	1	1	$1,461.42	$48.71	$1,461.42

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
EMSAM DIS 12MG/24H	1	1	$1,464.28	$48.81	$1,464.28
SUBTOTAL	**4**	**4**	**$5,876.42**	**$48.97**	**$1,469.11**
TRANYLCYPROMINE PRODUCTS					
TRANYLCYPROMINE 10MG	1	1	$83.23	$2.77	$83.23
SUBTOTAL	**1**	**1**	**$83.23**	**$2.77**	**$83.23**
PHENELZINE PRODUCTS					
PHENELZINE TAB 15MG	1	1	$52.31	$1.74	$52.31
SUBTOTAL	**1**	**1**	**$52.31**	**$1.74**	**$52.31**
TIER-3 SUBTOTAL	**2,154**	**398***	**$701,617.52**	**$10.57**	**$325.73**
SPECIAL PRIOR AUTHORIZATION (PA) MEDICATIONS					
FLUOXETINE PRODUCTS					
FLUOXETINE TAB 10MG	578	179	$13,364.25	$0.75	$23.12
FLUOXETINE TAB 20MG	144	31	$5,739.67	$1.34	$39.86
FLUOXETINE CAP 90MG DR	31	3	$4,511.42	$5.11	$145.53
FLUOXETINE TAB 60MG	11	3	$3,035.85	$9.64	$275.99
SUBTOTAL	**764**	**216**	**$26,651.19**	**$1.14**	**$34.88**
PAROXETINE PRODUCTS					
PAROXETINE TAB 37.5MG ER	147	19	$12,007.42	$2.75	$81.68
PAROXETINE TAB 25MG ER	140	18	$12,357.93	$2.92	$88.27
PAROXETIN TAB 12.5MG ER	43	8	$2,838.95	$2.23	$66.02
PEXEVA TAB 20MG	3	1	$1,126.92	$12.52	$375.64
SUBTOTAL	**333**	**46**	**$28,331.22**	**$2.85**	**$85.08**
VENLAFAXINE PRODUCTS					
VENLAFAXINE TAB 225MG ER	174	26	$56,663.41	$10.91	$325.65
VENLAFAXINE TAB 150MG ER	18	3	$1,795.00	$3.32	$99.72
VENLAFAXINE TAB 37.5MG ER	7	2	$717.35	$3.42	$102.48
VENLAFAXINE TAB 75MG ER	6	5	$1,164.55	$6.47	$194.09
SUBTOTAL	**205**	**36**	**$60,340.31**	**$9.85**	**$294.34**
FLUVOXAMINE PRODUCTS					
FLUVOXAMINE 150MG ER	74	10	$25,374.70	$11.97	$342.90
FLUVOXAMINE 100MG ER	31	6	$10,760.96	$11.52	$347.13
SUBTOTAL	**105**	**16**	**$36,135.66**	**$11.83**	**$344.15**
TRAZODONE PRODUCTS					
TRAZODONE TAB 300MG	1	1	$85.88	$2.86	$85.88
SUBTOTAL	**1**	**1**	**$85.88**	**$2.86**	**$85.88**
DULOXETINE PRODUCTS					
DULOXETINE CAP 40MG	1	1	$51.67	$7.38	$51.67
SUBTOTAL	**1**	**1**	**$51.67**	**$7.38**	**$51.67**
SPECIAL PA SUBTOTAL	**1,409**	**306***	**$151,595.93**	**$3.57**	**$107.59**
TOTAL	**394,431**	**71,661***	**$6,171,599.87**	**$0.45**	**$15.65**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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Appendix O

Fiscal Year 2019 Annual Review of Anticoagulants and Platelet Aggregation Inhibitors and 30-Day Notice to Prior Authorize Bevyxxa® (Betrixaban) and to Update the Current Xarelto® (Rivaroxaban) Prior Authorization Criteria

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

Aggrenox® (Aspirin/Dipyridamole Extended-Release) Approval Criteria:

1. An FDA approved indication for the prophylaxis of recurrent thromboembolic stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis; and
2. Member must be 18 years of age or older; and
3. A patient-specific, clinically significant reason why the member cannot use immediate-release dipyridamole and over-the-counter (OTC) aspirin in place of Aggrenox® must be provided; and
4. A quantity limit of 60 capsules per 30 days will apply.

Brilinta® (Ticagrelor) Approval Criteria:

1. The first 365 days of therapy with Brilinta® 90mg twice daily does not require prior authorization; and
2. After the first 365 days, a patient-specific, clinically significant reason for continuing the 90mg twice daily dosage must be provided, or the member should be switched to the 60mg twice daily dosage; and
3. Approvals will be for the duration of 1 year.

Zontivity® (Vorapaxar) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. History of myocardial infarction (MI); or
    b. Peripheral arterial disease (PAD); and
2. Zontivity® must be used in combination with aspirin and/or clopidogrel (not monotherapy); and
3. Zontivity® will not be approved for members with the following conditions:
    a. History of transient ischemic attack (TIA); or
    b. Stroke; or
    c. Intracranial hemorrhage (ICH); or
    d. Active pathological bleeding; and
4. A quantity limit of 30 tablets per 30 days will apply.

Eliquis® (Apixaban) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:

a. Non-valvular atrial fibrillation; or
b. Treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) or for the reduction in the risk of recurrent DVT and PE following initial therapy; or
c. PE or DVT prophylaxis in patients who have undergone hip or knee replacement surgery.

Pradaxa® (Dabigatran) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Non-valvular atrial fibrillation; or
    b. Treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) after treatment with a parenteral anticoagulant for 5 to 10 days; or
    c. To reduce the risk of recurrent DVT or PE in patients who have been previously treated; or
    d. For the prophylaxis of DVT and PE in patients who have undergone hip replacement surgery.

Savaysa® (Edoxaban) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. To reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular atrial fibrillation; or
    b. For the treatment of deep vein thrombosis (DVT) or pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant; and
2. For the treatment of DVT or PE the prescriber must verify that the member has undergone 5 to 10 days of initial therapy with a parenteral anticoagulant; and
3. For the diagnosis of non-valvular atrial fibrillation, the member must not have a creatinine clearance (CrCl) >95mL/min due to an increased risk of ischemic stroke compared to warfarin at the highest dose studied (60mg); and
4. A quantity limit of 30 tablets per 30 days will apply.

Xarelto® (Rivaroxaban) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Non-valvular atrial fibrillation; or
    b. Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), or to reduce the risk of recurrent DVT and PE; or
    c. Prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery; or
    d. In combination with aspirin, to reduce the risk of major cardiovascular (CV) events [CV death, myocardial infarction (MI), and stroke] in members with chronic coronary artery disease (CAD) or peripheral artery disease (PAD); and
2. For Xarelto® (rivaroxaban) 15mg and 20mg:
    a. A diagnosis of non-valvular atrial fibrillation, DVT, PE, or prophylaxis of recurrent DVT or PE will be required; or
3. For Xarelto® (rivaroxaban) 10mg:

a. One prescription for up to 35 days of therapy is allowed without prior authorization every 6 months to allow for DVT prophylaxis use in patients following hip or knee replacement surgery; or

4. For Xarelto® (rivaroxaban) 2.5mg:
   a. Must be used in combination with aspirin 75 to 100mg to reduce the risk of major CV events in members with chronic CAD or PAD.

Utilization of Anticoagulants and Platelet Aggregation Inhibitors: Fiscal Year 2019

Comparison of Fiscal Years: Anticoagulants

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	2,372	13,117	$2,764,369.23	$210.75	$6.42	571,180	430,522
2019	2,497	13,875	$3,627,020.25	$261.41	$8.16	636,264	444,734
% Change	**5.30%**	**5.80%**	**31.20%**	**24.00%**	**27.10%**	**11.40%**	**3.30%**
Change	**125**	**758**	**$862,651.02**	**$50.66**	**$1.74**	**65,084**	**14,212**

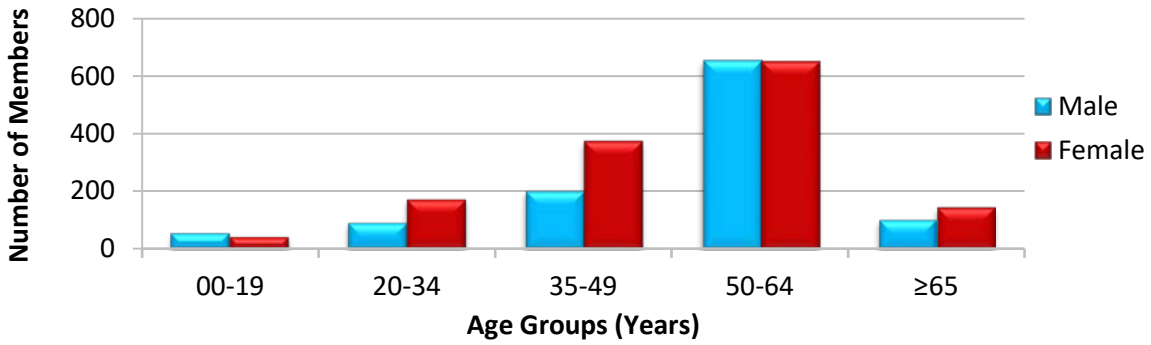
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Comparison of Fiscal Years: Platelet Aggregation Inhibitors

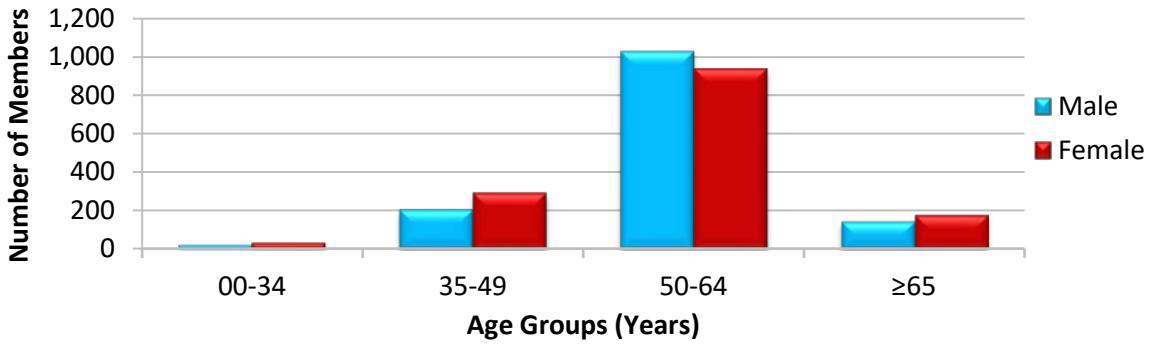
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	2,900	12,336	$652,377.35	$52.88	$1.18	586,048	553,146
2019	2,854	11,847	$654,218.54	$55.22	$1.18	597,575	554,060
% Change	**-1.60%**	**-4.00%**	**0.30%**	**4.40%**	**0.00%**	**2.00%**	**0.20%**
Change	**-46**	**-489**	**$1,841.19**	**$2.34**	**$0.00**	**11,527**	**914**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

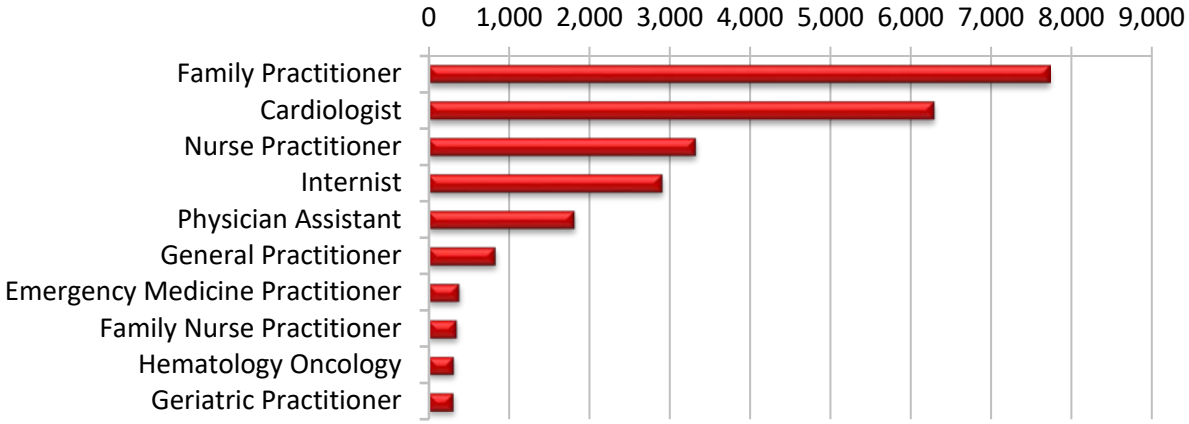
Demographics of Members Utilizing Anticoagulants



Demographics of Members Utilizing Platelet Aggregation Inhibitors



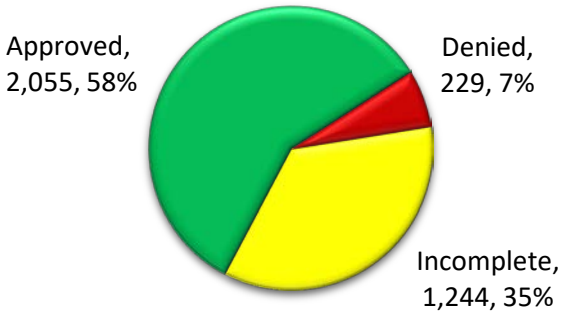
Top Prescriber Specialties of Anticoagulants and Platelet Aggregation Inhibitors by Number of Claims



Prior Authorization of Anticoagulants and Platelet Aggregation Inhibitors

There were 3,528 prior authorization requests submitted for anticoagulants and platelet aggregation inhibitors during fiscal year 2019. The following chart shows the status of the submitted petitions for fiscal year 2019.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Zontivity® (vorapaxar): May 2024

- Xarelto® (rivaroxaban): November 2024
- Savaysa® (edoxaban): March 2028
- Pradaxa® (dabigatran): January 2031
- Eliquis® (apixaban): February 2031
- Bevyxxa® (betrixaban): March 2031
- Brilinta® (ticagrelor): January 2036

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

- **June 2017:** The FDA approved Bevyxxa® (betrixaban) for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.
- **May 2019:** The FDA approved an age expansion for Fragmin® (dalteparin sodium injection) to reduce the recurrence of symptomatic VTE in pediatric patients 1 month of age and older, making it the first FDA-approved therapy to treat VTE in pediatric patients. The approval was based on evidence from 2 prospective, single-arm, multi-center clinical trials in 52 pediatric patients with or without cancer who had symptomatic DVT and/or PE. Patients were treated with dalteparin sodium subcutaneously (sub-Q) twice daily for up to 3 months, with starting doses determined by age and weight. The efficacy was based on the achievement of therapeutic anti-Xa levels (0.5 to 1.0 IU/mL) and supported by the number of patients with lack of VTE progression or recurrent VTE. A total of 48 patients (92%) achieved a therapeutic anti-Xa level. Upon study completion, no patients experienced progression of the qualifying VTE and 1 patient (2%) had recurrence of VTE.
- **October 2019:** The FDA approved the eighth indication to date for Xarelto® (rivaroxaban) for the prevention of VTE in hospitalized, acutely ill medical patients at risk for thromboembolic complications who are not at high-risk of bleeding. Rivaroxaban can now be initiated for these patients during hospitalization and continued after discharge for a total recommended duration of 31 to 39 days. The approval was based on evidence from the Phase 3 EXPLORER clinical program including the MAGELLAN and MARINER studies, which evaluated more than 20,000 patients with acute medical illness. MAGELLAN, published in 2013, evaluated the use of rivaroxaban in preventing VTE in hospitalized patients with acute medical illness and restricted mobility, starting with their hospital stay and continuing through post-hospital discharge. The study met its 2 co-primary efficacy endpoints, with rivaroxaban demonstrating non-inferiority to enoxaparin, a low-molecular weight heparin (LMWH), in short-term use (10±4 days) and superiority in long-term use (35±4 days) compared to short-term use of enoxaparin followed by placebo. The combined rates of major and non-major clinically relevant bleeding were higher in the rivaroxaban group. A post-hoc analysis from MAGELLAN found that, by applying 5 additional exclusionary criteria to remove patients at high-risk for bleeding due to active gastroduodenal ulcer, recent bleeding, active cancer, history of severe bronchiectasis or pulmonary cavitation, or dual antiplatelet therapy (DAPT) at baseline, researchers established a favorable benefit-risk profile for VTE prevention with rivaroxaban. Published in 2018, the Phase 3 MARINER trial was conducted in a similar

population of acutely ill patients and evaluated rivaroxaban for the prevention of VTE and VTE-related death following hospital discharge compared to placebo. While rivaroxaban did not reduce the composite endpoint of VTE and VTE-related death, it did significantly reduce symptomatic VTE with consistent and favorable safety, reinforcing the positive benefit-risk profile of rivaroxaban.

News:

- **October 2019:** The Institute for Clinical and Economic Review (ICER) published the final evidence report and meeting summary assessing the comparative clinical effectiveness and value of Vascepa® (icosapent ethyl) and Xarelto® (rivaroxaban) as additive therapies for cardiovascular disease (CVD). The Midwest Comparative Effectiveness Public Advisory Council (CEPAC) deliberated on key questions raised by ICER's report at a public meeting on September 26, 2019. A majority of panelists did find adequate evidence to demonstrate that the net health benefit of rivaroxaban plus aspirin is superior to that provided by aspirin alone. The panel did not find adequate evidence to demonstrate that the net health benefit of rivaroxaban plus aspirin is superior to that provided by DAPT with an oral P2Y12 inhibitor (e.g., clopidogrel, ticagrelor). In accordance with ICER's Value Assessment Framework, both therapies were deemed to be high long-term value for money by default (without a vote from the panel) based on their cost-effectiveness ranges. Policy recommendations point out there is a lack of clinical trial evidence in comparing rivaroxaban to DAPT plus aspirin due to limited head-to-head-trials and differing outcome measures. The report recommends that payers should not consider DAPT an appropriate candidate in a step therapy protocol as a first step prior to receiving coverage for rivaroxaban; clinical experts do not view these 2 treatment options as interchangeable, given their different mechanisms of action and risk profiles.

Guideline Update(s):

- **November 2018:** The American Society of Hematology published 2018 guidelines regarding optimal medication therapy for the management of VTE online in November 2018. These guidelines assume the choice of anticoagulant has already been made. A panel agreed on 25 recommendations and 2 good practice statements to optimize management of patients receiving anticoagulants. Strong recommendations included using patient self-management of international normalized ratio (INR) with home point-of-care INR monitoring for vitamin K antagonist therapy and against using periprocedural LMWH bridging therapy. Conditional recommendations included basing treatment dosing of LMWH on actual body weight, not using anti-factor Xa monitoring to guide LMWH dosing, using specialized anticoagulation management services, and resuming anticoagulation after episodes of life-threatening bleeding.
- **July 2019:** The 2019 American Heart Association (AHA)/American College of Cardiology (ACC)/Heart Rhythm Society (HRS) Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the ACC/AHA Task Force on Clinical Practice Guidelines and the HRS was published in the *Journal of the American College of Cardiology* in July 2019. A few key updates include:

- The addition of Savaysa® (edoxaban) to the list of non-vitamin K oral anticoagulants (NOACs) that can be used for stroke prevention
- NOACs are recommended over warfarin except in patients with moderate-to-severe mitral stenosis or a mechanical heart valve
- The decision to use an anticoagulant should not be influenced by whether the atrial fibrillation etiology is paroxysmal or persistent
- Renal and hepatic function should be tested before initiation of a NOAC and at least annually thereafter
- In atrial fibrillation patients with a CHA_2DS_2-VASc score ≥2 in men or ≥3 in women and a creatinine clearance (CrCl) <15 mL/min or who are on dialysis, it is reasonable to use warfarin or Eliquis® (apixaban) for oral anticoagulation
- In at-risk atrial fibrillation patients who have undergone coronary artery stenting, double therapy with clopidogrel and low-dose rivaroxaban (15mg daily) or dabigatran (150mg twice daily) is reasonable to reduce the risk of bleeding as compared to triple therapy
- Weight loss combined with risk factor modification is recommended for overweight and obese patients with atrial fibrillation

Bevyxxa® (Betrixaban Capsule) Product Summary[11,12]

Indication(s): Bevyxxa® (betrixaban) is a factor Xa (FXa) inhibitor indicated for the prophylaxis of VTE in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE.

- Limitations of Use: The safety and efficacy of betrixaban have not been established in patients with prosthetic heart valves because this population has not been studied.

Boxed Warning: Spinal/Epidural Hematoma

- Epidural or spinal hematomas may occur in patients treated with betrixaban who are receiving neuraxial anesthesia or undergoing spinal puncture.
- The risk of these events may be increased by the use of in-dwelling epidural catheters or the concomitant use of medical products affecting hemostasis.
- These hematomas may result in long-term or permanent paralysis.
- Risks should be considered when scheduling patients for spinal procedures.

Dosing:

- Bevyxxa® (betrixaban) is available as an oral capsule in 2 strengths: 40mg and 80mg.
- The recommended dose of betrixaban is an initial single dose of 160mg, followed by 80mg once daily, taken at the same time each day with food.
- The recommended duration of treatment is 35 to 42 days.
- For patients with severe renal impairment (CrCl ≥15 to <30 mL/min computed by Cockcroft-Gault using actual body weight), the recommended dose of betrixaban is an initial dose of 80mg followed by 40mg once daily on subsequent days.

- Use of betrixaban in patients with moderate-to-severe hepatic impairment should be avoided.
- If a dose of betrixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. The betrixaban dose should not be doubled to make up for a missed dose.

Mechanism of Action: Betrixaban is an oral factor Xa (FXa) inhibitor that selectively blocks the active site of FXa and does not require a cofactor (such as antithrombin III) for activity. Betrixaban inhibits free FXa and prothrombinase activity. By directly inhibiting FXa, betrixaban decreases thrombin generation. Betrixaban has no direct effect on platelet aggregation.

Contraindication(s):
- Active pathological bleeding
- Severe hypersensitivity reaction(s)n to betrixaban

Warnings and Precautions:
- Risk of Bleeding: Betrixaban can cause serious, potentially fatal bleeding. Signs and symptoms of blood loss should be promptly evaluated.
- Severe Renal Impairment: The dose of betrixaban should be reduced in patients with severe renal impairment due to an increased risk of bleeding events.
- Concomitant P-glycoprotein (P-gp) Inhibitors: The betrixaban dose should be reduced in patients taking concomitant P-gp inhibitors (e.g., amiodarone, azithromycin, verapamil, ketoconazole, clarithromycin) due to an increased risk of bleeding events.

Drug Interactions:
- P-gp inhibitors increase the blood levels of betrixaban, and the betrixaban dose should be reduced when used concomitantly.
- P-gp inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's wort) maybe decrease blood levels of betrixaban and should be avoided.
- Concomitant use of anticoagulants and betrixaban should be avoided.

Adverse Reactions: The most common adverse reaction (incidence >5%) experienced during clinical studies of betrixaban was bleeding.

Clinical Trials: The safety and efficacy of betrixaban were based on data from the randomized, double-blind APEX study of 7,513 patients hospitalized for an acute medical illness with VTE risk factors. Patients were randomized to treatment with betrixaban for 35 to 42 days or to treatment with enoxaparin for 6 to 14 days for VTE prophylaxis.
- The efficacy was measured in 7,441 patients by a composite of either the occurrence of asymptomatic or symptomatic proximal DVT, non-fatal PE, or VTE-related death.
- The composite outcome occurred in fewer patients receiving betrixaban (4.4%) versus those taking enoxaparin (6%) [relative risk (RR) 0.75; 95% confidence interval (CI): 0.61, 0.91].
- Fewer symptomatic events, defined as symptomatic DVT, non-fatal PE, or VTE-related death, were observed with betrixaban versus enoxaparin (0.9% vs. 1.5%, respectively; RR 0.64; 95% CI: 0.42, 0.98).

Wholesale Acquisition Cost (WAC): The WAC of Bevyxxa® is $15.00 per capsule, regardless of strength, which results in a treatment cost of $645.00, based on 160mg oral loading dose on day 1 followed by 80mg once daily for up to 42 days of treatment.

Recommendations

The College of Pharmacy recommends the prior authorization of Bevyxxa® (betrixaban) with the following criteria:

Bevyxxa® (Betrixaban) Approval Criteria:

1. An FDA approved indication for the prophylaxis of venous thromboembolism (VTE) in adult patients hospitalized for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE; and
2. If the member started on the medication in the hospital, number of days of treatment with betrixaban in the hospital must be provided; and
3. Approvals will be for a maximum duration of 42 days (including use accounted for while in hospital); and
4. A quantity limit of 43 capsules per 42 days will apply.

Additionally, the College of Pharmacy recommends updating the updating Xarelto® (rivaroxaban) prior authorization criteria with the following changes noted in red:

Xarelto® (Rivaroxaban) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Non-valvular atrial fibrillation; or
    b. Treatment of deep vein thrombosis (DVT), pulmonary embolism (PE), or to reduce the risk of recurrent DVT and PE; or
    c. Prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery; or
    d. In combination with aspirin, to reduce the risk of major cardiovascular events [cardiovascular (CV) death, myocardial infarction (MI), and stroke] in members with chronic coronary artery disease (CAD) or peripheral artery disease (PAD); or
    e. Prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding; and
2. For Xarelto® (rivaroxaban) 15mg and 20mg:
    a. A diagnosis of non-valvular atrial fibrillation, DVT, PE, or prophylaxis of recurrent DVT or PE will be required; or
3. For Xarelto® (rivaroxaban) 10mg:
    a. One prescription for up to ~~35~~ 39 days of therapy is allowed without prior authorization every 6 months to allow for DVT prophylaxis in patients following hip or knee replacement surgery or for prophylaxis of VTE in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding; or
4. For Xarelto® (rivaroxaban) 2.5mg:

a. Must be used in combination with aspirin 75 to 100mg to reduce the risk of major CV events in members with chronic CAD or PAD.

Utilization Details of Anticoagulants: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
WARFARIN PRODUCTS						
WARFARIN TAB 5MG	1,700	450	$19,557.89	$0.29	$11.50	0.54%
WARFARIN TAB 1MG	607	154	$8,207.17	$0.42	$13.52	0.23%
WARFARIN TAB 4MG	558	148	$6,891.37	$0.35	$12.35	0.19%
WARFARIN TAB 3MG	440	127	$5,489.42	$0.36	$12.48	0.15%
WARFARIN TAB 2MG	430	119	$5,337.52	$0.37	$12.41	0.15%
WARFARIN TAB 6MG	324	91	$4,521.68	$0.35	$13.96	0.12%
WARFARIN TAB 7.5MG	298	105	$3,659.35	$0.26	$12.28	0.10%
WARFARIN TAB 2.5MG	262	85	$3,263.34	$0.36	$12.46	0.09%
WARFARIN TAB 10MG	250	92	$3,144.23	$0.27	$12.58	0.09%
JANTOVEN TAB 5MG	24	8	$356.49	$0.33	$14.85	0.01%
JANTOVEN TAB 4MG	15	2	$155.37	$0.32	$10.36	0.00%
JANTOVEN TAB 1MG	13	3	$201.46	$0.52	$15.50	0.01%
JANTOVEN TAB 2MG	13	3	$201.69	$0.37	$15.51	0.01%
COUMADIN TAB 1MG	12	1	$2,919.12	$8.25	$243.26	0.08%
COUMADIN TAB 5MG	11	4	$1,428.47	$3.53	$129.86	0.04%
JANTOVEN TAB 3MG	10	2	$134.68	$0.45	$13.47	0.00%
JANTOVEN TAB 2.5MG	8	2	$125.73	$0.35	$15.72	0.00%
COUMADIN TAB 6MG	4	2	$890.43	$2.97	$222.61	0.02%
COUMADIN 2.5MG	1	1	$75.29	$2.51	$75.29	0.00%
SUBTOTAL	**4,980**	**1,399**	**$66,560.70**	**$0.35**	**$0.35**	**1.83%**
DABIGATRAN PRODUCTS						
PRADAXA CAP 150MG	170	24	$68,050.98	$13.03	$400.30	1.88%
PRADAXA CAP 75MG	13	3	$5,290.01	$12.60	$406.92	0.15%
PRADAXA CAP 110MG	7	1	$2,869.75	$13.67	$409.96	0.08%
SUBTOTAL	**190**	**28**	**$76,210.74**	**$13.02**	**$401.11**	**2.11%**
RIVAROXABAN PRODUCTS						
XARELTO TAB 20MG	2,551	440	$1,050,478.60	$14.01	$411.79	28.96%
XARELTO TAB 15MG	313	70	$125,437.59	$15.20	$400.76	3.46%
XARELTO TAB 10MG	312	137	$114,358.57	$13.98	$366.53	3.15%
XARELTO TAB 2.5MG	27	15	$10,982.31	$13.56	$406.75	0.30%
XARELTO START PAK	11	11	$7,862.58	$23.83	$714.78	0.22%
SUBTOTAL	**3,214**	**673**	**$1,309,119.65**	**$14.14**	**$407.32**	**36.09%**
APIXABAN PRODUCTS						
ELIQUIS TAB 5MG	4,845	988	$1,933,791.37	$13.83	$399.13	53.32%
ELIQUIS TAB 2.5MG	625	137	$233,371.44	$13.81	$373.39	6.43%
ELIQUIS ST P TAB 5MG	4	3	$2,132.70	$17.77	$533.18	0.06%
SUBTOTAL	**5,474**	**1,128**	**$2,169,295.51**	**$13.83**	**$396.29**	**59.81%**

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
EDOXABAN PRODUCTS						
SAVAYSA TAB 60MG	16	2	$5,472.52	$11.40	$342.03	0.15%
SAVAYSA TAB 30MG	1	1	$361.13	$12.04	$361.13	0.01%
SUBTOTAL	**17**	**3**	**$5,833.65**	**$11.44**	**$343.16**	**0.16%**
TOTAL	**13,875**	**2,497***	**$3,627,020.25**	**$8.16**	**$261.41**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Utilization Details of Platelet Aggregation Inhibitors: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
CLOPIDOGREL PRODUCTS						
CLOPIDOGREL 75MG	9,627	2,492	$111,400.60	$0.23	$11.57	17.03%
CLOPIDOGREL 300MG	1	1	$33.44	$33.44	$33.44	0.01%
SUBTOTAL	**9,628**	**2,493**	**$111,434.04**	**$0.23**	**$11.57**	**17.04%**
PRASUGREL PRODUCTS						
PRASUGREL TAB 10MG	648	108	$15,400.68	$0.79	$23.77	2.35%
PRASUGREL TAB 5MG	27	4	$722.11	$0.89	$26.74	0.11%
SUBTOTAL	**675**	**112**	**$16,122.79**	**$0.79**	**$23.89**	**2.46%**
TICAGRELOR PRODUCTS						
BRILINTA TAB 90MG	1,357	302	$462,361.85	$11.75	$340.72	70.67%
BRILINTA TAB 60MG	151	23	$53,703.50	$11.93	$355.65	8.21%
SUBTOTAL	**1,508**	**325**	**$516,065.35**	**$11.77**	**$342.22**	**78.88%**
VORAPAXAR PRODUCTS						
ZONTIVITY TAB 2.08MG	24	4	$7,483.64	$10.42	$311.82	1.14%
SUBTOTAL	**24**	**4**	**$7,483.64**	**$10.42**	**$311.82**	**1.14%**
ASPIRIN-DIPYRIDAMOLE PRODUCTS						
ASA/DIPYRIDA CAP 25-200MG	12	1	$3,112.72	$8.65	$259.39	0.48%
SUBTOTAL	**12**	**1**	**$3,112.72**	**$8.65**	**$259.39**	**0.48%**
TOTAL	**11,847**	**2,854***	**$654,218.54**	**$1.18**	**$55.22**	**100%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

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Appendix P

Fiscal Year 2019 Annual Review of Antiviral Medications and 30-Day Notice to Prior Authorize Avaclyr™ (Acyclovir 3% Ophthalmic Ointment)

Oklahoma Health Care Authority
November 2019

Current Prior Authorization Criteria

Sitavig® (Acyclovir Buccal Tablets), Xerese® (Acyclovir/Hydrocortisone Cream), and Denavir® (Penciclovir Cream) Approval Criteria:

1. An FDA approved diagnosis of recurrent herpes labialis (cold sores); and
2. A patient-specific, clinically significant reason why the member cannot use oral acyclovir, famciclovir, or valacyclovir tablets must be provided; and
3. A patient-specific, clinically significant reason why the member cannot use acyclovir cream must be provided.

Zovirax® (Acyclovir Ointment) Approval Criteria:

1. An FDA approved indication of management of initial genital herpes or in limited non-life-threatening mucocutaneous Herpes simplex virus (HSV) infections in immunocompromised patients; and
2. A patient-specific, clinically significant reason why the member cannot use oral acyclovir, famciclovir, or valacyclovir tablets must be provided.

Zovirax® (Acyclovir Suspension) Approval Criteria:

1. An age restriction of 7 years or younger will apply. Members older than 7 years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.

Generic Acyclovir (Zovirax®) 5% Cream Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use the brand formulation, which is available without prior authorization, must be provided.

RibaPak® (Ribavirin Dose Pack), Rebetol® (Ribavirin Solution), and Ribasphere® (Ribavirin 400mg and 600mg Tablets) Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use the 200mg tablets or 200mg capsules in place of the unique dosage formulations must be provided.

Prevymis™ (Letermovir Tablets and Injection) Approval Criteria:

1. An FDA approved indication of prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogenic hematopoietic stem cell transplant (HSCT); and
2. Member must be CMV R+; and
3. Member must have received a HSCT within the last 28 days; and

4. Members taking concomitant cyclosporine will only be approved for the 240mg dose; and
5. Member must not be taking the following medications:
    a. Pimozide; or
    b. Ergot alkaloids (e.g., ergotamine, dihydroergotamine); or
    c. Rifampin; or
    d. Atorvastatin, lovastatin, pitavastatin, simvastatin, or repaglinide when co-administered with cyclosporine; and
6. Prevymis™ must be prescribed by an oncology, hematology, infectious disease, or transplant specialist (or advanced care practitioner with a supervising physician who is an oncology, hematology, infectious disease, or transplant specialist); and
7. Prescriber must verify the member will be monitored for CMV reactivation while on therapy; and
8. Approvals will be for the duration of 100 days post-transplant:
    a. For Prevymis™ vials, authorization will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation; and
    b. Approval length for vial formulation will be based on duration of need; and
9. A quantity limit of 1 tablet or 1 vial per day will apply.

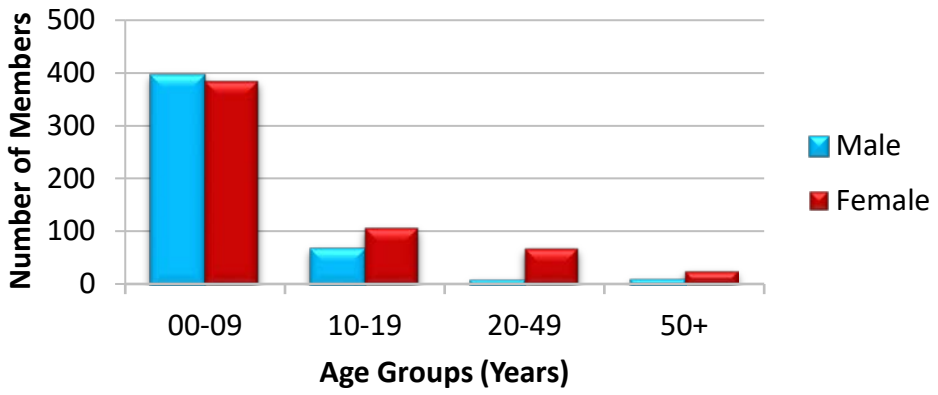
Utilization of Antiviral Medications: Fiscal Year 2019

Comparison of Fiscal Years

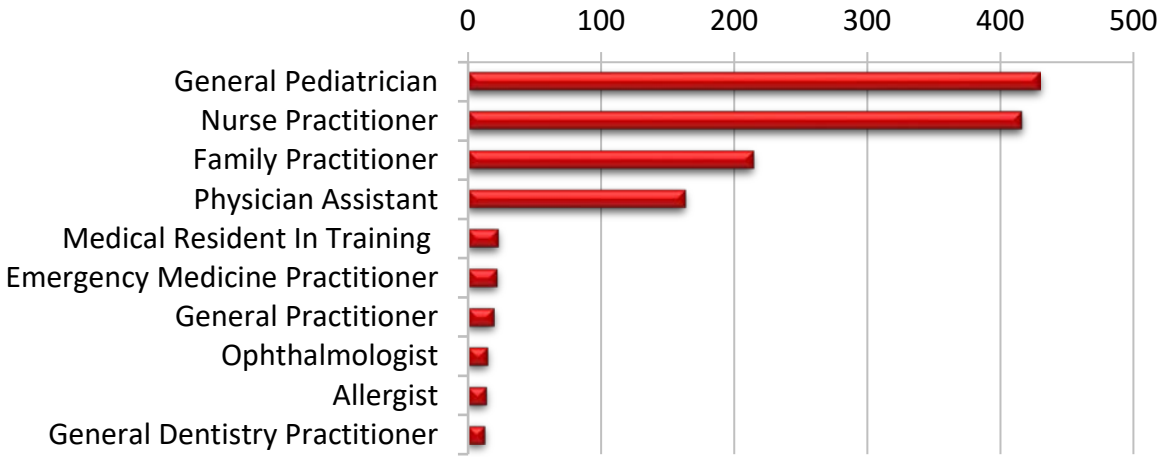
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2018	1,426	1,824	$481,857.99	$264.18	$19.27	228,464	25,005
2019	1,052	1,405	$453,406.74	$322.71	$19.91	161,435	22,777
% Change	**-26.2%**	**-23.0%**	**-5.9%**	**22.2%**	**3.3%**	**-29.3%**	**-8.9%**
Change	**-374**	**-419**	**-$28,451.25**	**$58.53**	**$0.64**	**-67,029**	**-2,228**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2018 = 07/01/2017 to 06/30/2018; Fiscal Year 2019 = 07/01/2018 to 06/30/2019

Demographics of Members Utilizing Antiviral Medications



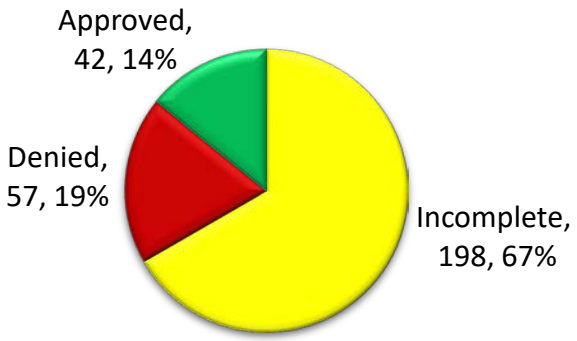
Top Prescriber Specialties of Antiviral Medications by Number of Claims



Prior Authorization of Antiviral Medications

There were 297 prior authorization requests submitted for antiviral medications during fiscal year 2019. The following chart shows the status of the submitted petitions for fiscal year 2019.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Denavir® (penciclovir 1% cream): June 2020
- Xerese® (acyclovir 5%/hydrocortisone 1% cream): November 2022
- Avaclyr™ (acyclovir 3% ophthalmic ointment): March 2026
- Sitavig® (acyclovir buccal tablets): June 2030

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

- **July 2018:** In July 2018, the FDA approved Tpoxx® (tecovirimat), the first drug with an indication for the treatment of smallpox. The effectiveness of tecovirimat against smallpox was established by studies conducted in animals infected with viruses that are closely related to the virus that causes smallpox and was based on measuring survival at the end of the studies. Four pivotal studies in nonhuman primates and 2 pivotal studies in rabbits were conducted. More animals treated with tecovirimat lived compared to

the animals treated with placebo. In aggregate, 1 of 20 nonhuman primates that received placebo survived infection with monkeypox virus, and no rabbits that received placebo survived rabbitpox virus infection. On the basis of the results of the first 2 studies in nonhuman primates, the minimum effective dose was determined to be 3 to 10mg/kg, which provided nearly full protection from death (i.e., a survival rate of approximately 95%, as compared with 5% in the placebo group) and reduced viral loads and lesion counts. The safety of tecovirimat was evaluated in 359 healthy human volunteers without a smallpox infection. The most frequently reported side effects were headache, nausea, and abdominal pain. Tecovirimat was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans. The FDA Antimicrobial Drugs Advisory Committee voted unanimously (17 to 0) that the benefits of tecovirimat outweigh its risks.

- **April 2019:** In April 2019, the FDA approved Fera Pharmaceuticals' New Drug Application (NDA) for Avaclyr™ (acyclovir 3% ophthalmic ointment) for the treatment of herpetic keratitis. The FDA also granted Orphan Drug exclusivity for Avaclyr™, which provides marketing exclusivity to the product for the next 7 years.

News:

- **February 2019:** Acyclovir's drug label now includes information for health care providers on recommended usage and dosage in newborns up to 3 months of age infected with herpes simplex virus (HSV). The data that informed this label change came from 2 studies led by DCRI primary investigators: "An Open-Label Study to Describe the Pharmacokinetics of Acyclovir in Premature Infants" and "Efficacy of Antiviral Suppression Therapy after Neonatal HSV Infection of the Central Nervous System". The first study, which determined the appropriate dosage of acyclovir for infants, was conducted at a single medical center in preterm and term infants with suspected HSV infection. The second study, which validated the safety and efficacy of the dosage, involved multiple medical centers and enrolled only preterm infants with suspected HSV infection.
- **July 2019:** SIGA Technologies, Inc. announced that it has been awarded a multi-year contract from the United States Department of Defense (DoD) to support work necessary to gain a potential label expansion for Tpoxx® (tecovirimat) that would include Post-Exposure Prophylaxis (PEP) of smallpox. The administration of a vaccine in combination with tecovirimat could provide significant potential benefit in reducing morbidity and mortality in a smallpox outbreak given that the symptoms of smallpox do not appear until approximately 14 days post-infection, while vaccines are only effective if administered prior to infection or no later than 4 days after infection.

Pipeline:

- **HSV529:** HSV529, a vaccine for herpes simplex virus 2 (HSV2), was shown to be safe and elicited antibody and T-cell responses in HSV seronegative (HSV-) adults. The Phase 1 trial included 60 adults 18 to 40 years of age divided into 3 serogroups that received the vaccine or a placebo at 0, 1, and 6 months. A total of 78% of HSV- vaccine recipients saw

antibody titer increases by 4 times or more after 3 doses of the vaccine, whereas none of the participants in the other serogroups had such responses.

Guideline Update(s):

- **January 2019:** The Centers for Disease Control and Prevention (CDC) updated its guideline for smallpox to include Tpoxx® (tecovirimat) as a treatment for smallpox.

Avaclyr™ (Acyclovir 3% Ophthalmic Ointment) Product Summary[9,10,11,12]

Indication(s): Avaclyr™ (acyclovir 3% ophthalmic ointment), an HSV nucleoside analog DNA polymerase inhibitor, is indicated for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with HSV1 and HSV2.

- Current HSV Epithelial Keratitis Treatment: There are 2 FDA approved ophthalmic antiviral agents with similar efficacy (ganciclovir and trifluridine). There are 3 oral antiviral agents (acyclovir, valacyclovir, and famciclovir) available in the United States. Oral antiviral agents appear to be as effective as topical antiviral agents (ganciclovir, trifluridine) in the treatment of HSV epithelial keratitis. In spite of their similar efficacy, there are differences and possible advantages to choosing 1 over the other in individual cases. There is no evidence that simultaneous use of 2 antiviral agents, whether topical or oral, accelerates healing of HSV epithelial keratitis.

Dosing:

- Avaclyr™ is supplied in a 3.5 gram tube containing 3% acyclovir topical sterile ointment.
- Patients should be instructed to apply a 1cm ribbon of ointment in the lower cul-de-sac of the affected eye 5 times per day until healed then 3 times per day for 7 days.

Mechanism of Action: Acyclovir is converted to acyclovir monophosphate by virus-specific thymidine kinase then further converted to acyclovir triphosphate by other cellular enzymes. Acyclovir triphosphate inhibits DNA synthesis and viral replication by competing with deoxyguanosine triphosphate for viral DNA polymerase and being incorporated into viral DNA.

Contraindication(s): Known hypersensitivity to acyclovir or valacyclovi

Adverse Reactions(s): The most common adverse reactions (2 to 10%) reported in patients during clinical studies of Avaclyr™ were eye pain (stinging), punctate keratitis, and follicular conjunctivitis.

Use in Specific Populations:

- Pregnancy: A prospective epidemiologic registry of acyclovir use from 1984 to 1999 indicated that the occurrence rate of birth defects in women exposed to systemically administered acyclovir during the first trimester of pregnancy (period of organogenesis) approximated what is found in the general population. Oral and subcutaneous (sub-Q) administration of acyclovir to pregnant mice, rats, and rabbits during organogenesis did not produce teratogenicity at clinically relevant doses.
- Lactation: Acyclovir concentrations have been documented in breast milk following oral administration of acyclovir. There is no information regarding the presence of acyclovir

in human milk following ocular administration, the effects on the breastfed infant, or the effects on milk production.

- Pediatric Use: The safety and efficacy of Avaclyr™ in pediatric patients younger than 2 years of age has not been established.
- Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients utilizing Avaclyr™.

Efficacy: Avaclyr™ was evaluated in 5 randomized, double-masked studies which enrolled a total of 238 subjects with dendritic herpetic keratitis. In all 5 studies, Avaclyr™ was either superior or as effective as idoxuridine ophthalmic ointment 0.5% or 1% in patients with dendritic ulcers. Clinical resolution (healed ulcers) at day 7 averaged 83% for acyclovir and 50% for idoxuridine.

Cost Comparison: There are several different formulations available for acyclovir and products for the treatment of acute herpetic keratitis (dendritic ulcers) in patients with HSV. The cost of Avaclyr™ is not yet available.

Medication	Cost Per Unit[+]	Cost Per Treatment
Avaclyr™ (acyclovir 3% ophthalmic ointment)	**NA**	**NA**
trifluridine 1% ophthalmic solution	$22.70	$170.25
acyclovir 400mg oral tablet	$0.08	$2.80

[+]Unit = milliliter (mL) or tablet; NA = not available
Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendations

The College of Pharmacy recommends the prior authorization of Avaclyr™ (acyclovir 3% ophthalmic ointment) with the following criteria:

Avaclyr™ (Acyclovir 3% Ophthalmic Ointment) Approval Criteria:

1. An FDA approved diagnosis of acute herpetic keratitis (dendritic ulcers) in patients with herpes simplex virus (HSV); and
2. A patient-specific, clinically significant reason why the member cannot use trifluridine 1% ophthalmic solution must be provided; and
3. A patient-specific, clinically significant reason why the member cannot use oral acyclovir, famciclovir, or valacyclovir must be provided.

Utilization Details of Antiviral Medications: Fiscal Year 2019

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
ACYCLOVIR PRODUCTS						
ACYCLOVIR SUS 200MG/5ML	955	729	$86,085.42	1.31	$9.23	$90.14
ZOVIRAX CRE 5%	360	263	$271,498.18	1.37	$25.09	$754.16
ACYCLOVIR CRE 5%	81	75	$62,385.08	1.08	$25.78	$770.19
ZOVIRAX SUS 200MG/5ML	2	2	$290.93	1.00	$24.24	$145.47

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
ACYCLOVIR OIN 5%	1	1	$70.55	1.00	$2.35	$70.55
SUBTOTAL	**1,399**	**1,051**	**$420,330.16**	**1.33**	**$18.59**	**$300.45**
LETERMOVIR PRODUCTS						
PREVYMIS TAB 480MG	6	1	$33,076.58	6.00	$196.88	$5,512.7
SUBTOTAL	**6**	**1**	**$33,076.58**	**6.00**	**$196.88**	**$5,512.7**
TOTAL	**1,405**	**1,052***	**$453,406.74**	**1.34**	**$19.91**	**$322.71**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2019 = 07/01/2018 to 06/30/2019

[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 10/2019. Last accessed 10/17/2019.

[2] U.S. Food and Drug Administration (FDA). FDA approves the first drug with an indication for treatment of smallpox. Available online at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-indication-treatment-smallpox. Last revised 07/13/2018. Last accessed 10/17/2019.

[3] Grosenbach DW, Honeychurch K, Rose EA, et al. Oral Tecovirimat for the Treatment of Smallpox. *N Engl J Med* 2018; 379(1):44-53. doi: 10.1056/NEJMoa1705688.

[4] Fera Pharmaceuticals. Fera Pharmaceuticals Announces FDA Approval of Avaclyr™ (acyclovir ophthalmic ointment). *BioSpace*. Available online at: https://www.biospace.com/article/releases/fera-pharmaceuticals-announces-fda-approval-of-avaclyr-acyclovir-ophthalmic-ointment-/. Issued 04/01/2019. Last accessed 10/17/2019.

[5] National Institutes of Health (NIH). Acyclovir labeling now includes details for treating premature infants infected with herpes virus. Available online at: https://www.nih.gov/news-events/news-releases/acyclovir-labeling-now-includes-details-treating-premature-infants-infected-herpes-virus. Issued 07/08/2019. Last accessed 10/17/2019.

[6] SIGA Technologies, Inc. SIGA Awarded Department of Defense Contract to Develop Expanded Indication for TPOXX® as Post-Exposure Prophylactic for Smallpox. *Globe Newswire*. Available online at: https://www.globenewswire.com/news-release/2019/07/08/1879366/0/en/SIGA-Awarded-Department-of-Defense-Contract-to-Develop-Expanded-Indication-for-TPOXX-as-Post-Exposure-Prophylactic-for-Smallpox.html. Issued 07/08/2019. Last accessed 10/17/2019.

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[8] Centers for Disease Control and Prevention (CDC): Smallpox Treatment. Available online at: https://www.cdc.gov/smallpox/clinicians/treatment.html. Last revised 02/15/2019. Last accessed 10/21/2019.

[9] Herpes Simplex Virus Keratitis: A Treatment Guideline - 2014. American Academy of Ophthalmology. https://www.aao.org/clinical-statement/herpes-simplex-virus-keratitis-treatment-guideline. Issued 07/27/2014. Last accessed 10/17/2019.

[10] FDA. Drugs@FDA: FDA Approved Drug Products. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/0202408s000lbl.pdf. Last accessed 10/17/2019.

[11] A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex virus epithelial keratitis. The Epithelial Keratitis Trial. The Herpetic Eye Disease Study Group. *Arch Ophthalmol* 1997; 115(9):1196.

[12] Collum LM, McGettrick P, Akhtar J, et al. Oral acyclovir (Zovirax) in herpes simplex dendritic corneal ulceration. *Br J Ophthalmol* 1986; 70(6):435.

Appendix Q

Industry News and Updates

Oklahoma Health Care Authority
November 2019

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]

News:

- **Vaccination:** According to a new *Vital Signs* report released in October 2019 by the Centers for Disease Control and Prevention (CDC), 65% of pregnant women have not received the influenza and pertussis vaccines. When pregnant women are vaccinated, they pass on antibodies to the fetus, which provides protection after birth, when babies are too young to be vaccinated. Newborns are at high risk of hospitalization and death if they get influenza or whooping cough. In addition, pregnant women have more than double the risk of hospitalization compared to nonpregnant women of childbearing age if they get influenza. The CDC recommends that all pregnant women should get an influenza vaccine during any trimester of each pregnancy and the tetanus, diphtheria, and pertussis (Tdap) vaccine during the early part of the third trimester of each pregnancy as part of routine prenatal care.
- **Real-World Data:** Dr. Janet Woodcock, director of the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research, stated that changes in the way data are being collected are on track to revolutionize the use of real-world data in drug approvals. She stated that the FDA has already approved numerous supplements and many drugs based on real-world evidence. She said that the widespread use of electronic health records has greatly improved the availability of health data. Another big factor, according to Woodcock, "is the digital revolution in general – people have wearables, a lot of people have iPhones, we have telehealth that's developing. All these things are coming together to provide rich data sources that we can turn into evidence. Our task is to take all the data out there and turn it into something that's actionable." One problem she noted with trying to make data more actionable is that "everyone resists standardization. Doctors, especially, want to do things their own way." In addition, the privacy tradeoffs involved in collecting data are also important to think about, pointed out former FDA Commissioner Dr. Robert Califf.

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[1] Centers for Disease Control and Prevention (CDC) Newsroom. Low Rates of Vaccination During Pregnancy Leave Moms, Babies Unprotected. Available online at: https://www.cdc.gov/media/releases/2019/p1008-vaccination-moms-babies-unprotected.html. Issued 10/08/2019. Last accessed 10/09/2019.

[2] Frieden J. Real-World Data Playing a Bigger Role in Drug Development. *MedPage Today*. Available online at: https://www.medpagetoday.com/publichealthpolicy/fdageneral/82711. Issued 10/11/2019. Last accessed 10/15/2019.

Appendix R

U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates (additional information can be found at http://www.fda.gov/Drugs/default.htm)

FDA NEWS RELEASE

For Immediate Release: October 3rd, 2019

FDA approves second drug to prevent HIV infection as part of ongoing efforts to end the HIV epidemic

The FDA approved Descovy® (emtricitabine 200mg/tenofovir alafenamide 25mg) in at-risk adults and adolescents weighing at least 35kg for HIV-1 pre-exposure prophylaxis (PrEP) to reduce the risk of HIV-1 infection from sex, excluding those who have receptive vaginal sex. Descovy® is not indicated in individuals at risk of HIV-1 infection from receptive vaginal sex because the effectiveness in this population has not been evaluated.

According to the Centers for Disease Control and Prevention (CDC), 38,739 people received an HIV diagnosis in the United States in 2017. To confront this epidemic, President Trump announced an initiative, Ending the HIV Epidemic: A Plan for America, in his State of the Union address on February 5, 2019. This opportunity to eliminate new HIV infections in our nation seeks to provide our hardest-hit communities with additional expertise, technology and resources required to address the HIV epidemic. The aim is to reduce new infections by 75% in the next 5 years and by 90% in the next 10 years, averting more than 250,000 HIV infections in that span.

PrEP, or pre-exposure prophylaxis, is an HIV prevention method in which people who do not have HIV take medicine on a daily basis to reduce their risk of getting HIV if they are exposed to the virus. Descovy® for PrEP should be used as part of a comprehensive strategy, including adherence to daily administration and safer sex practices, including condoms, to reduce the risk of sexually acquired infections.

The safety and efficacy of Descovy® for PrEP were evaluated in a randomized, double-blind, multinational trial in 5,387 HIV-negative men and transgender women who have sex with men and were at risk of HIV-1 infection. The trial compared once daily Descovy® to Truvada® (emtricitabine/tenofovir disoproxil fumarate 200mg/300mg), a daily fixed dose combination of 2 drugs approved in 2012 to prevent the sexual acquisition of HIV; participants were followed for 48 to 96 weeks. The primary endpoint was the rate of HIV-1 infection in each group. The trial showed that Descovy® was similar to Truvada® in reducing the risk of acquiring HIV-1 infection. The most common adverse reaction in individuals without HIV who were taking Descovy® for PrEP was diarrhea.

There is a boxed warning for individuals who take Descovy® who also have hepatitis B virus (HBV) to be aware of the risk of exacerbations of HBV in those who discontinue products with emtricitabine or tenofovir disproxil fumarate, and which may occur in individuals who discontinue Descovy®. Descovy® for HIV-1 PrEP is contraindicated in individuals with unknown or positive HIV-1 status and should only be prescribed to individuals confirmed to be HIV-negative immediately prior to initiating and at least every 3 months during use.

Descovy® was FDA approved in 2016 in combination with other antiretroviral drugs to treat HIV-1 infection in adults and pediatric patients. The FDA granted the approval of Descovy® to Gilead Sciences, Inc.

FDA NEWS RELEASE

For Immediate Release: October 8th, 2019

FDA approves first treatment to increase pain-free light exposure in patients with a rare disorder

The FDA granted approval to Scenesse® (afamelanotide) to increase pain-free light exposure in adult patients with a history of phototoxic reactions (damage to skin) from erythropoietic protoporphyria.

For patients who are suffering from erythropoietic protoporphyria, a rare disorder, exposure to light may be extremely painful. Erythropoietic protoporphyria is a rare disorder caused by mutations leading to impaired activity of ferrochelatase, an enzyme involved in heme production. Heme is an important component in hemoglobin, the oxygen carrying molecule in red blood cells. The decrease in ferrochelatase activity leads to an accumulation of protoporphyrin IX (PPIX) in the body. Light reaching the skin can react with PPIX causing intense skin pain and skin changes, such as redness and thickening. Scenesse® (afamelanotide), a melanocortin-1 receptor (MC1-R) agonist, increases the production of eumelanin in the skin independent of

exposure to sunlight or artificial light sources. It is an implant that is administered subcutaneously (inserted under the skin).
The efficacy of Scenesse was established in 2 parallel group clinical trials with patients with erythropoietic protoporphyria who received Scenesse® or placebo form of the implant subcutaneously every 2 months. The first clinical trial enrolled 93 subjects, of whom 48 received Scenesse®, and were followed for 180 days. The primary endpoint was the total number of hours over 180 days spent in direct sunlight between 10 a.m. and 6 p.m. on days with no pain. The median total number of hours over 180 days spent in direct sunlight between 10 a.m. and 6 p.m. on days with no pain was 64 hours for patients receiving Scenesse® and 41 hours for patients taking placebo.
The second clinical trial enrolled 74 patients, of whom 38 received Scenesse®, and were followed for 270 days. The primary endpoint was the total number of hours over 270 days spent outdoors between 10 a.m. and 3 p.m. on days with no pain for which “most of the day” was spent in direct sunlight. The analysis did not include sun exposure on days patients reported spending time in a combination of both direct sunlight and shade. The median total number of hours over 270 days spent outdoors between 10 a.m. and 3 p.m. on days with no pain for which “most of the day” was spent in direct sunlight was 6 hours for patients receiving Scenesse® and 0.75 hours for patients receiving placebo.
Scenesse®’s most common side effects are implant site reaction, nausea, oropharyngeal (part of the throat just behind the mouth, where the oral cavity starts) pain, cough, fatigue, skin hyperpigmentation, dizziness, melanocytic nevus (moles), respiratory tract infection, somnolence, non-acute porphyria (build-up of normally occurring molecules created during heme production), and skin irritation. Scenesse® should be administered by a health care professional who is proficient in the subcutaneous implantation procedure and has completed the applicant-provided training. Scenesse® may induce skin darkening, and a full body skin examination is recommended for patients twice a year. In addition, patients are encouraged to maintain sun protection measures during treatment with Scenesse® to prevent phototoxic reactions related to erythropoietic protoporphyria.
The FDA granted this application Priority Review designation. Scenesse® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.The approval of Scenesse® was granted to Clinuvel.

FDA NEWS RELEASE

For Immediate Release: October 11th, 2019

FDA approves new treatment for patients with migraine

The UFDA approved Reyvow™ (lasmiditan) tablets for the acute (active but short-term) treatment of migraine with or without aura (a sensory phenomenon or visual disturbance) in adults. Reyvow™ is not indicated for the preventive treatment of migraine.
Migraine headache pain is often described as an intense throbbing or pulsing pain in one area of the head. Additional symptoms include nausea and/or vomiting and sensitivity to light and sound. Approximately one-third of individuals who suffer from migraine also experience aura shortly before the migraine. An aura can appear as flashing lights, zig-zag lines, or a temporary loss of vision. Migraines can often be triggered by various factors including stress, hormonal changes, bright or flashing lights, lack of food or sleep, and diet. Migraine is 3 times more common in women than in men and affects more than 10% of people worldwide.
The effectiveness of Reyvow™ for the acute treatment of migraine was demonstrated in 2 randomized, double-blind, placebo-controlled trials. A total of 3,177 adult patients with a history of migraine with and without aura treated a migraine attack with Reyvow™ in these studies. In both studies, the percentages of patients whose pain resolved and whose most bothersome migraine symptom (nausea, light sensitivity, or sound sensitivity) resolved 2 hours after treatment were significantly greater among patients receiving Reyvow™ at all doses compared to those receiving placebo. Although patients were allowed to take a rescue medication 2 hours after taking Reyvow™, opioids, barbiturates, triptans and ergots were not allowed within 24 hours of the study drug’s administration. A total of 22% of patients were taking a preventive medication for migraine.
There is a risk of driving impairment while taking Reyvow™. Patients are advised not to drive or operate machinery for at least 8 hours after taking Reyvow™, even if they feel well enough to do so. Patients who cannot follow this advice are advised not to take Reyvow™. The drug causes central nervous system (CNS) depression, including dizziness and sedation. It should be used with caution if taken in combination with alcohol or other CNS depressants.The most common side effects that patients in the clinical trials reported were dizziness, fatigue, a burning or prickling sensation in the skin (paresthesia), and sedation.
The FDA granted the approval of Reyvow™ to Eli Lilly and Company.

FDA NEWS RELEASE

For Immediate Release: October 21st, 2019

FDA approves new breakthrough therapy for cystic fibrosis (CF)

The FDA approved Trikafta™ (elexacaftor/ivacaftor/tezacaftor), the first triple combination therapy available to treat patients with the most common CF mutation. Trikafta™ is approved for patients 12 years and older with CF who have at least 1 F508del mutation in the CF transmembrane conductance regulator (CFTR) gene, which is estimated to represent 90% of the CF population.

CF, a rare, progressive, life-threatening disease, results in the formation of thick mucus that builds up in the lungs, digestive tract, and other parts of the body. It leads to severe respiratory and digestive problems as well as other complications such as infections and diabetes. CF is caused by a defective protein that results from mutations in the CFTR gene. While there are approximately 2,000 known mutations of the CFTR gene, the most common mutation is the F508del mutation.

Trikafta™ is a combination of 3 drugs that target the defective CFTR protein. It helps the protein made by the CFTR gene mutation function more effectively. Currently available therapies that target the defective protein are treatment options for some patients with CF, but many patients have mutations that are ineligible for treatment. Trikafta™ is the first approved treatment that is effective for CF patients 12 years and older with at least 1 F508del mutation, which affects 90% of the population with CF or roughly 27,000 people in the United States.

The efficacy of Trikafta™ in patients with CF aged 12 years and older was demonstrated in 2 trials. The first trial was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients who had an F508del mutation and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor or tezacaftor/ivacaftor alone. The second trial was a 4-week, randomized, double-blind, active-controlled trial in 107 patients who had 2 identical F508del mutations. In each trial, the primary analysis looked at increases in the percent predicted forced expiratory volume in 1 second, known as ppFEV1, which is an established marker of CF lung disease progression. Trikafta™ increased the ppFEV1 in both trials. In the first trial, it increased mean ppFEV1 13.8% from baseline compared to placebo. In the second trial, it increased mean ppFEV1 10% from baseline compared to tezacaftor/ivacaftor. In the first trial, treatment with Trikafta™ also resulted in improvements in sweat chloride, number of pulmonary exacerbations (worsening respiratory symptoms and lung function), and body mass index (weight-to-height ratio) compared to placebo.

The safety profile of Trikafta™ is based on data from the 510 CF patients in the 2 trials. The safety profile was generally similar across all subgroups of patients. Serious adverse drug reactions that occurred more frequently in patients receiving Trikafta™ compared to placebo were rash and influenza (flu) events. The most common adverse drug reactions included headaches, upper respiratory tract infections, abdominal pains, diarrhea, rashes, increased liver enzymes (alanine aminotransferase and aspartate aminotransferase), nasal congestion, increased blood creatine phosphokinase (an enzyme that can be associated with muscle damage), rhinorrhea (mucus in the nasal cavity), rhinitis (swelling of the mucous membrane of the nose), influenza, sinusitis and increased blood bilirubin (may be caused by problems involving the liver, gallbladder or red blood cells).

The prescribing information for Trikafta™ includes warnings related to elevated liver function tests (transaminases and bilirubin), use at the same time with other products that are inducers or inhibitors of another liver enzyme called Cytochrome P450 3A4 (CYP3A), and the risk of cataracts. Patients and their caregivers should speak with a health care professional about these risks and any medicines they take before starting treatment.

Patients with CF should speak with a health care professional and have tests performed to understand which gene mutations they have. The presence of at least one F508del mutation should be confirmed using an FDA-cleared genotyping assay prior to treatment. The safety and effectiveness of Trikafta™ in patients with CF younger than 12 years of age have not been established.

The FDA granted this application Priority Review, in addition to Fast Track and Breakthrough Therapy Designation. Trikafta™ also received orphan drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases. Drugs approved under expedited programs are held to the same approval standards as other FDA approvals. Because of Trikafta™'s benefit to the CF community, the FDA reviewed and approved Trikafta™ in approximately 3 months, ahead of the March 19, 2020 review goal date. The approval of Trikafta™ was granted to Vertex Pharmaceuticals Incorporated, which will receive a Rare Pediatric Disease Priority Review Voucher for developing this therapy.

Safety Announcements

Statement on new testing results, including low levels of impurities in ranitidine drugs

[11/01/2019] Statement from Janet Woodcock M.D., Director, Center for Drug Evaluation and Research.

Americans deserve to have confidence in the quality of drugs the FDA regulates – from the prescription medicines they take to the over-the-counter (OTC) products they use in their daily lives. Helping assure the quality and safety of these products is one of our greatest responsibilities. Over the past several weeks, the FDA has been investigating the detection of a contaminant known as N-Nitrosodimethylamine (NDMA) in ranitidine medications, commonly known by the brand name Zantac®.

We set out to fully understand this issue and provide actionable information for Americans who use these medications. The information we've gathered as part of our ongoing ranitidine investigation has been vital to answering the questions we've received about the potential risk of these products. Throughout this process, we've been updating our website with new information, and we are again providing an update with the latest information.

The agency has tested numerous ranitidine products on the market over the past few months, and we're releasing a summary of the results we have to date. Through our testing so far, we have found levels of NDMA in ranitidine that are similar to the levels you would expect to be exposed to if you ate common foods like grilled or smoked meats. We also conducted tests that simulate what happens to ranitidine after it has been exposed to acid in the stomach with a normal diet and results of these tests indicate that NDMA is not formed through this process. Similarly, if ranitidine is exposed to a simulated small intestine environment, NDMA is not formed. However, we still must test the drugs in the human body to fully understand if ranitidine forms NDMA.

Although many of these levels of NDMA observed through FDA testing are much lower than the levels some third-party scientists first claimed, some levels still exceed what the FDA considers acceptable for these medicines. The calculated acceptable intake for NDMA in drugs is based on methods described in the 2018 ICH Guidance M7(R1) *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*. If we or the manufacturers find NDMA levels above the acceptable limits (96 nanograms per day or 0.32 ppm), we're now asking companies to voluntarily recall ranitidine. We would also ask manufacturers to voluntarily recall nizatidine, commonly known as Axid, if they found NDMA above the acceptable daily intake level because it is chemically similar to ranitidine.

We're also asking manufacturers to continue conducting their own laboratory testing to examine levels of NDMA in ranitidine and nizatidine as well as to send samples to the FDA to be tested by our scientists. Additionally, we have requested that manufacturers of nizatidine test their drugs. We are still working with manufacturers to investigate the true source of NDMA and to understand the root cause of the low levels of NDMA present in the drugs.

In the meantime, our recommendations for consumers and patients have not changed. Consumers taking OTC ranitidine or nizatidine can consider using other OTC products approved for their condition. So far, the FDA and industry testing of medicines in the histamine-2 (H2) blocker and proton pump inhibitor (PPI) classes has identified NDMA only in ranitidine and nizatidine. The FDA's tests of samples of alternatives such as Pepcid (famotidine), Tagamet (cimetidine), Nexium (esomeprazole), Prevacid (lansoprazole) and Prilosec (omeprazole) show no NDMA impurities in the medicines.

Patients taking prescription ranitidine or nizatidine should speak with their health care professional about other treatment options. There are multiple drugs approved for the same or similar uses as ranitidine and nizatidine. Additionally, in our testing of ranitidine syrup, primarily used in neonates and pediatric patients, some samples yielded levels of NDMA above the acceptable daily intake level in some lots. Medicines with unacceptable levels are being recalled. We understand the concern we've been hearing from parents and pediatricians, and we'll continue to investigate. Testing of ranitidine for injection is still ongoing.

We've been asked if testing methods have changed since these products were approved, and whether, in light of this situation, we should look at the safety of other older drugs. Drug manufacturers and the FDA continually gain knowledge about drugs, which is why the FDA constantly evaluates quality and safety information as it is learned. As testing methods have become more sophisticated and sensitive, the FDA and industry can identify and mitigate previously unknown risks to patients. This is something we are thoroughly aware of, and we have ongoing assessment, surveillance, compliance and pharmaceutical quality efforts across every product area to work to ensure similar impurities can be kept out of our drug supply.

We also maintain a robust practice of postmarket surveillance and risk evaluation programs to identify adverse events that did not appear during the product development process. Evaluations occur on more than two million adverse event reports submitted every year to the FDA Adverse Event Reporting System (FAERS) through the MedWatch Program by patients, family members and health care providers, as well as adverse

event reports submitted by regulated industry. We use this information to identify safety concerns and recommend actions to improve product safety and protect the public. Patients and health care professionals are encouraged to report any adverse reaction to the agency's MedWatch program.
We know impurities in medicines are of great concern to patients and consumers who rely on safe and effective medicines approved by the FDA, and we are working with manufacturers and global regulators to provide clear and actionable information. These investigations take time and do not provide instantaneous answers. The FDA is committed to sharing all findings when we have adequate understanding of the situation and of what actions should be taken. We will continue to work with drug manufacturers to ensure safe, effective, and high-quality drugs for the American public.

Current Drug Shortages Index (as of Nov 4th, 2019):

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

Alogliptin Tablets	***Currently in Shortage***
Aminophylline Injection, USP	***Currently in Shortage***
Amphetamine Aspartate; Amphetamine Sulfate; Dextroamphetamine Saccharate; Dextroamphetamine Sulfate Tablets	***Currently in Shortage***
Anagrelide Hydrochloride Capsules	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Atropine Sulfate Ophthalmic Ointment	***Currently in Shortage***
Bacitracin Ophthalmic Ointment	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Bumetanide Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride and Epinephrine Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride Injection, USP	***Currently in Shortage***
Buspirone HCl Tablets	***Currently in Shortage***
Calcitriol Injection USP 1MCG /ML	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Capreomycin Injection, USP	***Currently in Shortage***
Carisoprodol Tablets, USP	***Currently in Shortage***
Cefazolin Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cefoxitin for Injection, USP	***Currently in Shortage***
Dexamethasone Sodium Phosphate Injection	***Currently in Shortage***
Dexrazoxane Injection	***Currently in Shortage***
Dextrose 25% Injection	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Diazepam Injection, USP	***Currently in Shortage***
Dicyclomine Oral Tablets/Capsules	***Currently in Shortage***
Diltiazem Hydrochloride	***Currently in Shortage***
Diltiazem Hydrochloride ER (Twice-a-Day) Capsules	***Currently in Shortage***
Diphenhydramine Injection	***Currently in Shortage***
Disulfiram Tablets	***Currently in Shortage***
Dobutamine Hydrochloride Injection	***Currently in Shortage***
Dopamine Hydrochloride Injection	***Currently in Shortage***

Dorzolamide HCl and Timolol Maleate (Cosopt) Ophthalmic Solution	***Currently in Shortage***
Dorzolamide Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Echothiophate Iodide (Phospholine Iodide) Ophthalmic Solution	***Currently in Shortage***
Enalaprilat Injection, USP	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Epinephrine Injection, Auto-Injector	***Currently in Shortage***
Eprosartan Mesylate Tablets	***Currently in Shortage***
Erythromycin Lactobionate for Injection, USP	***Currently in Shortage***
Erythromycin Ophthalmic Ointment	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fluorescein Injection	***Currently in Shortage***
Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Fluorescein Strips	***Currently in Shortage***
Flurazepam Hydrochloride Capsules	***Currently in Shortage***
Fluvoxamine ER Capsules	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Guanfacine Hydrochloride Tablets	***Currently in Shortage***
Haloperidol Tablets	***Currently in Shortage***
Heparin Sodium and Sodium Chloride 0.9% Injection	***Currently in Shortage***
Hydromorphone Hydrochloride Injection, USP	***Currently in Shortage***
Hydroxyzine Pamoate Oral Capsules	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Isocarboxazid Tablets	***Currently in Shortage***
Ketamine Injection	***Currently in Shortage***
Ketoprofen Capsules	***Currently in Shortage***
Ketorolac Tromethamine Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Latanoprost Ophthalmic Solution 0.005%	***Currently in Shortage***
Letermovir (Prevymis) Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Levetiracetam Extended-Release Oral Tablets, USP	***Currently in Shortage***
Levetiracetam Immediate-Release Oral Tablets, USP	***Currently in Shortage***
Lidocaine HCl (Xylocaine) and Dextrose Injection Solution-Premix Bags	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Lorazepam Injection, USP	***Currently in Shortage***
Methadone Hydrochloride Injection	***Currently in Shortage***
Methocarbamol Tablets	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methyldopa Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLIVANT XR) for Ext-Release Oral Susp	***Currently in Shortage***
Metoprolol Tartrate Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Morphine Sulfate Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nalbuphine Hydrochloride Injection	***Currently in Shortage***

Nelarabine (Arranon) Injection	***Currently in Shortage***
Nystatin Oral Suspension	***Currently in Shortage***
Olmesartan Medoxomil Tablets	***Currently in Shortage***
Ondansetron Hydrochloride Injection	***Currently in Shortage***
Pantoprazole Sodium for Injection	***Currently in Shortage***
Parathyroid Hormone (Natpara) Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Physostigmine Salicylate Injection, USP	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Acetate Injection, USP	***Currently in Shortage***
Primaquine Phosphate Tablet, EQ 15mg Base	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	***Currently in Shortage***
Ropivacaine Hydrochloride Injection	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine Transdermal System	***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 Chloride Injection USP, 0.9% Vials and Syringes	***Currently in Shortage***
Tacrolimus Capsules	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Thioridazine Hydrochloride Tablets	***Currently in Shortage***
Thiothixene Capsules	***Currently in Shortage***
Timolol Maleate Tablets	***Currently in Shortage***
Triamcinolone Acetonide (Triesence) Injection, Suspension	***Currently in Shortage***
Trifluoperazine Hydrochloride Tablets	***Currently in Shortage***
Trifluridine Ophthalmic Solution	***Currently in Shortage***
Valsartan Tablets	***Currently in Shortage***
Vinblastine Sulfate Injection	***Currently in Shortage***
Vincristine Sulfate Injection, USP (Preservative-Free)	***Currently in Shortage***