Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
February 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 – February 13, 2019

DATE: February 4, 2019

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

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

Call to Order

Public Comment Forum

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

Update on Medication Coverage Authorization Unit/Academic Detailing Program Update – Appendix B

Narrow Therapeutic Index (NTI) Drug List – Appendix C

Action Item – Vote to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension) – Appendix D

Action Item – Vote to Prior Authorize Revcovi™ (Elapegademase-lvlr) – Appendix E

Action Item – Vote to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab) and to Update the Prior Authorization Criteria for Arnuity® Ellipta® (Fluticasone Furoate), ArmonAir™ RespiClick® (Fluticasone Propionate), AirDuo™ RespiClick® (Fluticasone Propionate/Salmeterol), Breo® Ellipta® (Fluticasone Furoate/Vilanterol), Trelegy™ Ellipta® (Fluticasone Furoate/Umeclidinium/Vilanterol), Xolair® (Omalizumab), and Fasenra™ (Benralizumab) – Appendix F

Action Item – Vote to Prior Authorize Lokelma™ (Sodium Zirconium Cyclosilicate) and to Update the Veltassa® (Patiromer) Prior Authorization Criteria – Appendix G

Action Item – Vote to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag) – Appendix H

Action Item – Vote to Prior Authorize Carbaglu® (Carglumic Acid) – Appendix I

Action Item – Vote to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion) – Appendix J

Action Item – Vote to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector] – Appendix K

Action Item – Vote to Prior Authorize Akynzeo® IV [Fosnetupitant/Palonosetron Injection for Intravenous (IV) Use] – Appendix L

Annual Review of Anticonvulsants and 30-Day Notice to Prior Authorize Epidiolex® (Cannabidiol), Diacomit® (Stiripentol), and Sympazan™ (Clobazam Oral Film) – Appendix M

Annual Review of Anti-Migraine Medications and 30-Day Notice to Prior Authorize Aimovig™ (Erenumab-aooe), Ajovy™ (Fremanezumab-vfrm), and Emgality™ (Galcanezumab-gnlm) – Appendix N

30-Day Notice to Prior Authorize Gamifant® (Emapalumab-lzsg) – Appendix O

30-Day Notice to Prior Authorize Firdapse® (Amifampridine) – Appendix P

Annual Review of Erythropoietin Stimulating Agents (ESAs) and 30-Day Notice to Prior Authorize Retacrit™ (Epoetin Alfa-epbx) – Appendix Q

Annual Review of Parkinson's Disease (PD) Medications and 30-Day Notice to Prior Authorize Inbrija™ (Levodopa Inhalation) and Osmolex ER™ [Amantadine Extended-Release (ER)] – Appendix R

Industry News and Updates – Appendix S

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – February 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

A. Acknowledgment of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. December 12, 2018 DUR Minutes – Vote
B. December 12, 2018 DUR Recommendations Memorandum
C. January 9, 2019 DUR Recommendations Memorandum

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

4. Update on Medication Coverage Authorization Unit/Academic Detailing Program Update – See Appendix B

A. Medication Coverage Activity for January 2019
B. Pharmacy Helpdesk Activity for January 2019
C. Academic Detailing Program Update

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

5. Narrow Therapeutic Index (NTI) Drug List – See Appendix C

A. Introduction
B. SoonerCare NTI Drug List

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

6. Action Item – Vote to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension) – See Appendix D

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Revcovi™ (Elapegademase-lvlr) – See Appendix E

A. Introduction
B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab) and to Update the Prior Authorization Criteria for Arnuity® Ellipta® (Fluticasone Furoate), ArmonAir™ RespiClick® (Fluticasone Propionate), AirDuo™ RespiClick® (Fluticasone Propionate/Salmeterol), Breo® Ellipta® (Fluticasone Furoate/Vilanterol), Trelegy™ Ellipta® (Fluticasone Furoate/Umeclidinium/ Vilanterol), Xolair® (Omalizumab), and Fasenra™ (Benralizumab) – See Appendix F

A. Introduction
B. Market News and Updates

C. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize Lokelma™ (Sodium Zirconium Cyclosilicate) and to Update the Veltassa® (Patiromer) Prior Authorization Criteria – See Appendix G

A. Introduction
B. College of Pharmacy Recommendations

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

10. Action Item – Vote to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag) – See Appendix H

A. Introduction
B. Market News and Updates
C. College of Pharmacy Recommendations

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

11. Action Item – Vote to Prior Authorize Carbaglu® (Carglumic Acid) – See Appendix I

A. Introduction
B. College of Pharmacy Recommendations

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

12. Action Item – Vote to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion) – See Appendix J

A. Introduction
B. College of Pharmacy Recommendations

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

13. Action Item – Vote to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector] – See Appendix K

A. Introduction
B. College of Pharmacy Recommendations

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

14. Action Item – Vote to Prior Authorize Akynzeo® IV [Fosnetupitant/Palonosetron Injection for Intravenous (IV) Use] – See Appendix L

A. Introduction
B. College of Pharmacy Recommendations

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

15. Annual Review of Anticonvulsants and 30-Day Notice to Prior Authorize Epidiolex® (Cannabidiol), Diacomit® (Stiripentol), and Sympazan™ (Clobazam Oral Film) – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of Anticonvulsants
C. Prior Authorizations of Anticonvulsants
D. Market News and Updates
E. Epidiolex® (Cannabidiol Oral Solution) Product Summary
F. Diacomit® (Stiripentol) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Anticonvulsants

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

16. Annual Review of Anti-Migraine Medications and 30-Day Notice to Prior Authorize Aimovig™ (Erenumab-aooe), Ajovy™ (Fremanezumab-vfrm), and Emgality™ (Galcanezumab-gnlm) – See Appendix N

A. Current Prior Authorization Criteria
B. Utilization of Anti-Migraine Medications
C. Prior Authorization of Anti-Migraine Medications
D. Market News and Updates

E. Aimovig™ (Erenumab-aooe) Product Summary
F. Ajovy™ (Fremanezumab-vfrm) Product Summary
G. Emgality™ (Galcanezumab-gnlm) Product Summary
H. Cost Comparison
I. College of Pharmacy Recommendations
J. Utilization Details of Anti-Migraine Medications

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

17. 30-Day Notice to Prior Authorize Gamifant® (Emapalumab-lzsg) – See Appendix O
A. Introduction
B. Gamifant® (Emapalumab-lzsg) Product Summary
C. College of Pharmacy Recommendations

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

18. 30-Day Notice to Prior Authorize Firdapse® (Amifampridine) – See Appendix P
A. Introduction
B. Market News and Updates
C. Firdapse® (Amifampridine) Product Summary
D. College of Pharmacy Recommendations

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

19. Annual Review of Erythropoietin Stimulating Agents (ESAs) and 30-Day Notice to Prior Authorize Retacrit™ (Epoetin Alfa-epbx) – See Appendix Q
A. Current Prior Authorization Criteria
B. Utilization of ESAs
C. Prior Authorization of ESAs
D. Market News and Updates
E. College of Pharmacy Recommendations
F. Utilization Details of ESAs (Pharmacy Claims)
G. Utilization Details of ESAs (Medical Claims)

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

20. Annual Review of Parkinson's Disease (PD) Medications and 30-Day Notice to Prior Authorize Inbrija™ (Levodopa Inhalation) and Osmolex ER™ [Amantadine Extended-Release (ER)] – See Appendix R
A. Current Prior Authorization Criteria
B. Utilization of PD Medications
C. Prior Authorization of PD Medications
D. Market News and Updates
E. Inbrija™ (Levodopa Inhalation) Product Summary
F. Osmolex ER™ (Amantadine ER) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of PD Medications

Non-Presentation; Questions Only:

21. Industry News and Updates – See Appendix S
A. Introduction
B. News and Updates

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

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

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

23. Future Business* (Upcoming Product and Class Reviews)
A. Multiple Sclerosis Medications
B. Lymphoma Medications
C. Chronic Lymphocytic Leukemia Medications

D. Hereditary Angioedema Medications
E. Osteoporosis Medications
**Future business subject to change.*

24. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF DECEMBER 12, 2018

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	
Carla Hardzog-Britt, M.D.	x	
Ashley Huddleston, Pharm.D.; BCOP		x
John Muchmore, M.D.; Ph.D.; Chairman	x	
Lee Munoz, D.Ph.	x	
James Osborne, Pharm.D.		x
Paul Louis Preslar, D.O.; MBA; Vice Chairman	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	
Sarai Connell, Pharm.D.; MBA; Resident	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	
Shellie Keast, Ph.D.; Assistant Professor	x	
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Regan Smith, Pharm.D.; Clinical Pharmacist		x
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist		x
Graduate Students: Philip Looper, Pharm.D.	x	
Michael Nguyen, Pharm.D.	x	
Laura Tidmore, Pharm.D.		x
Corby Thompson, Pharm.D.		x
Reagan Williams, Pharm.D.	x	
Visiting Pharmacy Student(s): N/A		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Melody Anthony, Deputy State Medicaid Director		x
Marlene Asmussen, R.N.; Population Care Management Director	x	
Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.; Sr. Director of Pharmacy	x	
Kelli Brodersen, Marketing Coordinator		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
Maria Maule, J.D.; Senior Director Legal Services	x	
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Thomas Nunn, D.O.; Medical Director	x	
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Paul Konovodoff, Osiris	Don Nopper, Dova Pharmaceuticals	Erica Brumleve, GSK
Tim Hambacher, Otsuka	Jim Dunlap, PhRMA	Dana Pipkin, Sarepta
Evie Knisely, Novartis	Clint Degner, Novartis	James Depp, OUHSC
Marc Parker, Sunovion	Travis Tate, HealthChoice	Brian Maves, Pfizer
Kathrin Kucharski, Sarepta	Ashley Simmons, Dova Pharmaceuticals	

PRESENT FOR PUBLIC COMMENT:	
Ashley Simmons	Dova Pharmaceuticals
Kathrin Kucharski	Sarepta

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. 11 ASHLEY SIMMONS

2B: AGENDA ITEM NO. 15 KATHRIN KUCHARSKI

ACTION: NONE REQUIRED

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

3A: NOVEMBER 14, 2018 DUR MINUTES – VOTE

3B: NOVEMBER 14, 2018 DUR RECOMMENDATIONS MEMORANDUM

3C: CORRESPONDENCE

Materials included in agenda packet; presented by Dr. Cothran

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/CHRONIC MEDICATION ADHERENCE PROGRAM UPDATE

4A: MEDICATION COVERAGE ACTIVITY FOR NOVEMBER 2018

4B: PHARMACY HELPDESK ACTIVITY FOR NOVEMBER 2018

4C: CHRONIC MEDICATION ADHERENCE PROGRAM UPDATE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE HEMLIBRA® (EMICIZUMAB-KXWH), FEIBA® (ANTI-INHIBITOR COAGULANT COMPLEX), NOVOSEVEN® RT [COAGULATION FACTOR VIIA (RECOMBINANT)], AND JIVI® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), PEGYLATED-AUCL]

5A: INTRODUCTION

5B: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Ratterman

Dr. Preslar moved to approve; seconded by Dr. Hardzog-Britt

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE ONPATTRO™ (PATISIRAN) AND TEGSEDI™ (INOTERSEN)

6A: INTRODUCTION

6B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: **VOTE TO PRIOR AUTHORIZE ZEMDRI™ (PLAZOMICIN), XERAVA™ (ERAVACYCLINE), NUZYRA™ (OMADACYCLINE), SEYSARA™ (SARECYCLINE), AND XIMINO™ (MINOCYCLINE EXTENDED-RELEASE)**

7A: INTRODUCTION
7B: COST COMPARISON: MINOCYCLINE PRODUCTS
7C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Adams
Dr. Broyles moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: **VOTE TO PRIOR AUTHORIZE SIGNIFOR® LAR (PASIREOTIDE)**

8A: INTRODUCTION
8B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Connell
Dr. Munoz moved to approve; seconded by Dr. Hardzog-Britt
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: **VOTE TO PRIOR AUTHORIZE SYMDEKO® (TEZACAFTOR/IVACAFTOR) AND ORKAMBI® (LUMACAFTOR/IVACAFTOR ORAL GRANULES) AND TO UPDATE THE KALYDECO® (IVACAFTOR) PRIOR AUTHORIZATION CRITERIA**

9A: INTRODUCTION
9B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Nawaz
Dr. Anderson moved to approve; seconded by Dr. Broyles
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: **ANNUAL REVIEW OF MAINTENANCE ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE LONHALA® MAGNAIR® (GLYCOPYRROLATE INHALATION SOLUTION), YUPELRI™ (REVEFENACIN INHALATION SOLUTION), AND DUPIXENT® (DUPILUMAB INJECTION)**

10A: CURRENT PRIOR AUTHORIZATION CRITERIA
10B: UTILIZATION OF MAINTENANCE ASTHMA AND COPD MEDICATIONS
10C: PRIOR AUTHORIZATION OF MAINTENANCE ASTHMA AND COPD MEDICATIONS
10D: MARKET NEWS AND UPDATES
10E: LONHALA® MAGNAIR® (GLYCOPYRROLATE INHALATION SOLUTION) PRODUCT SUMMARY
10F: YUPELRI™ (REVEFENACIN INHALATION SOLUTION) PRODUCT SUMMARY
10G: COLLEGE OF PHARMACY RECOMMENDATIONS
10H: UTILIZATION DETAILS OF MAINTENANCE ASTHMA AND COPD MEDICATIONS
10I: UTILIZATION DETAILS OF INHALED CORTICOSTEROIDS

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

AGENDA ITEM NO. 11: **ANNUAL REVIEW OF THROMBOCYTOPENIA MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE TAVALISSE™ (FOSTAMATINIB), DOPTELET® (AVATROMBOPAG), AND MULPLETA® (LUSUTROMBOPAG)**

11A: CURRENT PRIOR AUTHORIZATION CRITERIA
11B: UTILIZATION OF THROMBOCYTOPENIA MEDICATIONS
11C: PRIOR AUTHORIZATION OF THROMBOCYTOPENIA MEDICATIONS
11D: MARKET NEWS AND UPDATES
11E: TAVALISSE™ (FOSTAMATINIB) PRODUCT SUMMARY
11F: DOPTELET® (AVATROMBOPAG) PRODUCT SUMMARY
11G: MULPLETA® (LUSUTROMBOPAG) PRODUCT SUMMARY
11H: COLLEGE OF PHARMACY RECOMMENDATIONS
11I: UTILIZATION DETAILS OF THROMBOCYTOPENIA MEDICATIONS

Materials included in agenda packet; presented by Dr. Abbott

ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: ANNUAL REVIEW OF INHALED ANTI-INFECTIVE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ARIKAYCE® (AMIKACIN LIPOSOME INHALATION SUSPENSION)

12A: INTRODUCTION
12B: CURRENT PRIOR AUTHORIZATION CRITERIA
12C: UTILIZATION OF INHALED ANTI-INFECTIVE MEDICATIONS
12D: PRIOR AUTHORIZATION OF INHALED ANTI-INFECTIVE MEDICATIONS
12E: MARKET NEWS AND UPDATES
12F: ARIKAYCE® (AMIKACIN LIPOSOME INHALATION SUSPENSION) PRODUCT SUMMARY
12G: COLLEGE OF PHARMACY RECOMMENDATIONS
12H: UTILIZATION DETAILS OF INHALED ANTI-INFECTIVE MEDICATIONS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF ANTI-EMETIC MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE AKYNZEO® IV [FOSNETUPITANT/PALONOSETRON INJECTION FOR INTRAVENOUS (IV) USE]

13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF ANTI-EMETIC MEDICATIONS
13C: PRIOR AUTHORIZATION OF ANTI-EMETIC MEDICATIONS
13D: MARKET NEWS AND UPDATES
13E: COST COMPARISON
13F: COLLEGE OF PHARMACY RECOMMENDATIONS
13G: UTILIZATION DETAILS OF ANTI-EMETIC MEDICATIONS

Materials included in agenda packet; presented by Dr. Adams

ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: 30-DAY NOTICE TO PRIOR AUTHORIZE CARBAGLU® (CARGLUMIC ACID)

14A: INTRODUCTION
14B: CARBAGLU® (CARGLUMIC ACID) PRODUCT SUMMARY
14C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Connell

ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: ANNUAL REVIEW OF MUSCULAR DYSTROPHY MEDICATIONS

15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF MUSCULAR DYSTROPHY MEDICATIONS
15C: PRIOR AUTHORIZATION OF MUSCULAR DYSTROPHY MEDICATIONS
15D: MARKET NEWS AND UPDATES
15E: COST CHANGES
15F: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

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)**

NO LIVE MEETING SCHEDULED FOR JANUARY. JANUARY 2019 WILL BE A PACKET ONLY MEETING.

18A: GLAUCOMA MEDICATIONS

18B: REVCOVI™ (ELAPEGADEMASE-LVLR)

18C: INJECTABLE AND VAGINAL PROGESTERONE PRODUCTS

18D: HYPERKALEMIA MEDICATIONS

18E: ZILRETTA® [TRIAMCINOLONE EXTENDED-RELEASE (ER) INJECTION]

**Future business subject to change.*

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: **ADJOURNMENT**

The meeting was adjourned at 5:16p.m.

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

Memorandum

Date: December 13, 2018

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

Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.
Pharmacy Director
OHCA

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of December 12, 2018

Recommendation 1: Chronic Medication Adherence Program Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Hemlibra® (Emicizumab-kxwh), Feiba® (Anti-Inhibitor Coagulant Complex), NovoSeven® RT [Coagulation Factor VIIa (Recombinant)], and Jivi® [Antihemophilic Factor (Recombinant), PEGylated-aucl]

MOTION CARRIED by unanimous approval.

The OHCA recommends the prior authorization of Jivi® [antihemophilic factor (recombinant) PEGylated-aucl], Hemlibra® (emicizumab-kxwh), Feiba® (anti-inhibitor coagulant complex), and NovoSeven® RT [coagulation factor VIIa (recombinant)] with the following criteria:

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

1. An FDA approved indication; and
2. Requested medication must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders; and
3. A patient-specific, clinically significant reason why the member cannot use the following:
    a. Hemophilia A: Advate® or current factor VIII replacement product; or
    b. Hemophilia B: Benefix® or current factor IX replacement product; and
4. A half-life study must be performed to determine the appropriate dose and dosing interval; and
5. Initial approvals will be for the duration of the half-life study. If the half-life study shows significant benefit in prolonged half-life, subsequent approvals will be for the duration of one year.

Hemlibra® (Emicizumab-kxwh) Approval Criteria:

1. Member must have a diagnosis of hemophilia A; and
2. Hemlibra® must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders; and
3. Prescriber must be able to monitor appropriate blood clotting tests and levels utilizing testing which accounts for the interaction of Hemlibra® and blood factors by following the Medical and Scientific Advisory Council (MASAC) guidance; and
4. For members with hemophilia A with an inhibitor to factor VIII:
    a. Member must have failed immune tolerance induction (ITI) or is not a good candidate for ITI; and
    b. Member's hemophilia cannot be managed without the use of bypassing agent(s) (e.g., Feiba®, NovoSeven® RT) as prophylaxis for prevention of bleeding episodes, or the member is unable to maintain venous access for daily infusions; and
    c. Member's hemophilia is not currently controlled with the use of bypassing agent(s); and
    d. Prescriber must counsel member and/or caregiver on the risks of utilizing Feiba® for breakthrough bleeding while on Hemlibra®, and member should be monitored closely if any bypassing agent is given; or
5. For members with hemophilia A without an inhibitor:
    a. Member's current prophylaxis therapy is not adequate to prevent spontaneous bleeding episodes, or the member is unable to maintain venous access for prophylactic infusions; and
    b. Treatment plan must be made to address breakthrough bleeds and procedures; and
    c. Routine lab screening must occur for factor VIII inhibitor while using Hemlibra® since this would change the treatment plan for bleeds and procedures; and
6. First dose must be given in a health care facility; and
7. In order to calculate appropriate dosing, the member's recent weight must be provided and have been taken within the last 3 months; and

8. Initial approvals will be for 3 months of therapy. Subsequent approvals will be the duration of 1 year if there has been a decrease in the member's spontaneous bleeding episodes since beginning Hemlibra® treatment.

Feiba® (Anti-Inhibitor Coagulation Complex) Approval Criteria:

1. Member must be diagnosed with hemophilia A or B with an inhibitor; and
2. Feiba® must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders.

NovoSeven® RT [Coagulation Factor VIIa (Recombinant)] Approval Criteria:

1. An FDA approved diagnosis of one of the following:
   a. Hemophilia A or B with inhibitors; or
   b. Congenital factor VII deficiency; or
   c. Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets; or
   d. Acquired hemophilia; and
2. NovoSeven® RT must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders.

Recommendation 3: Vote to Prior Authorize Onpattro™ (Patisiran) and Tegsedi™ (Inotersen)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Onpattro™ (patisiran) and Tegsedi™ (inotersen) with the following 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 that 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 reactions; and
6. Onpattro™ will not be approved for concomitant use with Tegsedi™; and

7. 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; 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 patient or caregiver will be performed under the guidance of a health care professional; and
7. Prescriber must confirm the patient or caregiver has been trained by a health care professional on the subcutaneuos (sub-Q) administration and proper storage of Tegsedi™; and
8. Tegsedi™ will not be approved for concomitant use with Onpattro™; 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 four syringes per 28 days will apply.

Recommendation 4: Vote to Prior Authorize Zemdri™ (Plazomicin), Xerava™ (Eravacycline), Nuzyra™ (Omadacycline), Seysara™ (Sarecycline), and Ximino™ [Minocycline Extended-Release (ER)]

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Zemdri™ (plazomicin vial for IV infusion), Xerava™ (eravacycline vial for IV infusion), Nuzyra™ (omadacycline tablet and vial for IV infusion), and Seysara™ (sarecycline tablet) with the following criteria:

Zemdri™ (Plazomicin) Approval Criteria:

1. An FDA approved diagnosis of complicated urinary tract infection (cUTI), including pyelonephritis, caused by designated susceptible microorganisms; and

2. A patient-specific, clinically significant reason why the member cannot use an appropriate alternative aminoglycoside (e.g., gentamicin, tobramycin) or other cost-effective therapeutic equivalent alternative(s); and
3. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Xerava™ (Eravacycline) Approval Criteria:

1. An FDA approved diagnosis of complicated intra-abdominal infections (cIAI) 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 penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenam (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s); 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.

Nuzyra™ (Omadacycline) Approval Criteria [Community-Acquired Bacterial Pneumonia (CABP) Diagnosis]:

1. An FDA approved diagnosis of 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, monotherapy with a respiratory fluoroquinolone (e.g., levofloxacin, gemifloxacin), or other cost-effective therapeutic equivalent alternative(s); and
4. Approval quantity will be based on Nuzyra™ prescribing information and FDA approved dosing regimen(s); and
    a. For Nuzyra™ vials, an initial quantity limit of 4 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 tablet formulation for the remainder of therapy.

Nuzyra™ (Omadacycline) Approval Criteria [Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Diagnosis]:

1. An FDA approved diagnosis of ABSSSI 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 vancomycin, linezolid, doxycycline, trimethoprim/sulfamethoxazole, or other cost-effective therapeutic equivalent alternative(s); and

4. Use of Nuzyra™ vials will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation; and
5. Approval quantity will be based on Nuzyra™ prescribing information and FDA approved dosing regimen(s).

Seysara™ (Sarecycline) Approval Criteria:

1. An FDA approved diagnosis of inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris; and
2. Member must be 9 years of age or older; and
3. Seysara™ is not covered for members older than 20 years of age; and
4. A patient-specific, clinically significant reason why the member cannot use minocycline, doxycycline, tetracycline, or other cost-effective therapeutic equivalent alternative(s); and
5. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate strength according to package labeling; and
6. A quantity limit of 30 tablets per 30 days will apply.

The College of Pharmacy also recommends the following changes to the Various Systemic Antibiotics Prior Authorization category:

1. Add Ximino™ (minocycline extended-release capsules) to the Antibiotic Special Formulation category. Current special formulation criteria will apply.
2. Update the current approval criteria for Avycaz® (ceftazidime/avibactam) based on the new FDA approved indication for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP).

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

Oral Antibiotic Special Formulation Approval Criteria:

1. Member must have a patient-specific, clinically significant reason why the immediate-release formulation and/or other cost-effective therapeutic equivalent alternative(s) cannot be used.
2. The following oral antibiotics currently require prior authorization and the special formulation approval criteria will apply:
   - Amoxicillin 500mg tablets
   - Amoxicillin/clavulanate potassium extended-release (ER) tablets (Augmentin XR®)
   - Amoxicillin 775mg ER tablets (Moxatag®)
   - Cephalexin 250mg and 500mg tablets
   - Cephalexin 750mg capsules
   - Doxycycline hyclate 75mg and 100mg tablets (Acticlate®)
   - Doxycycline hyclate delayed-release (DR) tablets (Doryx®)
   - Doxycycline monohydrate 75mg and 150mg capsules and tablets
   - Doxycycline monohydrate 40mg DR capsules (Oracea®)
   - Minocycline ER capsules (Ximino™)
   - Minocycline ER tablets (Minolira™)
   - Minocycline ER tablets (Solodyn®)

Avycaz® (Ceftazidime/Avibactam) Approval Criteria:

1. An FDA approved diagnosis of one of the following infections caused by designated susceptible microorganisms:
    a. Complicated intra-abdominal infections (cIAI), used in combination with metronidazole; or
    b. Complicated urinary tract infections (cUTI), including pyelonephritis; 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, 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 carbapenam (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s); and
5. A quantity limit of 42 vials per 14 days will apply.

Recommendation 5: Vote to Prior Authorize Signifor® LAR (Pasireotide)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Signifor® LAR (pasireotide) with the following criteria:

Signifor® LAR (Pasireotide) Approval Criteria:

1. An FDA approved diagnosis of one of the following:
    a. Members with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option; or
    b. Members with Cushing's disease from a pituitary tumor for whom pituitary surgery is not an option or has not been curative; and
2. For a diagnosis of acromegaly, the member must have a documented trial with octreotide long-acting or lanreotide depot with an inadequate response or have a patient-specific, clinically significant reason why the other long-acting somatostatin analogs (SSAs) are not appropriate for the member; and
3. Pasireotide LAR must be prescribed by an endocrinologist or in consultation with an endocrinologist; and
4. Pasireotide LAR must be administered by a health care professional; and
5. Prescriber must document that the member has had an inadequate response to surgery or is not a candidate for surgery; and
6. Prescriber must verify liver function tests (LFTs) (e.g., ALT, AST, bilirubin) will be monitored when starting treatment and periodically thereafter; and
7. Authorizations will be for the duration of 12 months; and
8. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Recommendation 6: Vote to Prior Authorize Symdeko® (Tezacaftor/Ivacaftor) and Orkambi® (Lumacaftor/Ivacaftor Oral Granules) and to Update the Kalydeco® (Ivacaftor) Prior Authorization Criteria

MOTION CARRIED by unanimous approval.

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

Symdeko® (Tezacaftor/Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in patients 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 patient'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 12 years of age or older; and
4. Members using Symdeko® must be supervised by a pulmonary specialist; and
5. If the 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. The prescriber must verify that the member has been counseled on proper administration of Symdeko® including taking with a fat-containing food; and
7. The 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. Members 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 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®.

Orkambi® (Lumacaftor/Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in patients who are homozygous for the *F508del* mutation in the CF transmembrane conductance regulator (*CFTR*) gene detected by genetic testing; and
2. If the member's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene; and

3. Orkambi® will not be approved for patients with CF other than those homozygous for the *F508del* mutation; and
4. Member must be ~~6~~ 2 years of age or older; and
5. Members using Orkambi® must be supervised by a pulmonary specialist; and
6. The prescriber must verify that ALT, AST, and bilirubin will be assessed prior to initiating Orkambi®, every 3 months during the first year of treatment, and annually thereafter; and
7. Members must not be taking any of the following medications concomitantly with Orkambi®: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort; and
8. A quantity limit of 4 tablets per day or 112 tablets per 28 days will apply or a quantity limit of 2 granule packets per day or 56 granule packets per 28 days will apply; and
9. An age restriction of 2 years to 5 years of age will apply to Orkambi® 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
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 FEV_1, will be required for continued approval.

Kalydeco® (Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of 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 ~~2~~ 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 1 year to less 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 FEV_1, will be required for continued approval.

Recommendation 7: Annual Review of Maintenance Asthma and Chronic Obstructive Pulmonary Disease (COPD) Medications and 30-Day Notice to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab Injection)

NO ACTION REQUIRED.

Recommendation 8: Annual Review of Thrombocytopenia Medications and 30-Day Notice to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag)

NO ACTION REQUIRED.

Recommendation 9: Annual Review of Inhaled Anti-Infective Medications and 30-Day Notice to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension)

NO ACTION REQUIRED.

Recommendation 10: Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Akynzeo® IV [Fosnetupitant/Palonosetron Injection for Intravenous (IV) Use]

NO ACTION REQUIRED.

Recommendation 11: 30-Day Notice to Prior Authorize Carbaglu® (Carglumic Acid)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Muscular Dystrophy Medications

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.

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

Memorandum

Date: January 10, 2019

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

Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.
Pharmacy Director
OHCA

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Packet of January 9, 2019

Recommendation 1: U.S. Food and Drug Administration (FDA) Safety Alerts

NO ACTION REQUIRED.

Recommendation 2: Annual Review of Injectable and Vaginal Progesterone Products and 30-Day Notice to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector]

NO ACTION REQUIRED.

Recommendation 3: Annual Review of Glaucoma Medications and 30-Day Notice to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion)

NO ACTION REQUIRED.

Recommendation 4: 30-Day Notice to Prior Authorize Revcovi™ (Elapegademase-lvlr)

NO ACTION REQUIRED.

Recommendation 5: Annual Review of Hyperkalemia Medications and 30-Day Notice to Prior Authorize Lokelma™ (Sodium Zirconium Cyclosilicate) and to Update the Veltassa® (Patiromer) Prior Authorization Criteria

NO ACTION REQUIRED.

Recommendation 6: Annual Review of Mepsevii™ (Vestronidase Alfa-vjbk)

NO ACTION REQUIRED.

Recommendation 7: Annual Review of Nuedexta® (Dextromethorphan/ Quinidine)

NO ACTION REQUIRED.

Recommendation 8: Annual Review of Zilretta® [Triamcinolone Acetonide Extended-Release (ER) Injection]

NO ACTION REQUIRED.

Recommendation 9: Industry News and Updates

NO ACTION REQUIRED.

Recommendation 10: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

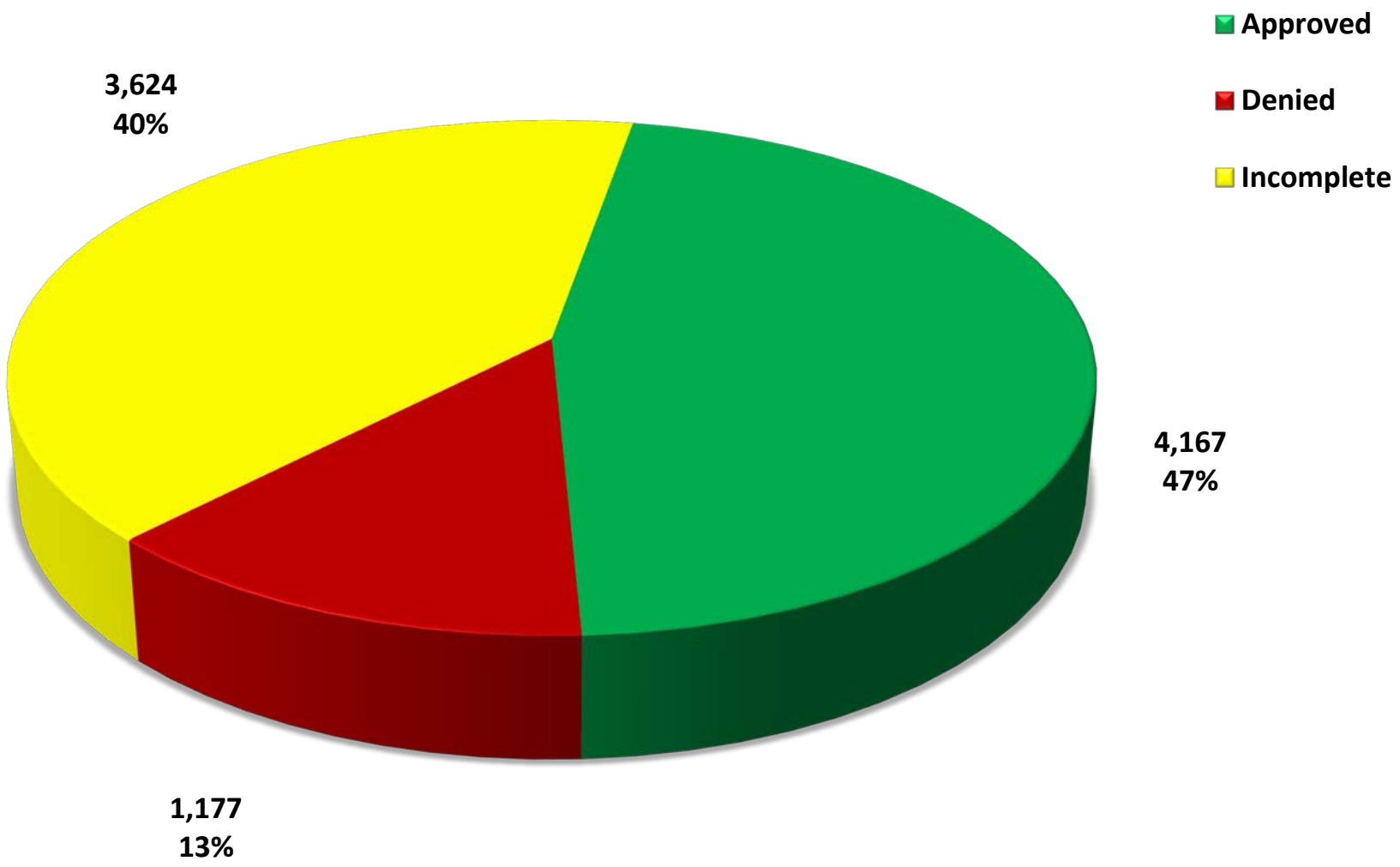
NO ACTION REQUIRED.

Recommendation 11: Future Business

NO ACTION REQUIRED.

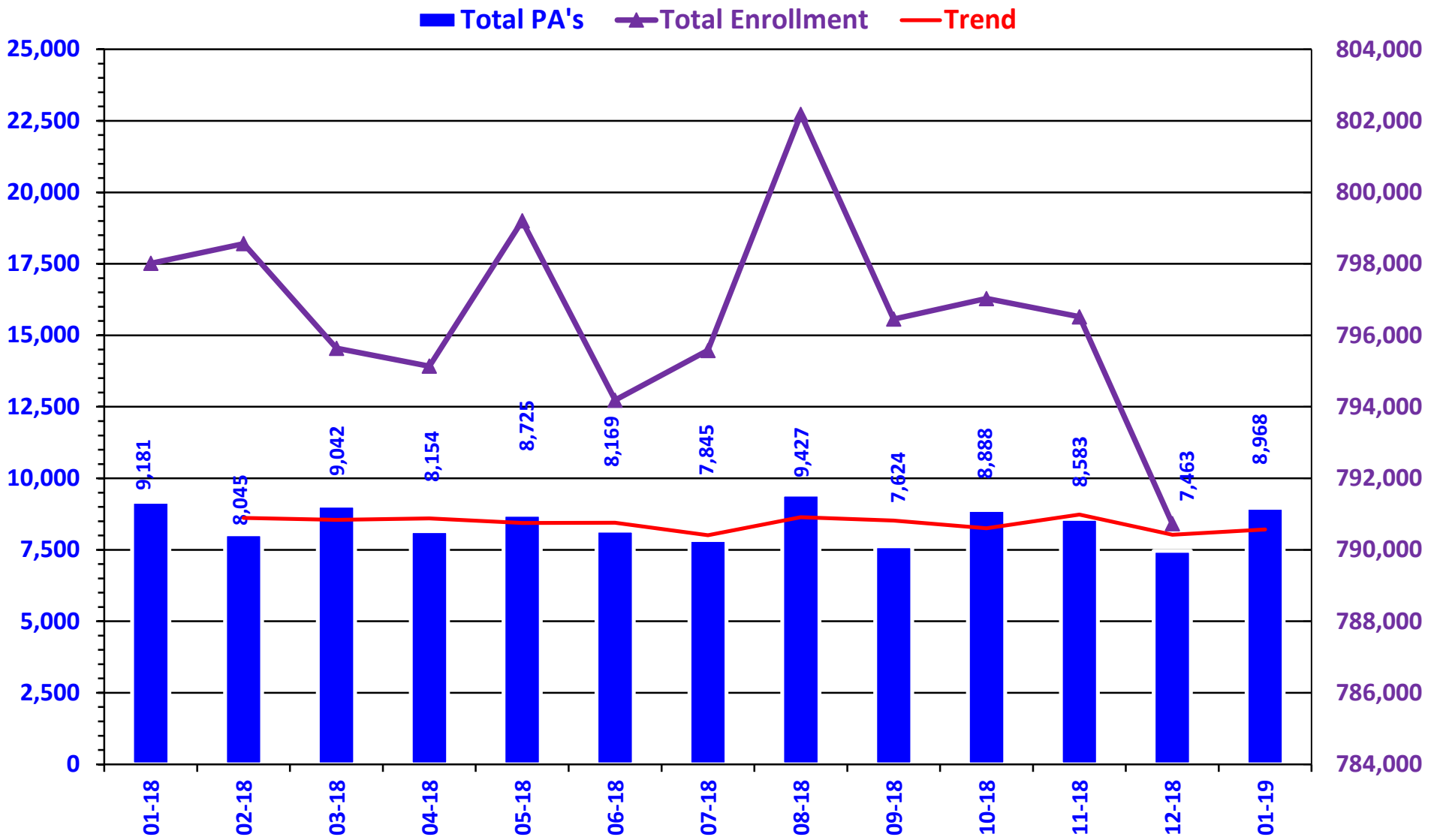
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: JANUARY 2019



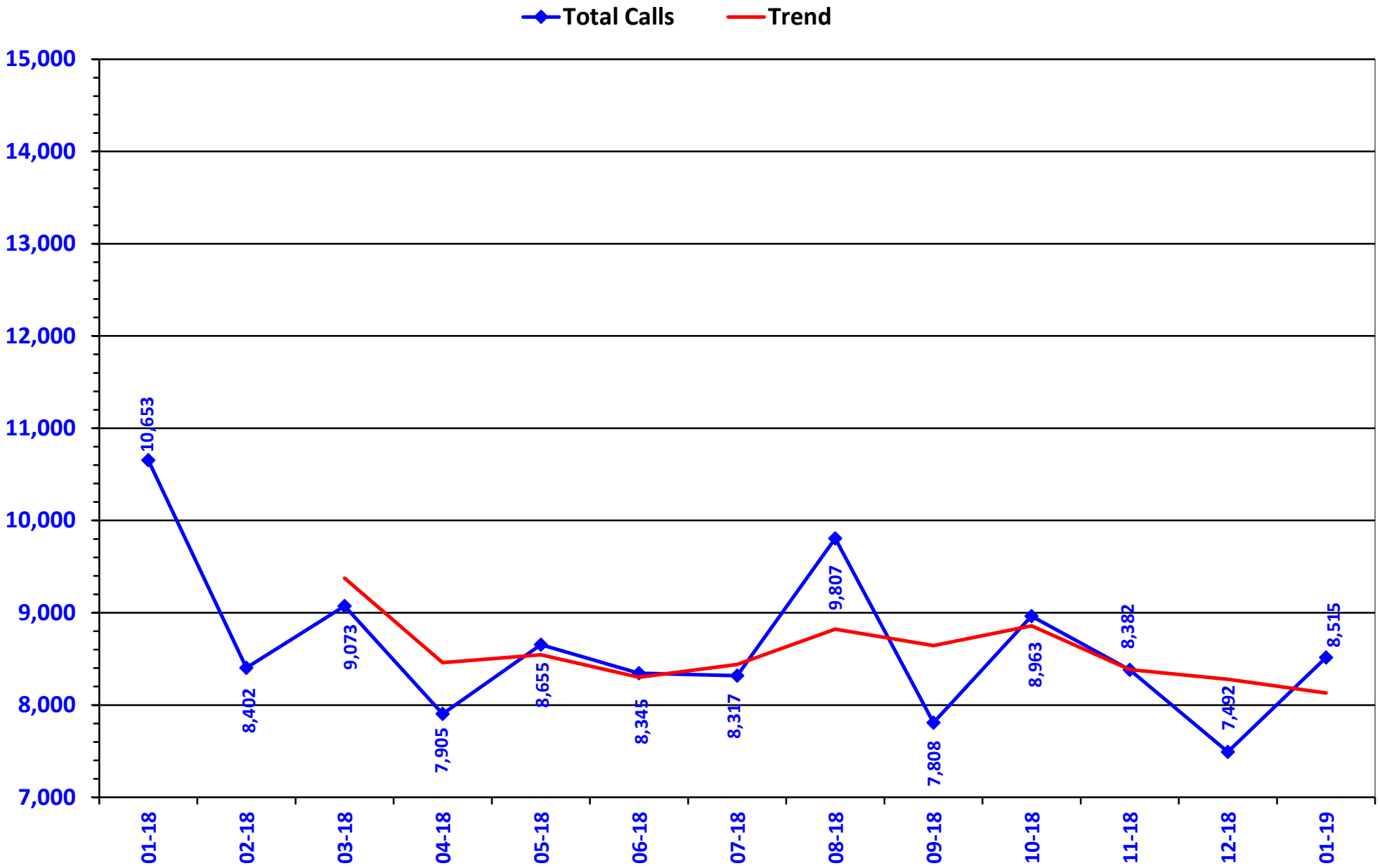
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: JANUARY 2019 – JANUARY 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
JANUARY 2019 – JANUARY 2018



Prior Authorization Activity

1/1/2019 Through 1/31/2019

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	106	10	32	64	324
Analgesic - NonNarcotic	16	0	1	15	0
Analgesic - Narcotic	412	165	57	190	161
Angiotensin Receptor Antagonist	42	6	12	24	358
Antiasthma	110	33	22	55	284
Antibiotic	34	20	1	13	244
Anticonvulsant	192	80	17	95	260
Antidepressant	191	47	25	119	316
Antidiabetic	261	92	45	124	337
Antihistamine	20	4	5	11	285
Antimigraine	105	7	31	67	141
Antineoplastic	75	45	4	26	158
Antiparasitic	57	5	7	45	12
Antiulcers	155	42	47	66	105
Anxiolytic	25	1	4	20	19
Atypical Antipsychotics	220	131	10	79	341
Biologics	133	70	14	49	314
Bladder Control	55	19	12	24	336
Blood Thinners	291	161	20	110	332
Botox	34	23	8	3	357
Buprenorphine Medications	490	345	19	126	73
Cardiovascular	64	33	10	21	316
Chronic Obstructive Pulmonary Disease	161	25	45	91	318
Constipation/Diarrhea Medications	160	28	56	76	275
Contraceptive	21	12	2	7	275
Corticosteroid	11	2	4	5	207
Dermatological	356	114	80	162	139
Diabetic Supplies	532	298	10	224	217
Diuretic	11	6	0	5	336
Endocrine & Metabolic Drugs	174	103	6	65	134
Erythropoietin Stimulating Agents	16	10	0	6	121
Fibromyalgia	47	11	3	33	80
Gastrointestinal Agents	109	30	26	53	189
Growth Hormones	120	88	5	27	157
Hematopoietic Agents	15	8	3	4	84
Hepatitis C	173	102	17	54	8
HFA Rescue Inhalers	70	2	15	53	188
Insomnia	45	4	14	27	220
Insulin	144	41	22	81	301
Miscellaneous Antibiotics	23	5	1	17	36
Multiple Sclerosis	34	14	6	14	212
Muscle Relaxant	52	6	14	32	81
Nasal Allergy	76	13	25	38	104
Neurological Agents	94	31	25	38	211
Neuromuscular Agents	10	8	0	2	330
NSAIDs	52	0	10	42	0
Ocular Allergy	19	2	5	12	84
Ophthalmic Anti-infectives	13	1	2	10	25
Osteoporosis	22	6	8	8	357

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

Other*	333	58	92	183	250
Otic Antibiotic	21	3	3	15	9
Prenatal Vitamins	11	1	0	10	215
Respiratory Agents	27	20	0	7	181
Statins	14	3	1	10	172
Stimulant	941	433	107	401	344
Synagis	99	61	13	25	67
Testosterone	43	10	9	24	358
Topical Antifungal	26	3	3	20	38
Topical Corticosteroids	54	1	30	23	54
Vitamin	93	34	28	31	148
Pharmacotherapy	96	92	0	4	292
Emergency PAs	0	0	0	0	
Total	**7,406**	**3,028**	**1,093**	**3,285**	

Overrides					
Brand	59	41	2	16	296
Compound	19	18	0	1	70
Cumulative Early Refill	1	0	0	1	0
Diabetic Supplies	4	3	0	1	62
Dosage Change	275	253	0	22	12
High Dose	10	8	0	2	152
Ingredient Duplication	12	8	1	3	51
Lost/Broken Rx	65	62	3	0	11
NDC vs Age	333	208	43	82	270
Nursing Home Issue	26	25	0	1	10
Opioid MME Limit	39	17	1	21	66
Opioid Quantity	44	34	2	8	167
Other*	42	40	0	2	14
Prescriber Temp Unlock	1	1	0	0	358
Quantity vs. Days Supply	566	378	23	165	235
STBS/STBSM	21	15	3	3	73
Stolen	11	11	0	0	11
Third Brand Request	34	17	6	11	13
Overrides Total	**1,562**	**1,139**	**84**	**339**	
Total Regular PAs + Overrides	**8,968**	**4,167**	**1,177**	**3,624**	

Denial Reasons	
Unable to verify required trials.	2,892
Does not meet established criteria.	1,205
Lack required information to process request.	690

Other PA Activity	
Duplicate Requests	644
Letters	11,729
No Process	16
Changes to existing PAs	809
Helpdesk Initiated Prior Authorizations	639
PAs Missing Information	33

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

Academic Detailing Program Update

Oklahoma Health Care Authority
February 2019

Background[1]

The Oklahoma Health Care Authority (OHCA) is responsible for controlling costs of state-purchased health care while assuring that standards of care are met as part of a progressive system. Combining standards of care with the most current peer-reviewed studies and presenting these in an unbiased, independent, evidence-based manner is known as Academic Detailing (AD). AD programs link prescribers with an educator resulting in improved patient health and cost outcomes. While not specifically designed to be a tool of cost containment, traditionally AD programs save $2 for every dollar spent.

In July 2015, under the direction of the OHCA, Pharmacy Management Consultants (PMC) developed an AD program to improve implementation of published guidelines and standards of care. PMC pharmacists analyzed prescription claims data to determine initial AD topics. A clinical pharmacist received specialized AD training through the National Resource Center for Academic Detailing (NaRCAD). In November 2015, PMC assisted the OHCA in securing ongoing grant funding for the AD program through the Health Service Initiative under the Children's Health Insurance Program (CHIP). AD visits began in January 2016 and topics have included the following:

- Diagnosis and Treatment of Attention-Deficit/Hyperactivity Disorder (ADHD)
- Use of Atypical Antipsychotic Medications
- Treatment of Upper Respiratory Infections

The AD pharmacist prepares educational materials in consultation with NaRCAD and offers the program to selected prescribers. Educational materials include the following:

- Clinical treatment guidelines
- Provider resources
- Patient and parent resources
- Diagnostic and treatment tools
- Topic-specific continuing medical education (CME) course listings
- Drug alerts and statements from the U.S. Food and Drug Administration (FDA)
- National quality measures [e.g., Healthcare Effectiveness Data and Information Set (HEDIS)]
- OHCA Product Based Prior Authorization (PBPA) coverage criteria

Topic: Diagnosis and Treatment of ADHD[2]

The first AD topic was regarding the treatment of pediatric patients with ADHD. The American Academy of Pediatrics (AAP) has published standards of care for the treatment of ADHD. These AAP standards of care are well-established and have remained unchanged since 2011. They

served as the primary source for development of the ADHD-AD curriculum. Additional recommendations from peer-reviewed publications since 2011 were included when relevant.

Individual counties and prescribers with high utilization of ADHD medications were identified for ADHD-AD outreach. Oklahoma, Stephens, Pittsburg, and Muskogee were the selected counties. Prescribers within the targeted counties were chosen from non-specialists, in keeping with recommended AD best practices. Data from paid SoonerCare pharmacy claims and prior authorization (PA) submissions were used to identify prescribers whose prescribing patterns differed significantly from their peers. Prescribing data used for comparison included the following:

- Number and cost of ADHD claims for members 0 to 4 years of age
- Number and cost of ADHD claims for members 0 to 18 years of age
- Number of ADHD PAs submitted
- Number of ADHD PAs denied

AD was delivered in-person by the AD pharmacist. Initially, a study arm was planned to include AD provided via web-based platform (Revation LiveLink). However, prescribers are thus far unwilling to participate in web-based AD sessions owing to factors including the following:

- Incomplete computer knowledge
- Desire for face-to-face interaction
- Lack of necessary computer components

Results: Diagnosis and Treatment of ADHD[2]

Inappropriate Prescribing:

Potentially inappropriate ADHD prescribing has been assessed by 2 separate, evidence-based measures. The first measure involves the use of ADHD medication by children 4 years of age and younger. The 2009 AAP guidelines describe the use of any ADHD medication for this age group as a second-line treatment and recommends medications only be used as an addition to behavioral therapy. The decreases in ADHD claims for patients 4 years of age and younger are shown in Figure 1.

Figure 1: ADHD Medication Paid Claims, 0 to 4 Years of Age*

	180 Days Before AD	180 Days After AD	Percent Change
Number of claims	24	10	-58.33%
Total cost of claims	$3,671.03	$1,127.65	-69.28%

*Negative indicates improvement. Costs do not reflect rebated prices or net costs.

The second measure involves use of high tiered ADHD medications. The ADHD clinical criteria used by OHCA mirrors the 2009 AAP ADHD guidelines by providing Tier-1 coverage for multiple long-acting and short-acting stimulants as well as non-stimulant medications. Requests for higher tiered medications can reasonably be described as personal preferences rather than evidence-based.

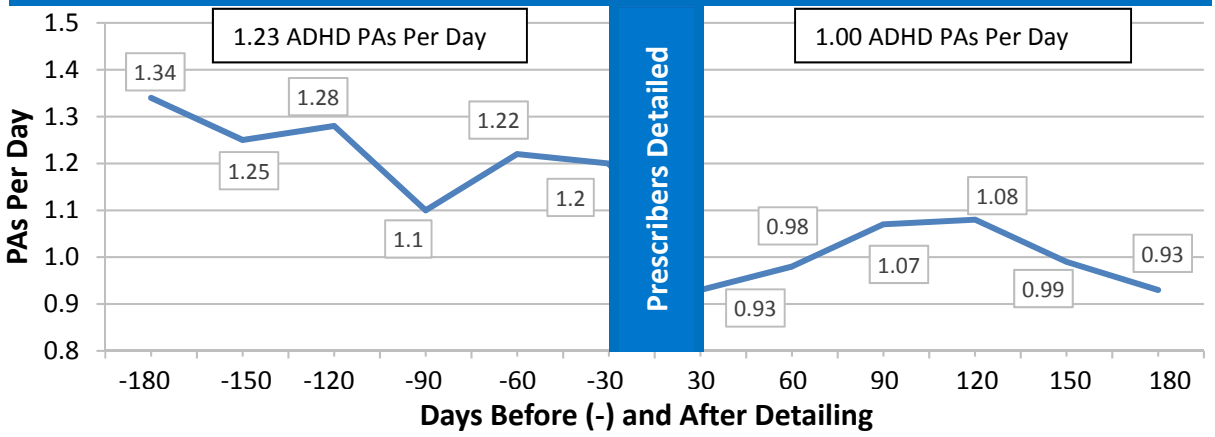
PA Submissions:

Providers' PA submissions for ADHD medications were assessed in the 6 months preceding ADHD-AD. They were then compared to themselves 6 months after detailing. Changes in ADHD

PA submissions are shown in Figure 2. Detailed providers submitted 18.7% fewer ADHD PAs per day after detailing. During the analysis period, non-detailed providers submitted 1.13% fewer ADHD PAs in the post-detailing time period. It has been estimated that each PA submitted results in approximately $20 in cost to OHCA. Changes in PA submissions are not attributable to changes in the submission process or tier structure, as the ADHD medication PA criteria were not modified during the ADHD-AD detailing period.

By decreasing the number of PA submissions by detailed providers, OHCA has saved an estimated $3.74 per provider, per day. During the 6 months of the post-detailing period, this resulted in a total estimated savings of $30,294 for all detailed providers.

Figure 2: ADHD Medication PAs Per Day



Medication Costs:

The total ADHD medication cost savings are shown in Figure 3. ADHD-AD visits began in January 2016, and paid claims from detailed providers for ADHD medications were assessed in the 6 months preceding ADHD-AD. The same providers were then compared to themselves 6 months after detailing. The resulting nearly 14% decrease is inclusive of all federal and supplemental rebates, thus reflecting an actual demonstrated savings of more than $80,000 from ADHD-AD.

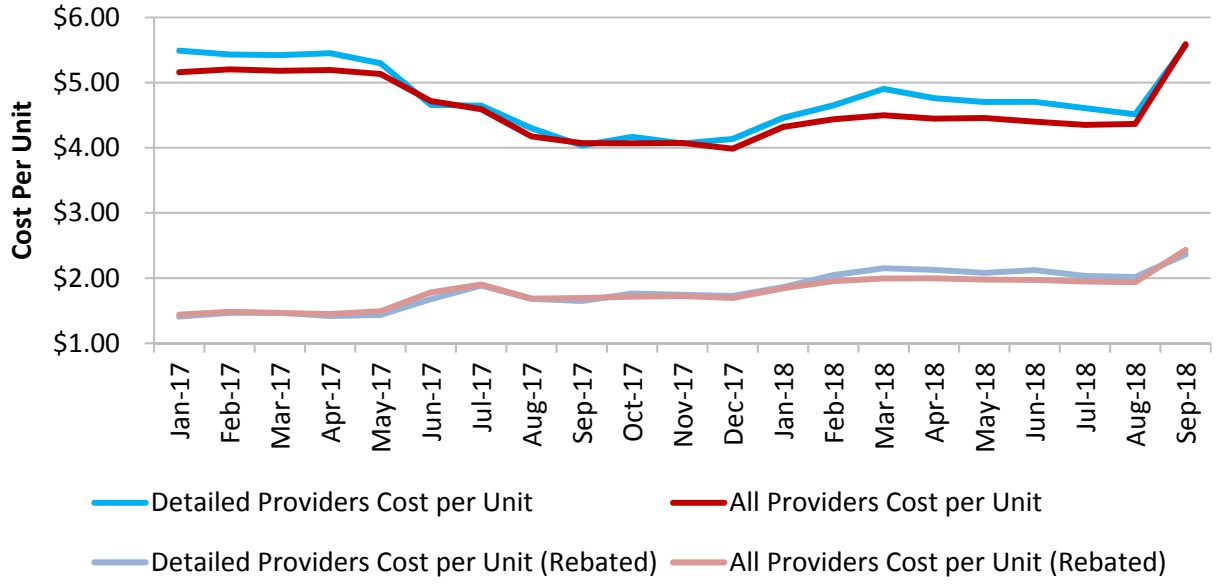
Figure 3: ADHD Medication Paid Claims from Detailed Providers*

	Cost of Claims	Number of Claims	Cost per Claim
Pre-detailing	$619,186.92	9,873	$62.72
Post-detailing	$538,835.03	9,984	$53.97
Change due to AD	-$80,351.88	+111	-$8.75
% change	**12.98% decrease**	**1.12% increase**	**13.94% decrease**

*Negative indicates improvement.

Nearly 90% of the ADHD-AD sessions were completed by the end of 2016. Until October 2017 (Figure 4), detailed providers demonstrated a prescribing pattern of lower cost per ADHD claim than their non-detailed peers. Detailed providers' cost per claim before applicable rebates was higher than their non-detailed peers. This difference indicates detailed providers prescribed more heavily rebated, or lower tiered, ADHD medications than their non-detailed peers during the same time period. During Federal Fiscal Year (FFY) 2017, detailed providers prescribed ADHD medications for 2,215 pediatric members covered by SoonerCare.

Figure 4: ADHD Medication Cost Per Unit



As shown, detailed providers prescribed less costly ADHD medications and requested fewer higher tiered drugs than non-detailed peers. Achieving a nearly 60% reduction in ADHD medication usage by very young patients and transitioning patients to less costly, but equally effective, alternatives represents significant improvements in both cost and quality of care.

Topic: Use of Atypical Antipsychotic Medications[3,4]

The second AD topic was regarding the treatment of pediatric patients using atypical, or second-generation antipsychotic (SGA) medications. Multiple groups have expressed concerns over the trends in pediatric use of SGAs, particularly for children in foster care and those covered by Medicaid. A majority of SGAs for pediatric patients are used off-label since most drug manufacturers specifically exclude children from Phase 3 clinical trials. The American Academy of Child and Adolescent Psychiatry (AACAP) has issued both on- and off-label guidance for SGA use in specific psychiatric disorders. These recommendations served as the primary source for development of the SGA-AD curriculum. As was the case for ADHD-AD, publications that were more recent since the guidelines were published were also included when relevant.

Prescribers previously detailed through ADHD-AD were offered the opportunity to participate in SGA-AD visits. Additional prescribers were identified through SoonerCare prescription claims data using the same points of comparison as described previously for ADHD-AD.

Results: Use of Atypical Antipsychotic Medications[3]

Inappropriate Prescribing:

Potentially inappropriate SGA prescribing has been assessed by 2 separate, evidence-based measures. The first measure involves the use of SGA medication by children 4 years of age and younger. The 2009 AACAP SGA guidelines include only 1 study of preschool-aged children, and the organization published recommendations only for children between 5 and 18 years of age. The decreases in SGA claims for patients 4 years of age and younger are shown in Figure 5.

Figure 5: SGA Medication Paid Claims, 0 to 4 Years of Age*

	180 Days Before AD	180 Days After AD	Percent Change
Number of claims	8	4	-50.00%
Total cost of claims	$85.35	$56.93	-33.30%

*Negative indicates improvement. Costs do not reflect rebated prices or net costs.

The second measure involves use of higher tiered SGA medications. The SGA clinical criteria used by the OHCA mirrors the 2009 AACAP guidelines by providing Tier-1 coverage for multiple SGAs. AACAP guidelines describe specific diagnoses which may be treated more appropriately with certain agents. However, as most SGAs are used off-label, these recommendations do not contribute significantly toward directing prescribers to preferred agents for treatment. Requests for higher tiered medications can reasonably be described as personal preferences rather than evidence-based.

PA Submissions:

Providers' PA submissions for SGA medications were assessed in FFY 2017 and 2018. Changes in SGA PA submissions are shown in Figure 6. Several changes were made to the SGA medication PA criteria during the detailing and post-detailing period, so specific savings due to decreased PA submission cannot be reliably determined. However, detailed providers submitted nearly half as many SGA PAs as their non-detailed peers resulting in a savings of at least $1,440.

Figure 6: SGA Medication PA Submissions*

	Detailed PAs	Total PAs
FFY 2017	284	5,641
FFY 2018	212	4,804
Difference	-72	-837
% Difference	-33.96%	-17.42%

*Negative indicates improvement.

Medication Costs:

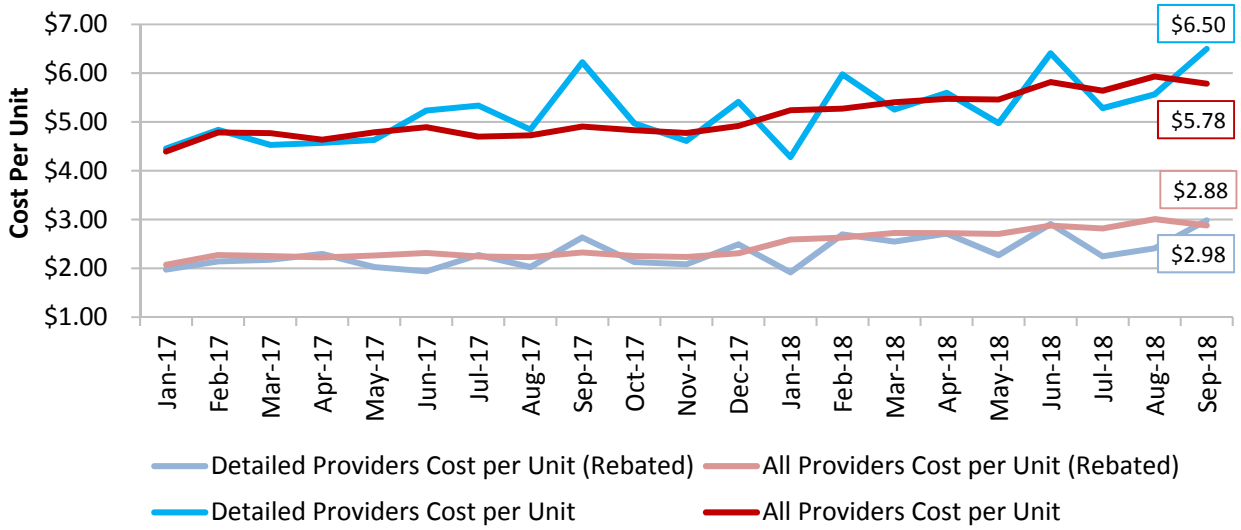
The SGA medication cost savings (not including rebate data) are shown in Figure 7. SGA-AD visits began in late November 2016 and paid claims from detailed providers for SGA medications were assessed for FFY 2016 and 2017. The observed decrease of nearly 39% is not inclusive of all federal and supplemental rebates. During FFY 2016, detailed providers represented 4.04% of the total cost of all SGA claims. During FFY 2017, that percentage decreased to 3.1% of the total cost of all SGA claims.

Figure 7: SGA Medication Paid Claims*			
	Detailed Cost	**Total Cost**	**Non-Detailed Cost**
FFY 2017	$1,199,090.25	$38,709,038.00	$37,509,947.75
FFY 2016	$1,951,660.99	$48,288,815.40	$46,337,154.41
Difference	-$752,570.74	-$9,579,777.40	-$8,827,207.66
% Difference	-38.56%	-19.84%	-19.05%

*Negative indicates improvement. Costs do not reflect rebated prices or net costs.

All SGA-AD detailing sessions were completed by the end of August 2017.

Figure 8: SGA Medication Cost Per Unit



With currently available rebate data, detailed providers continue, with few exceptions, to demonstrate a prescribing pattern of lower cost per SGA claim than their non-detailed peers as shown in Figure 8. Detailed providers' cost per claim before applicable rebates was inconsistent, but trended toward being higher than their non-detailed peers. This difference indicates a trend toward detailed providers prescribing more heavily rebated, or lower tiered SGA drugs than their non-detailed peers during the same time period. As shown in Figure 9, detailed prescribers cost per unit was an average $0.15 less than their peers. This resulted in a total savings of $99,764.87.

Figure 9: SGA Medication Paid Claims, 1/1/17 to 9/30/18*			
	Total Cost	**Total Units**	**Avg. Cost Per Unit**
Detailed Providers	$1,580,628.57	681,454	$2.3283
All Providers	$35,438,057.77	14,322,547	$2.4746
Difference	Not Applicable	Not Applicable	-$0.1464
% Difference	Not Applicable	Not Applicable	-5.91%

*Negative indicates improvement.

During FFY 2018, detailed providers prescribed SGA medications for 1,063 pediatric members covered by SoonerCare.

As shown previously, detailed providers prescribed less costly SGA medications and requested fewer higher tiered drugs than their non-detailed peers. **Achieving a 50% reduction in SGA medication usage by very young patients and transitioning patients to less costly, but equally effective, alternatives represents significant improvements in both cost and quality of care.**

Topic: Treatment of Upper Respiratory Infections (URIs)

The third AD topic was regarding the treatment of URIs in pediatric patients. Multiple organizations, including the Centers for Disease Control and Prevention (CDC), have published concerns about antibiotic (ABX) resistance and the need to reduce the use of ABX for patients experiencing URIs. While not a large contributor to overall drug cost, ABX overuse has significant individual and public health consequences. Guidelines from the Infectious Diseases Society of America (IDSA), the American Academy of Family Physicians (AAFP), the CDC, and the AAP served as the source material for development of the ABX-AD curriculum.

Prescribers detailed through ADHD-AD or SGA-AD were offered the opportunity to participate in ABX-AD. Additional prescribers were identified through SoonerCare prescription claims data. Prescribing data used for comparison included the following:

- Having a 50% or more increase in number of ABX claims from 2016 to 2017
- Having 50% more ABX claims than the average for their prescriber specialty
- Being 1 of the top 50 prescribers of ABX across the entire state
- Being 1 of the top 200 prescribers of ABX for both 2016 and 2017

Prescribers meeting 3 or more of the aforementioned criteria were selected for ABX-AD. Detailing visits began in March 2018 and were largely completed in September 2018. Data analysis will begin upon completion of the 2018-2019 influenza season.

Topic: PA Submission and Future Topics

Providers and staff also receive PA-AD focused on improving submission of PA materials in order to decrease the overall financial burden to the OHCA. Future pediatric AD topics will include treatment of asthma and both type-1 and type-2 diabetes. Future adult AD topics are anticipated to align with current changes to Medicaid drug utilization requirements and may include use of opioids, both alone and in combination with benzodiazepines, or SGAs. An expansion of pediatric SGA-AD to additional SGA prescribers is also anticipated.

Provider Satisfaction

Targeted providers were frequently in practice settings with non-targeted providers. These non-targeted providers received the benefit of AD, but were not used for purposes of comparison. To date, 232 providers have received an AD visit for at least 1 topic. Only 4 providers have been excluded due to an unwillingness to participate; other reasons for exclusion of targeted providers included the following:

- No longer treating ADHD
- Retired, moved out of state, or inactive license
- No longer treating pediatric patients
- No longer treating SoonerCare members

Targeted and non-targeted co-practice partners were given satisfaction surveys in order to determine their acceptance of the program and to predict the likelihood of participation in future AD topics. Participants in the detailing sessions were given a 1 page survey and survey results are shown in Figure 10.

Figure 10: Provider Satisfaction

The information provided was:	**% choosing agree or strongly agree**
Easily understood	96.85%
Clearly presented	99.21%
Evidence-based	96.06%

Based on the information, I intend to:	**% choosing agree or strongly agree**
Make practice changes as a result	82.68%
Recommend this program to colleagues	88.98%
Participate in future topics	89.76%

Academic Meeting Presentation(s)

Since July 2016, the PMC-AD program leaders have been invited to present program outcomes and breakout sessions at the International Conference on Academic Detailing, the Academy of Managed Care Pharmacy (AMCP), and the American Drug Utilization Review Society (ADURS). Additionally, a poster presentation featuring ADHD-AD results was awarded a silver ribbon at the Nexus 2017 meeting of AMCP.

Summary

As a result of AD interventions, medication costs, PA submissions, and potentially inappropriate prescribing have all been reduced substantially. Prescription data was analyzed using rebated and non-rebated data, pre-and post-detailing patterns for individual providers, and FFY and calendar year comparisons. Each analysis shows improvements following delivery of AD services. When combined with the savings realized from medication claims and decreased PA submissions, the ADHD-AD and SGA sessions resulted in $211,850.75 total savings, inclusive of all federal and supplemental rebates.

Providers report satisfaction with the program and intend to participate in future topics. The AD program was well received by providers. Targeted providers have fulfilled their stated intentions to make practice changes as prompted by the AD sessions. Continued implementation and expansion of the OHCA AD program is expected to increase delivery of evidence-based health care and reduce health care costs to OHCA.

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[1] Soumerai SB, Avorn J. Economic and Policy Analysis of University-Based Drug "Detailing." *Medical Care* 1986; 24(4):313-331.
[2] ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management. *Pediatrics* 2011; 128(5):1007-1022.
[3] Walkup J. Practice Parameter on the Use of Psychotropic Medication in Children and Adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry* 2009; 48(9):961-973.
[4] Wilson D. Child's Ordeal Shows Risks of Psychosis Drugs for Young. *New York Times*. Available online at: https://www.nytimes.com/2010/09/02/business/02kids.html. Issued 09/01/2010. Last accessed 01/16/2019.

Appendix C

Narrow Therapeutic Index (NTI) Drug List

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3]

The U.S. Food and Drug Administration (FDA) defines narrow therapeutic index (NTI) drugs as drugs where small differences in dose or blood concentration may lead to serious therapeutic failures or adverse drug reactions. NTI drugs generally have the following characteristics:

- Little separation between therapeutic and toxic doses
- Sub-therapeutic concentration may lead to serious therapeutic failure
- Drugs are subject to therapeutic drug monitoring based on pharmacokinetic (PK) or pharmacodynamic (PD) measures
- In clinical practice, doses are often adjusted in very small increments (<20%)

The FDA Office of Generic Drugs assesses brand/generic interchangeability standards for NTI drugs. NTI drugs analyzed for bioequivalence by the FDA include warfarin, lithium, digoxin, theophylline, tacrolimus, phenytoin, levothyroxine, and carbamazepine. Other groups, including Health Canada, also include cyclosporine and sirolimus in their NTI drug classification group.

The Oklahoma Health Care Authority (OHCA) policy and rules state the following regarding brand necessary certification (317:30-5-77):

> "For certain narrow therapeutic index drugs, a prior authorization will not be required. The DUR Board will select and maintain the list of narrow therapeutic index drugs."

The purpose of this report is to provide the Drug Utilization Review (DUR) Board with an updated list of the current NTI drug list maintained by the OHCA. Medications included in the NTI list are set up to bypass brand/generic substitution requirements in the claims processing system. Action by the DUR Board is not required unless the board recommends changes to the current NTI drug list.

SoonerCare NTI Drug List

- Carbamazepine
- Clozapine
- Cyclosporine
- Digoxin
- Levothyroxine
- Lithium
- Phenytoin
- Sirolimus
- Tacrolimus
- Theophylline
- Warfarin

[1] U.S. Food and Drug Administration (FDA). FY2015 Regulatory Science Research Report: Narrow Therapeutic Index Drugs. Available online at: https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm500577.htm. Last revised 05/09/2017. Last accessed 01/15/2019.

[2] Yu LX. Quality and Bioequivalence Standards for Narrow Therapeutic Index Drugs. FDA. Available online at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm292676.pdf. Issued 2011. Last accessed 01/15/2019.

[3] Jiang W. Building Confidence in Generic Narrow Therapeutic Index (NTI) Drugs. FDA. Available online at: https://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM620779.pdf. Issued 09/18/2018. Last accessed 01/15/2019.

Appendix D

Vote to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension)

Oklahoma Health Care Authority
February 2019

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

Mycobacterium avium complex (MAC) is a type of nontuberculous mycobacteria (NTM) that is transmitted via inhalation or ingestion of contaminated water or soil. MAC is primarily a pulmonary pathogen that affects individuals who are immunocompromised [e.g., from Human Immunodeficiency Virus (HIV), hairy cell leukemia, immunosuppressive chemotherapy], and MAC lung disease occurs rarely in immunocompetent hosts (estimated incidence of MAC is 1 per 100,000 persons per year).

Symptoms of MAC in immunocompromised patients can include sweating, weight loss, fatigue, diarrhea, dyspnea, osteomyelitis, tenosynovitis, synovitis, and disseminated disease involving the lymph nodes, the central nervous system (CNS), the liver, the spleen, and the bone marrow. Symptoms of MAC in immunocompetent patients are nonspecific and consist of persistent cough, fatigue, malaise, weakness, dyspnea, chest discomfort, and occasionally hemoptysis. Fever and weight loss can occur but are more common in disseminated MAC disease. Severe disability or death can result from respiratory failure.

The clinical course of pulmonary MAC infection in HIV-negative patients is usually indolent. Treatment success rates in HIV-negative patients have ranged from 20 to 90% in various studies. HIV-positive patients have a poorer prognosis; however, patients with non-disseminated disease receiving antiretroviral therapy and anti-MAC treatment have treatment results similar to non-HIV-infected patients. Recommended treatment for MAC consists of a 3-drug regimen of a macrolide (e.g., azithromycin), a rifamycin (e.g., rifampin), and ethambutol for a minimum of 12 months; the addition of an injectable aminoglycoside may also be considered. Sputum conversion often requires 3 to 6 months of treatment, resulting in a usual treatment duration of 15 to 18 months. Treatment failure is typically defined as failure to achieve culture conversion after 6 to 12 months of therapy.

Arikayce® (amikacin liposome inhalation suspension) is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of MAC lung disease as part of a combination antibacterial drug regimen in patients with refractory lung disease defined as those who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. Arikayce® is supplied as a sterile, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590mg/8.4mL; Arikayce® is packaged as a 28-vial kit with a Lamira™ Nebulizer System. Amikacin inhalation vials should be refrigerated at 2°C to 8°C (36°F to 46°F), and can be stored at room temperature for up to 4 weeks (if the product is not used within 4 weeks after removal from refrigeration, the remaining medication should be discarded). The recommended dose of amikacin inhalation is 590mg/8.4mL via inhalation once daily. The Wholesale Acquisition Cost

(WAC) per mL of Arikayce® is $363.00 resulting in a cost per dose of $3,049.20 and cost per 28-day supply of $85,377.60.

Recommendations

The College of Pharmacy recommends the prior authorization of Arikayce® (amikacin liposome inhalation suspension) with the following criteria:

Arikayce® (Amikacin Liposome Inhalation Suspension) Approval Criteria:

1. An FDA approved indication for the treatment of *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no alternative treatment options; and
2. Member must have had a minimum of 6 consecutive months of a multidrug background regimen therapy used compliantly and not achieved negative sputum cultures within the last 12 months. Dates of previous treatments and regimens must be listed on the prior authorization request; and
    a. If claims for a multidrug background regimen are not in the member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the prescriber; and
3. Member must continue a multidrug background regimen therapy while on Arikayce®, unless contraindicated, or provide reasoning why continuation of a multidrug background regimen is not appropriate for the member; and
4. A patient-specific, clinically significant reason why the member requires an inhaled aminoglycoside in place of an intravenous or intramuscular aminoglycoside (e.g., amikacin, streptomycin) must be provided; and
5. Arikayce® will not be approved for patients with non-refractory MAC lung disease; and
6. Arikayce® must be prescribed by or in consultation with a pulmonary disease or infectious disease specialist (or be an advanced care practitioner with a supervising physician who is a pulmonary disease or infectious disease specialist); and
7. Initial approvals will be for the duration of 6 months after which time the prescriber must document the member is responding to treatment for continued approval.
8. A quantity limit of 28 vials per 28 days will apply.

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[1] Arikacye® Prescribing Information. Insmed, Inc. Available online at: https://www.arikayce.com/pdf/full-prescribing-information.pdf. Last revised 09/2018. Last accessed 01/08/2019.

[2] Griffith DE. Overview of nontuberculous mycobacterial infections in HIV-negative patients. *UpToDate*. Available online at: https://www.uptodate.com/contents/overview-of-nontuberculous-mycobacterial-infections-in-hiv-negative-patients?search=mycobacterium%20avium%20complex%20infection&source=search_result&selectedTitle=1~137&usage_type=default&display_rank=1. Last revised 11/29/2018. Last accessed 02/04/2019.

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[5] U.S. Food and Drug Administration (FDA). FDA News Release. FDA approves a new antibacterial drug to treat a serious lung disease using a novel pathway to spur innovation. Available online at: https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm622048.htm. Issued 09/28/2018. Last accessed 02/04/2019.

Appendix E

Vote to Prior Authorize Revcovi™ (Elapegademase-lvlr)

Oklahoma Health Care Authority
February 2019

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

Adenosine deaminase (ADA) deficiency is an autosomal recessive genetic disorder caused by mutations in the *ADA* gene. The ADA enzyme is found in all cells, including red and white blood cells, and works by catalyzing the deamination of adenosine and deoxyadenosine (dAXP) which are then excreted. In the absence of functional ADA enzyme, there is intracellular accumulation of dAXP and adenosine and subsequent cellular toxicity. Additionally, excessive levels of dAXP can block DNA synthesis. In approximately 90% of cases, ADA deficiency leads to severe combined immunodeficiency (ADA-SCID) with dysfunction of T, B, and natural killer (NK) cells that presents in the first few months of life.

ADA deficiency has an overall incidence of 1 in 200,000 live births. Most ADA-SCID patients present with life-threatening infections, chronic persistent diarrhea, and failure to thrive in the first months of life. Neurologic abnormalities including cognitive deficits can occur as a result of the metabolic abnormalities of ADA deficiency. ADA-SCID is typically fatal in the first 2 years of life without treatment. Diagnosis of ADA deficiency is established by demonstrating absent or very low (<1% of normal) ADA activity in red blood cells (RBCs), which is accompanied by increased levels of adenosine and 2'dAXP in plasma. Increased dAXP in RBCs is indicative for ADA deficiency. The addition of T-cell receptor excision circles (TRECS) testing, a surrogate marker for new T-cell production, to newborn screening tests has led to significant improvements in the diagnosis of ADA-SCID. Additionally, the guidelines from the American Academy of Allergy, Asthma, and Immunology (AAAAI) recommend testing for biallelic mutations in the *ADA* gene to further confirm ADA deficiency.

Exposure to contagious illnesses should be minimized as best as possible. The ADA-SCID treatment guidelines recommend that all patients initially receive enzyme replacement therapy (ERT) as an immediate stabilizing measure, while planning definitive treatment with either of 2 equal, first-line options: human leukocyte antigen (HLA)-matched sibling or family donor allogenic hematopoietic stem cell transplantation (HSCT) or autologous hematopoietic stem cell gene therapy (HSC-GT). HSC-GT is not currently available in the United States. If HLA-matched sibling donor/family donor HSCT or HSC-GT are not available or have failed, ERT can be continued or reinstituted and HSCT with alternative donors should be considered.

ERT has the potential to protect from neurologic injury caused by increased levels of adenosine and dAXP. ERT leads to a rapid increase in plasma ADA activity and over a period of 4 to 8 weeks, results in the return of RBC dAXP levels to nearly undetectable levels. An increase in B-cell numbers is evident within the first month of therapy in some patients, whereas T-cell numbers typically begin to increase by 2 to 4 months. Production of antibodies also normalizes. Early treatment can reverse metabolic toxicity to the thymus and nonlymphoid organs, further stabilizing patients before HSCT or HSC-GT. In most patients, ERT should be used as a "bridge"

for relatively short periods (a few months to approximately 2 years) before undergoing HSCT or HSC-GT. The deterioration in lymphocyte counts and function over time might lead to a decrease in antiviral immunity and tumor surveillance, contributing to an increased risk of malignancies. For these reasons, the guidelines do not recommend that continuous ERT treatment last beyond 5 to 8 years, and that long-term ERT treatment is only appropriate for patients when neither HSCT nor HSC-GT have been available or effective.

Revcovi™ (elapegademase-lvlr) was approved in October 2018 by the U.S. Food and Drug Administration (FDA) as an ERT for the treatment of ADA-SCID in pediatric and adult patients. Elapegademase eliminates the need to source the enzyme from animals via recombinant technology and works by supplementing levels of the ADA enzyme. Approval of elapegademase is based on 2 open-label trials which showed increases in ADA activity, reduced concentrations of toxic metabolites, and improved total lymphocyte counts in ADA-SCID patients. Prior to approval of elapegademase, the primary ERT used in ADA-SCID patients was Adagen® (pegademase bovine), a modified enzyme sourced from bovine intestine for ERT in patients who did not qualify for a bone marrow transplant. Revcovi™ is supplied as 2.4mg/1.5mL single-dose vials for intramuscular (IM) administration. The recommended starting dosage of elapegademase for patients transitioning from pegademase bovine is 0.2mg/kg IM weekly. Pegademase bovine-naïve patients should start at an elapegademase dose of 0.4mg/kg IM weekly, based on ideal body weight, divided into 2 doses (0.2mg/kg twice per week). The optimal long-term dose and schedule of administration should be established by the treating physician for each patient individually and may be adjusted based on the laboratory values for trough ADA activity, trough deoxyadenosine (dAXP) level, and/or on the treating physician's medical assessment of the patient's clinical status. The treatment of ADA-SCID with elapegademase should be monitored by measuring trough plasma ADA activity, trough dAXP levels, and/or total lymphocyte counts. Blood samples for the analysis of trough plasma ADA activity and trough dAXP level should be collected prior to the first administration of elapegademase.

Cost Comparison:

Medication	Cost Per Vial	Cost Per Week	Cost Per 28 Days
Revcovi™ (elapegademase-lvlr) 2.4mg/1.5mL vial	**$9,856.01**	**$49,280.05 - $98,560.10***	**$197,120.20- $394,240.40***
Adagen® (pegademase bovine) 375units/1.5mL vial	$5,207.00	$26,035.00+	$104,140.00+

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.
*Dosing based on FDA approved regimen of 0.2mg/kg to 0.4mg/kg weekly in a 60kg patient.
+Dosing based on FDA approved regimen of 30units/kg weekly in a 60kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Revcovi™ (elapegademase-lvlr) with the following criteria:

Revcovi™ (Elapegademase-lvlr) Approval Criteria:

1. An FDA approved diagnosis of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients; and
    a. Diagnosis of ADA deficiency should be confirmed by demonstrating biallelic mutations in the *ADA* gene; and
2. Revcovi™ must be prescribed by or in consultation with a physician who specializes in the treatment of immune deficiency disorders; and
3. The member must have failed to respond to a bone marrow transplant or not be a current suitable candidate for a bone marrow transplant; and
4. A patient-specific, clinically significant reason why Adagen® (pegademase bovine) is not appropriate for the member; or
5. Previous failure of Adagen® (pegademase bovine) used compliantly. Failure is defined as the inability to maintain ADA activity or reduce erythrocyte deoxyadenosine nucleotides (dAXP), or the member is experiencing adverse effects associated with Adagen® therapy that are not expected to occur with Revcovi™; and
6. Prescriber must agree to monitor trough plasma ADA activity, trough dAXP levels, and/or total lymphocyte counts to ensure efficacy and compliance and to monitor for neutralizing antibodies when suspected; and
7. 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; and
8. Initial approvals will be for the duration of 6 months at which time the prescriber must confirm improvement or stabilization in ADA activity or dAXP levels or improvement in immune function. Subsequent approvals will require the prescriber to verify the member is still not a current suitable candidate for a bone marrow transplant.

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[3] Rubinstein A. Adenosine deaminase deficiency: treatment. *UpToDate*. Available online at: https://www.uptodate.com/contents/adenosine-deaminase-deficiency-treatment-and-prognosis?search=Adenosine%20deaminase%20deficiency:%20treatment&source=search_result&selectedTitle=1~27&usage_type=default&display_rank=1. Last revised 01/21/2019. Last accessed 01/25/2019.

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[5] Leadiant Biosciences, Inc. FDA Approves Revcovi™, a New Enzyme Replacement Therapy Developed by Leadiant Biosciences, for the Treatment of ADA-SCID in Pediatric and Adult Patients. Available online at: https://leadiant.com/fda-approves-revcovi-new-enzyme-replacement-therapy-developed-leadiant-biosciences-treatment-ada-scid-pediatric-adult-patients/. Issued 10/05/2018. Last accessed 01/25/2019.

[6] Leadiant Biosciences, Inc. What is Adagen? Available online at: http://www.adagen.com/what_is_adagen.html. Last accessed 01/25/2019.

[7] Taylor P. Leadiant gets FDA OK for bubble boy disease drug. *PMLiVE*. Available online at: http://www.pmlive.com/pharma_news/leadiant_gets_fda_ok_for_bubble_boy_disease_drug_1254869. Issued 10/08/2018. Last accessed 01/25/2019.

Appendix F

Vote to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab) and to Update the Prior Authorization Criteria for Arnuity® Ellipta® (Fluticasone Furoate), ArmonAir™ RespiClick® (Fluticasone Propionate), AirDuo™ RespiClick® (Fluticasone Propionate/Salmeterol), Breo® Ellipta® (Fluticasone Furoate/Vilanterol), Trelegy™ Ellipta® (Fluticasone Furoate/Umeclidinium/Vilanterol), Xolair® (Omalizumab), and Fasenra™ (Benralizumab)

Oklahoma Health Care Authority
February 2019

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

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

- **Lonhala® Magnair® (glycopyrrolate inhalation solution):** The FDA approved Lonhala® Magnair®, an anticholinergic, for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) in December 2017. Lonhala® Magnair® is supplied as a sterile 1mL vial containing 25mcg of glycopyrrolate for inhalation twice daily. Lonhala® vials should only be used with the Magnair® Nebulizer System.
- **Yupelri™ (revefenacin inhalation solution):** The FDA approved Yupelri™, an anticholinergic, for the maintenance treatment of patients with COPD in November 2018. Yupelri™ is supplied in a unit-dose vial containing 175mcg revefenacin per 3mL. The recommended regimen for Yupelri™ is 1 vial once daily with a standard jet nebulizer with a mouthpiece connected to an air compressor.

New Indication(s):

- **Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/vilanterol):** In April 2018, the FDA approved an expanded indication for Trelegy™ Ellipta® for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema. Trelegy™ Ellipta® is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. Trelegy™ Ellipta® was originally FDA approved in September 2017 for the long-term, once-daily, maintenance treatment of COPD patients who are receiving fluticasone furoate/vilanterol and require additional bronchodilation or who are receiving fluticasone furoate/vilanterol and umeclidinium.
- **Arnuity® Ellipta® (fluticasone furoate):** In May 2018, the FDA expanded the approval age for the use of Arnuity® Ellipta®, a once-daily inhaled corticosteroid (ICS) for the maintenance treatment of asthma. The expanded approval is for the use of Arnuity®

Ellipta® as maintenance treatment of asthma as prophylactic therapy in children 5 to 11 years of age, delivered as a 50mcg once-daily dose using the Ellipta® inhaler. Arnuity® Ellipta® (100mcg and 200mcg) was previously FDA approved in August 2014 for the maintenance treatment of asthma in patients 12 years of age and older.

- **Dupixent® (dupilumab):** In October 2018, the FDA approved Dupixent® as an add-on maintenance therapy for the treatment of moderate-to-severe asthma in patients 12 years of age and older with an eosinophilic phenotype or with oral corticosteroid (OCS)-dependent asthma. Dupilumab inhibits the overactive signaling of interleukin-4 (IL-4) and IL-13, 2 key proteins that contribute to the Type 2 (T2) inflammation that may underlie moderate-to-severe asthma. Dupilumab was originally FDA approved in March 2017 for the treatment of adults with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

Guideline Update(s):

- **European guidelines for the treatment of urticaria:** In January 2018, the most recent update of the European guidelines for the treatment of chronic urticaria were published in the journal *Allergy* and marks the fourth update by the group since 2006. The updated 2017 European guidelines were written in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI), the European Union (EU)-founded network of excellence, the Global Allergy and Asthma European Network (GA^2LEN), the European Dermatology Forum (EDF), and the World Allergy Organization (WAO). The American Academy of Allergy, Asthma, and Immunology (AAAAI) and the American College of Allergy, Asthma, and Immunology (ACAAI) also participated in the review and update. Previously in 2014, the American group, along with the Joint Council of Allergy, Asthma, and Immunology (JCAAI), published guidelines (called "Practice Parameters") in *The Journal of Allergy and Clinical Immunology*. As in the 2014 guidelines, the 2017 guidelines continue to recommend a stepwise approach for the treatment of chronic urticaria beginning with avoidance of triggers and treatment with an H_1-antihistamine. Second-generation H_1-antihistamines are recommended over first-generation H_1-antihistamines because of their better safety profile. Approximately 40 to 50% of patients with chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU), will not respond to standard doses of H_1-antihistamines. The next step would be to increase the dose of the second-generation H_1-antihistamine. The guideline states that the majority of patients with urticaria not responding to standard doses will benefit from up-dosing of antihistamines and highlights studies that have documented the benefit of using up to 4-fold higher than licensed approved dosing. In contrast to the 2014 guidelines, and because of insufficient evidence in the literature, the 2017 revision does not recommend adding another second-generation H_1-antihistamine, a H_2-antagonist, a leukotriene receptor antagonist (LTRA), or a first-generation H_1-antihistamine as next steps in treatment of antihistamine-resistant cases of chronic urticaria. While many patients respond to up-dosing with second-generation H_1-antihistamines, around half of chronic urticaria patients will not achieve satisfactory control with antihistamine treatment even at 4 times the standard dose. For such

patients, the 2017 guideline recommends adding Xolair® (omalizumab) to the second-generation H_1-antihistamine. If response to Xolair® is not satisfactory, then cyclosporin A is recommended as an add-on treatment to second-generation H_1-antihistamines, if not contraindicated. The use of systemic corticosteroids in the treatment of chronic urticaria is generally to be avoided, and long-term use of systemic corticosteroids is not recommended because of the myriad of associated side effects. The 2017 guideline suggests that a short course of OCS of up to 10 days may be helpful in reducing disease duration/activity in acute urticaria or exacerbations of CSU.

Market News and Updates[9]

News:

- **December 2018:** The California Technology Assessment Forum (CTAF) convened to review the Institute for Clinical and Economic Review (ICER)'s assessment of biologic therapies for treatment of asthma associated with T2 inflammation in November 2018. The Final Evidence Report and Report-at-a-Glance were published on December 20, 2018 and concluded that all 5 biologic medications currently approved for uncontrolled moderate-to-severe asthma [Dupixent® (dupilumab), Xolair® (omalizumab), Nucala® (mepolizumab), Cinqair® (reslizumab), and Fasenra™ (benralizumab)] modestly reduce asthma exacerbations and improve daily quality of life (QOL). However, the treatments' net prices appear to be way out of alignment with these incremental clinical benefits, according to the report. The report concluded that to align costs with the added benefits for patients, the entire therapy class would need price discounts of at least 50% to reach commonly cited thresholds for cost-effectiveness.

Recommendations

The College of Pharmacy recommends the placement of Lonhala® Magnair® (glycopyrrolate inhalation solution) and Yupelri™ (revefenacin inhalation solution) into Tier-2 of the Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA) Product Based Prior Authorization (PBPA) category with the following criteria:

Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA) Tier-2 Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema; and
3. A 4-week trial of at least 1 LABA and a 4-week trial of 1 LAMA within the past 90 days; or
4. A documented adverse effect, drug interaction, or contraindication to all available Tier-1 products; and
5. A clinical exception may apply for members who are unable to effectively use hand-actuated devices, such as Spiriva® Handihaler®, or who are stable on nebulized therapy.

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

*Combination agents that contain a long-acting beta$_2$ agonist (LABA) ingredient qualify as Tier-1 agents.
Tier-1 medications do not require prior authorization for members with a COPD diagnosis.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
+Unique criteria applies for a diagnosis of asthma.

The College of Pharmacy also recommends updating the current prior authorization criteria for Dupixent® (dupilumab), Arnuity® Ellipta® (fluticasone furoate), ArmonAir™ RespiClick® (fluticasone propionate), AirDuo™ RespiClick® (fluticasone propionate/salmeterol), Breo® Ellipta® (fluticasone furoate/vilanterol), Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/ vilanterol), Xolair® (omalizumab), and Fasenra™ (benralizumab). The following criteria would apply (changes noted in red):

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

1. An FDA approved indication for add-on maintenance treatment of patients 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. The 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 recommended dosing requirements.

Arnuity® Ellipta® (Fluticasone Furoate) and ArmonAir™ RespiClick® (Fluticasone Propionate) Approval Criteria:

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

AirDuo™ RespiClick® (Fluticasone Propionate/Salmeterol) Approval Criteria:

1. An FDA approved diagnosis of asthma; and
2. Member must be at or above the minimum age indicated; and
3. Failure of Advair®, Dulera®, and Symbicort® or a reason why Advair®, Dulera®, and Symbicort® are not appropriate for the member; and
4. Member must have used an inhaled corticosteroid for at least 1 month immediately prior; and
5. Member must be considered uncontrolled by provider [required rescue medication >2 days a week (not for prevention of exercise induced bronchospasms) and/or needed oral systemic corticosteroids]; or
6. A clinical situation warranting initiation with combination therapy due to the severity of asthma.

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

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) or chronic bronchitis and/or emphysema associated with COPD; and
    a. For a diagnosis of COPD or chronic bronchitis and/or emphysema associated with COPD, trials of Advair® and Symbicort®, consisting of at least 30 days each within the last 90 days that did not adequately control COPD symptoms; or
2. An FDA approved diagnosis of asthma in patients 18 years of age and older; and
    a. For a diagnosis of asthma, trials of Advair®, Dulera®, and Symbicort® consisting of at least 30 days each within the last ~~90~~ 120 days that did not adequately control asthma symptoms.

Trelegy™ Ellipta® (Fluticasone Furoate/Umeclidinium/Vilanterol) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, or to reduce exacerbations of COPD in patients with a history of exacerbations; and
2. A 4-week trial of at least 1 long-acting beta$_2$ agonist (LABA) and a 4-week trial of 1 long-acting muscarinic antagonist (LAMA) within the past 90 days used concomitantly with an inhaled corticosteroid (ICS); and
3. A patient-specific, clinically significant reason why the member requires the triple combination therapy in place of the individual components or use of an ICS/LABA combination with a LAMA.

Xolair® (Omalizumab Injection) Approval Criteria [Chronic Idiopathic Urticaria Diagnosis]:

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

Fasenra™ (Benralizumab Injection) Approval Criteria:

1. An FDA approved indication for add-on maintenance treatment of patients with severe eosinophilic phenotype asthma; and
2. Member must be 12 years of age or older; and
3. Member must have a baseline blood eosinophil count of ~~300~~ ≥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 medications, 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. Fasenra™ must be administered in a health care setting by a health care professional prepared to manage anaphylaxis; and
8. Fasenra™ 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. A quantity limit of 1 prefilled syringe per 56 days will apply.

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[1] Lonhala® Magnair® (glycopyrrolate inhalation solution) Prescribing Information. Sunovion. Available online at: https://www.lonhalamagnair.com/LonhalaMagnair-Prescribing-Information.pdf. Last revised 01/2018. Last accessed 01/02/2019.

[2] Yupelri™ (revefenacin inhalation solution) Prescribing Information. Theravance Biopharma Ireland Limited. Available online at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=6dfebf04-7c90-436a-9b16-750d3c1ee0a6&type=display. Last revised 11/2018. Last accessed 01/02/2019.

[3]GlaxoSmithKline. Once-daily Trelegy™ Ellipta® Gains Expanded Indication in the US for the Treatment of Patients with COPD. Available online at: https://www.gsk.com/en-gb/media/press-releases/once-daily-trelegy-ellipta-gains-expanded-indication-in-the-us-for-the-treatment-of-patients-with-copd/. Issued 04/24/2018. Last accessed 01/02/2019.

[4] GlaxoSmithKline. GSK Receives US Approval of Arnuity® Ellipta® for Use in Children From 5 Years Old Who Suffer From Asthma. Available online at: https://www.gsk.com/en-gb/media/press-releases/gsk-receives-us-approval-of-arnuity-ellipta-for-use-in-children-from-5-years-old-who-suffer-from-asthma/. Issued 05/21/2018. Last accessed 01/02/2019.

[5] Sanofi. Sanofi and Regeneron Announce FDA Approval of Dupixent® (Dupilumab), the First Targeted Biologic Therapy for Adults with Moderate-to-Severe Atopic Dermatitis. Available online at: http://www.news.sanofi.us/2017-03-28-Sanofi-and-Regeneron-Announce-FDA-Approval-of-Dupixent-R-dupilumab-the-First-Targeted-Biologic-Therapy-for-Adults-with-Moderate-to-Severe-Atopic-Dermatitis. Issued 03/28/2017. Last accessed 01/02/2019.

[6] Regeneron. FDA Approves Asthma Indication for Dupixent® (Dupilumab). Available online at: https://investor.regeneron.com/news-releases/news-release-details/fda-approves-asthma-indication-dupixentr-dupilumab. Issued 10/19/2018. Last accessed 01/02/2019.

[7] Torjesen I. Chronic Urticaria Guidelines Updated. *Dermatology Times*. Available online at: http://www.dermatologytimes.com/treatment-guidelines/chronic-urticaria-guidelines-updated. Issued 06/04/2018. Last accessed 01/02/2019.

[8] Zuberbier T, et al. The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis, and Management of Urticaria. Available online at: https://onlinelibrary.wiley.com/doi/full/10.1111/all.13397. Issued 01/15/2018. Last accessed 01/02/2019.

[9] Institute for Clinical and Economic Review (ICER). A Look at Biologics for Asthma. Available online at: https://icer-review.org/wp-content/uploads/2018/12/Asthma-RAAG_12202018.pdf. Issued 12/20/2018. Last accessed 01/02/2019.

Appendix G

Vote to Prior Authorize Lokelma™ (Sodium Zirconium Cyclosilicate) and to Update the Veltassa® (Patiromer) Prior Authorization Criteria

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3,4]

Hyperkalemia is a common clinical problem most often a result of impaired urinary potassium excretion due to kidney disease and/or drugs or disorders that inhibit the renin-angiotensin-aldosterone system (RAAS). The urgency of treatment varies with the presence or absence of signs and symptoms of hyperkalemia, severity of potassium level elevation, and the cause of hyperkalemia. Most patients with hyperkalemia have chronic or mild-to-moderate hyperkalemia (potassium >5.5mEq/L) that can be safely managed in an outpatient setting. However, acute hyperkalemia requires urgent correction, and severe hyperkalemia (potassium >6.5mEq/L) should be managed in an inpatient setting. Common etiologies of hyperkalemia include chronic kidney disease (CKD), heart failure, and potassium-altering medications [e.g., angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), potassium supplements, potassium sparing diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs)]. Many patients with hyperkalemia are asymptomatic, but if symptoms occur, they are often non-specific and can range from paresthesia, muscle weakness, and fatigue to electrocardiogram (EKG) changes and fatal ventricular arrhythmias.

Management of hyperkalemia is a patient-specific process usually involving multiple simultaneous strategies including dietary modifications and pharmacological intervention. First-line strategies for patients without a hyperkalemic emergency who can have their potassium lowered slowly include limiting dietary potassium and adding a potassium-eliminating diuretic (thiazide or loop diuretic). Patients who continue to have moderate hyperkalemia despite dietary modification and diuretics can be treated chronically with gastrointestinal (GI) cation exchangers. Patiromer and sodium zirconium cyclosilicate are nonabsorable compounds that exchange calcium or sodium and hydrogen for potassium. Sodium polystyrene sulfonate (SPS) is not recommended for chronic therapy due to severe side effects including intestinal necrosis, which may be fatal.

Veltassa® (patiromer) was approved by the U.S. Food and Drug Administration (FDA) in October 2015 for the treatment of hyperkalemia. Veltassa® is available as a non-absorbable oral powder in single-use packets to be mixed with water and works by exchanging calcium ions for potassium in the intestinal lumen. Patiromer was effective in clinical trials at lowering potassium levels in hyperkalemic patients with CKD who were on at least 1 drug that inhibited the RAAS. Patiromer should be separated from all other medications by at least 3 hours to prevent potential drug interactions. Patiromer has a delayed-onset of action and should not be used as an emergency treatment for life-threatening hyperkalemia.

Lokelma™ (sodium zirconium cyclosilicate) was FDA approved in May 2018 for the treatment of adults with hyperkalemia. Lokelma™ is available as an insoluble, non-absorbable powder for oral suspension in single-use packets to be mixed with water. In general, other oral medications should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate. Sodium zirconium cyclosilicate was shown to be effective in lowering potassium levels in patients with CKD, heart failure, diabetes mellitus, and in those taking RAAS inhibitor therapy. Sodium zirconium cyclosilicate should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

Recommendations

The College of Pharmacy recommends the prior authorization of Lokelma™ (sodium zirconium cyclosilicate) and recommends updating the prior authorization criteria for Veltassa® (patiromer). The following criteria would apply (changes noted in red):

Lokelma™ (Sodium Zirconium Cyclosilicate) Approval Criteria:

1. An FDA approved diagnosis of hyperkalemia; and
2. Medications known to cause hyperkalemia [e.g., angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs)] have been discontinued or reduced to the lowest effective dose where clinically appropriate; and
3. A trial of a potassium-eliminating diuretic or documentation why a diuretic is not appropriate for the member; and
4. Documentation of a low potassium diet; and
5. A quantity limit of 30 packets per month will apply. Quantity limit overrides will be granted to allow for initial 3 times daily dosing.

Veltassa® (Patiromer) Approval Criteria:

1. An FDA approved diagnosis of hyperkalemia; and
2. Medications known to cause hyperkalemia [e.g., angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), aldosterone antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs)] have been discontinued or reduced to the lowest effective dose where clinically appropriate; and
3. A trial of a potassium-eliminating diuretic or documentation why a diuretic is not appropriate for the member; and
4. Documentation of a low potassium diet; and
5. ~~A patient-specific, clinically significant reason why member cannot use sodium polystyrene sulfonate powder which is available without a prior authorization; and~~
6. A quantity limit of 30 packets per month will apply.

[1] Mount D. Treatment and Prevention of Hyperkalemia in Adults. *UpToDate*. Available online at: https://www.uptodate.com/contents/treatment-and-prevention-of-hyperkalemia-in-adults?search=hyperkalemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Last revised 12/18/2017. Last accessed 01/14/2019.

[2] Relypsa Newsroom. Relypsa Announces FDA Approval of Veltassa™ (Patiromer) for Oral Suspension for the Treatment of Hyperkalemia. *Globe Newswire*. Available online at: https://www.relypsa.com/file.cfm/118/docs/RLYP_News_2015_10_21_General_Releases.pdf. Issued 10/21/2015. Last accessed 01/14/2019.

[3] Relypsa Newsroom. FDA Approves Supplemental New Drug Application for Veltassa Removing Boxed Warning Regarding Drug-Drug Interactions. Available online at: http://www.relypsa.com/newsroom/press-releases/112716/. Issued 11/27/2016. Last accessed 01/14/2019.

[4] AstraZeneca. Lokelma™ Approved in the US for the Treatment of Adults with Hyperkalemia. Available online at: https://www.astrazeneca.com/media-centre/press-releases/2018/lokelma-approved-in-the-us-for-the-treatment-of-adults-with-hyperkalaemia-21052018.html. Issued 05/18/2018. Last accessed 01/14/2019.

Appendix H

Vote to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag)

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3]

Tavalisse™ (fostamatinib) is a kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Tavalisse™ is supplied as 100mg and 150mg tablets. The recommended initial dose of fostamatinib is 100mg orally twice daily with or without food. After 4 weeks, it is recommended to increase the dose to 150mg twice daily, if needed, to achieve platelet counts of ≥50 x 10^9/L as necessary to reduce the risk of bleeding. If the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 12 weeks of treatment, it is recommended to discontinue fostamatinib. The Wholesale Acquisition Cost (WAC) per 100mg tablet is $157.50, resulting in a cost per month of $9,450.00.

Doptelet® (avatrombopag) is a thrombopoietin (TPO) receptor agonist indicated for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure. Doptelet® is supplied as 20mg tablets. It is recommended to begin dosing avatrombopag 10 to 13 days prior to a scheduled procedure, and patients should undergo their procedure within 5 to 8 days after the last dose of avatrombopag. The recommended dose of avatrombopag ranges from 40mg to 60mg daily and is based on the patient's platelet count prior to a scheduled procedure. It is recommended to take avatrombopag orally with food once daily for 5 consecutive days. The WAC is $944.00 per tablet, resulting in a cost $9,440.00 to $14,160.00 per treatment, depending on the patient's platelet count.

Mulpleta® (lusutrombopag) is a TPO receptor agonist indicated for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure. Mulpleta® is supplied as 3mg tablets. The recommended dose is 3mg orally once daily with or without food for 7 days. It is recommended to begin lusutrombopag dosing 8 to 14 days prior to a scheduled procedure, and patients should undergo their procedure 2 to 8 days after the last dose of lusutrombopag. The WAC is $1,214.29 per tablet, resulting in a cost of $8,500.03 per treatment.

Market News and Updates[4]

News:

- **December 2018:** The U.S. Food and Drug Administration (FDA) expanded the indication of Nplate® (romiplostim) to include the treatment of pediatric patients 1 year of age and older with ITP for a minimum of 6 months and who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Recommendations

The College of Pharmacy recommends the prior authorization of Tavalisse™ (fostamatinib), Doptelet® (avatrombopag), and Mulpleta® (lusutrombopag) with the following criteria:

Tavalisse™ (Fosamatinib) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment; and
2. Member must be 18 years of age or older (Tavalisse™ is not recommended for use in patients younger than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies); and
3. Member must have a clinical diagnosis of persistent/chronic ITP for at least 3 months; and
4. Previous insufficient response with at least 2 of the following treatments:
    a. Corticosteroids; or
    b. Immunoglobulins; or
    c. Splenectomy; or
    d. Thrombopoietin receptor agonists; and
5. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
6. Must be prescribed by, or in consultation with, a hematologist or oncologist;
7. Prescriber must verify the member's complete blood count (CBC), including platelet counts, will be monitored monthly until a stable platelet count (at least 50 X 10^9/L) is achieved and will be monitored regularly thereafter; and
8. Prescriber must verify liver function tests (LFTs) (e.g., ALT, AST, bilirubin) will be monitored monthly; and
9. Prescriber must verify member's blood pressure will be monitored every 2 weeks until establishment of a stable dose, then monthly thereafter; and
10. Female members must not be pregnant and must have a negative pregnancy test immediately prior to therapy initiation. Female members of reproductive potential must be willing to use effective contraception while on therapy and for at least 1 month after therapy completion; and
11. Prescriber must verify member is not breastfeeding; and
12. Member must not be taking strong CYP3A4 inducers (e.g., rifampicin) concurrently with Tavalisse™; and
13. Initial approvals will be for the duration of 12 weeks; and
14. Discontinuation criteria:
    a. Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 12 weeks of therapy; and
15. A quantity limit of 2 tablets daily will apply.

Doptelet® (Avatrombopag) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure; and
2. A patient-specific, clinically significant reason why the member cannot use Mulpleta® (lusutrombopag); and

3. Date of procedure must be listed on the prior authorization request; and
4. Prescriber must verify the member will have the procedure within 5 to 8 days after the member receives the last dose of Doptelet®; and
5. Member must have a baseline platelet count <50 X 10^9/L (recent baseline platelet count must be provided); and
6. Must be prescribed by, or in consultation with, a hematologist, gastroenterologist, or hepatologist; and
7. Doptelet® must not be used in an attempt to normalize platelet counts; and
8. A quantity limit of 15 tablets per scheduled procedure will apply.

Mulpleta® (Lusutrombopag) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure; and
2. Date of procedure must be listed on the prior authorization request; and
3. Prescriber must verify the member will have the procedure 2 to 8 days after the member receives the last dose of Mulpleta®; and
4. Member must have a baseline platelet count <50 X 10^9/L (recent baseline platelet count must be provided); and
5. Must be prescribed by, or in consultation with, a hematologist, gastroenterologist, or hepatologist; and
6. Mulpleta® must not be used in an attempt to normalize platelet counts; and
7. A quantity limit of 7 tablets per scheduled procedure will apply.

Additionally, the College of Pharmacy recommends removing the prior authorization for Nplate® (romiplostim) and Promacta® (eltrombopag), based on net cost and appropriate utilization.

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[1] Tavalisse™ (fostamatinib) Prescribing Information. Rigel Pharmaceuticals, Inc. Available online at: https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf. Last revised 04/2018. Last accessed 01/15/2019.

[2] Doptelet® (avatrombopag) Prescribing Information. AkaRx, Inc. Available online at: https://dova.com/pdf/doptelet-fda-prescribing-information.pdf. Last revised 05/2018. Last accessed 01/15/2019.

[3] Mulpleta® (lusutrombopag) Prescribing Information. Shionogi & Co., Ltd. Available online at: https://www.shionogi.com/pdf/pi/wp-content/themes/pdfs/mulpleta.pdf. Last revised 07/2018. Last accessed 01/15/2019.

[4] Rossi K. FDA Green Lights Romiplostim for Pediatric Patients with Immune Thrombocytopenia. *Rare Disease Report*. Available online at: https://www.raredr.com/news/fda-green-lights-romiplostim-pediatric-patients-immune-thrombocytopenia. Issued 12/14/2018. Last accessed 01/15/2019.

Appendix I

Vote to Prior Authorize Carbaglu® (Carglumic Acid)

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3,4]

N-acetylglutamate synthase (NAGS) deficiency is a rare genetic disorder characterized by complete or partial lack of the enzyme NAGS. The lack of NAGS enzyme results in excessive ammonia in the blood. Treatment of NAGS deficiency is aimed at preventing excessive ammonia from being formed or at removing excessive ammonia during hyperammonemic episodes.

Carbaglu® (carglumic acid) was approved by the U.S. Food and Drug Administration (FDA) in 2010 and is the only FDA approved medication for the chronic treatment of patients with NAGS deficiency to reduce blood ammonia levels. Carglumic acid is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator indicated as adjunctive therapy for the acute treatment of hyperammonemia due to NAGS deficiency and the maintenance treatment of chronic hyperammonemia due to NAGS deficiency. Carbaglu® is supplied as a 200mg scored tablet for oral suspension, and the recommended dosing for acute and maintenance therapy is based on weight and clinical titration. The recommended dosage of carglumic acid for the acute treatment of hyperammonemia is 100 to 250mg/kg/day titrated based on plasma ammonia level and clinical symptoms. The recommended maintenance dose of carglumic acid for chronic hyperammonemia is 10 to 100mg/kg/day titrated to a normal plasma ammonia level for the patient's age.

Cost:

Medication	Cost Per Tablet	Acute Treatment Cost Per 3 Days	Maintenance Treatment Cost Per 30 Days
Carbaglu® (carglumic acid) 200mg tablet	**$192.35**	**$4,616.40 - $10,963.95**	**$5,770.35 - $46,164.00**

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.
Dosing based on average weight of 4-year-old male (15kg).

Recommendations

The College of Pharmacy recommends the prior authorization of Carbaglu® (carglumic acid) with the following criteria:

Carbaglu® (Carglumic Acid) Approval Criteria:

1. An FDA approved diagnosis of N-acetylglutamate synthase (NAGS) deficiency; and
2. Carbaglu® must be prescribed by, or in consultation with, a geneticist; and
3. Documentation of active management with a low protein diet; and
4. Initial approvals will be for the duration of 1 year. After that time, reauthorization will require the prescriber to verify the member is responding well to therapy.

[1] N-acetylglutamate synthase deficiency. National Organization for Rare Disorders. Available online at: https://rarediseases.org/rare-diseases/n-acetylglutamate-synthetase-deficiency/. Last accessed 01/18/2019.

[2] N-acetylglutamate synthase deficiency. NIH U.S. National Library of Medicine. *Genetics Home Reference.* Available online at: https://ghr.nlm.nih.gov/condition/n-acetylglutamate-synthase-deficiency#statistics. Last revised 01/15/2019. Last accessed 01/18/2019.

[3] Carbaglu® Prescribing Information. Recordati Rare Diseases, Inc. Available online at: https://www.carbaglu.net/wp-content/uploads/2016/04/carbaglu-pi.pdf. Last revised 11/2017. Last accessed 01/15/2019.

[4] Centers for Disease Control and Prevention (CDC). 2 to 20 years: Boys Stature-for-age and Weight-for-age percentiles. Available online at: https://www.cdc.gov/growthcharts/data/set1clinical/cj41c021.pdf. Last revised 11/21/2000. Last accessed 02/04/2019.

Appendix J

Vote to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion)

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3]

Xelpros™ (latanoprost 0.005% emulsion) is a prostaglandin $F_{2\alpha}$ analog indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT). Xelpros™ is supplied as an isotonic, sterile, buffered, preservative-free emulsion of latanoprost 0.005% (50mcg/mL) in a 2.5mL bottle with a dropper tip. The recommended dosage is 1 drop into the affected eye(s) once daily in the evening. The dosage of Xelpros™ should not exceed once daily. Xelpros™ is preservative-free and does not contain benzalkonium chloride (BAK). BAK is a preservative that has been associated with adverse effects and is in many topical treatments for glaucoma.

Cost Comparison:

Medication	Cost Per Milliliter	Cost Per Bottle
Xelpros™ (latanoprost 0.005% emulsion)	**$22.00**	**$55.00**
latanoprost 0.005% solution (generic Xalatan®)	$2.04	$5.10

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 following changes to the Glaucoma Medications Product Based Prior Authorization (PBPA) category:

1. The placement of Xelpros™ (latanoprost 0.005% emulsion) into the Special Prior Authorization (PA) Tier. Current Special PA criteria will apply.
2. Moving methazolamide (Neptazane®) from Tier-1 to the Special PA Tier based on net cost. Current Special PA criteria will apply. Current users will be grandfathered.
3. Removing Travatan® (travoprost 0.004%) based on product discontinuation.

Proposed changes are shown in red in the following Glaucoma Medications Tier Chart.

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
Alpha-2 Adrenergic Agonists		
brimonidine (Alphagan® 0.2%)	apraclonidine (Iopidine® 0.5%, 1%)	brimonidine (Alphagan-P® 0.15%)
brimonidine (Alphagan-P® 0.1%)		
brimonidine/timolol (Combigan® 0.2%/0.5%)		
brinzolamide/brimonidine (Simbrinza® 0.2%/1%)		

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
Beta-Blockers		
brimonidine/timolol (Combigan® 0.2%/0.5%)	betaxolol (Betoptic® 0.5%, Betoptic-S® 0.25%)	dorzolamide/timolol (Cosopt® PF 2%/0.5%)
carteolol (Ocupress® 1%)		timolol maleate (Timoptic Ocudose® 0.25%, 0.5%; Timoptic-XE® 0.25%, 0.5%)
dorzolamide/timolol (Cosopt® 22.3mg/mL/6.8mg/mL)		
levobunolol (Betagan® 0.25%, 0.5%)		
timolol maleate (Istalol® 0.5%, Timoptic® 0.25%, 0.5%)		
Carbonic Anhydrase Inhibitors		
acetazolamide (Diamox® 500mg caps; 125mg, 250mg tabs)+		dorzolamide/timolol (Cosopt® PF 2%/0.5%)
brinzolamide (Azopt® 1%)		**methazolamide (Neptazane® 25mg, 50mg tabs)+**
brinzolamide/brimonidine (Simbrinza® 0.2%/1%)		
dorzolamide (Trusopt® 2%)		
dorzolamide/timolol (Cosopt® 22.3mg/mL/6.8mg/mL)		
Cholinergic Agonists/Cholinesterase Inhibitors		
echothiophate iodide (Phospholine Iodide® 0.125%)	pilocarpine (Isopto® Carpine 1%, 2%, 4%)	
Prostaglandin Analogs		
latanoprost (Xalatan® 0.005%)	bimatoprost (Lumigan® 0.01%, 0.03%)	**latanoprost (Xelpros™ 0.005%)**
travoprost (Travatan-Z® 0.004%)	tafluprost (Zioptan® 0.0015%)	latanoprostene bunod (Vyzulta® 0.024%)
	~~**travoprost (Travatan® 0.004%)**~~	
Rho Kinase Inhibitors		
netarsudil (Rhopressa® 0.02%)		

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

+Indicates available oral medications.

Please note: Combination products are included in both applicable pharmaceutical classes; therefore, combination products are listed twice in the tier chart.

caps = capsules; tabs = tablets; PA = prior authorization

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[1] Xelpros™ Prescribing Information. Sun Pharmaceutical Industries, Inc. Available online at: https://myxelpros.com/pdf/XelprosPI.pdf. Last revised 09/2018. Last accessed 01/02/2019.

[2] Rouland JF, Traverso CE, Stalmans I, et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol* 2013; 97:196-200.

[3] Walimbe T, Chelerkar V, Bhagat P, et al. Effect of benzalkonium chloride-free latanoprost ophthalmic solution on ocular surface in patients with glaucoma. *Clin Ophthalmol* 2016; 10:821-827.

Appendix K

Vote to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector]

Oklahoma Health Care Authority
February 2019

Introduction[1,2]

Makena® (hydroxyprogesterone caproate sub-Q auto-injector) was approved by the U.S. Food and Drug Administration (FDA) in February 2018 to reduce the risk of preterm birth in women pregnant with a single baby who have a history of singleton spontaneous preterm birth. The prefilled Makena® sub-Q auto-injector offers a new administration option for patients and providers and contains a shorter, thinner, non-visible needle compared to the intramuscular (IM) Makena® injection. Makena® 250mg/mL IM injection was FDA approved in 2011 and is available in a 1mL single-dose vial (SDV) and a 5mL multi-dose vial (MDV). The effectiveness of Makena® is based on improvement in the proportion of women who delivered <37 weeks of gestation. There are no controlled trials demonstrating a direct clinical benefit, such as improvement in neonatal mortality and morbidity. While there are many risk factors for preterm birth, the safety and efficacy of Makena® have been demonstrated only in women with a prior spontaneous singleton preterm birth, and Makena® is not indicated for women with multiple gestations or other risk factors for preterm birth. The most common adverse effect reported with the use of Makena® sub-Q auto-injector (and higher than with the use of Makena® IM injection) was injection site pain. Makena® sub-Q auto-injector is supplied as a 275mg/1.1mL prefilled, single-use auto-injector. The recommended dosing of Makena® sub-Q auto-injector is 275mg (1.1mL) administered sub-Q via the auto-injector once weekly in the back of either upper arm by a health care provider, beginning between 16 weeks, 0 days of gestation and 20 weeks, 6 days of gestation and continuing until week 37 (through 36 weeks, 6 days) of gestation or delivery, whichever occurs first. The Wholesale Acquisition Cost (WAC) of Makena® sub-Q auto-injector is $803.00 per 1.1mL single-use auto-injector.

Recommendations

The College of Pharmacy recommends the prior authorization of Makena® (hydroxyprogesterone caproate sub-Q auto-injector) with the following criteria (changes noted in red):

Makena® [Hydroxyprogesterone Caproate Intramuscular (IM) Injection and Subcutaneous (Sub-Q) Auto-Injector] Approval Criteria:

1. Documented history of previous singleton spontaneous preterm delivery (SPTD) prior to 37 weeks gestation; and
2. Current singleton pregnancy; and
3. Gestational age between 16 weeks, 0 days and 26 weeks, 6 days of gestation; and
4. Authorizations will be for once weekly administration by a health care professional through 36 weeks, 6 days of gestation; and

5. For Makena® sub-Q auto-injector:
    a. Initial dose must be administered by a health care professional; and
    b. Member and caregiver must be trained by a health care professional on sub-Q administration and storage of Makena® sub-Q auto-injector; and
    c. A patient-specific, clinically significant reason why Makena® IM injection cannot be used must be provided.* (*The manufacturer of Makena® has currently provided a supplemental rebate to make the net cost per injection of the sub-Q auto-injector equivalent to the IM injection and therefore make the sub-Q auto-injector available with the current Makena® criteria; however, use of Makena® sub-Q auto-injector will require a reason why Makena® IM injection cannot be used if the manufacturer chooses not to participate in supplemental rebates.)

[1] AMAG Pharmaceuticals News Release. AMAG Pharmaceuticals Announces FDA Approval of Makena® (Hydroxyprogesterone Caproate Injection) Subcutaneous Auto-Injector to Reduce the Risk of Preterm Birth in Certain At-Risk Women. Available online at: https://www.amagpharma.com/news/amag-pharmaceuticals-announces-fda-approval-of-makena-hydroxyprogesterone-caproate-injection-subcutaneous-auto-injector-to-reduce-the-risk-of-preterm-birth-in-certain-at-risk-women/. Issued 02/14/2018. Last accessed 01/10/2019.

[2] Makena® (Hydroxyprogesterone Caproate Injection) Prescribing Information. AMAG Pharmaceuticals. Available online at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a1998c1d-8337-4f00-8dcb-af3b54d39b77. Last revised 02/2018. Last accessed 01/10/2019.

Appendix L

Vote to Prior Authorize Akynzeo® IV [Fosnetupitant/ Palonosetron Injection for Intravenous (IV) Use]

Oklahoma Health Care Authority
February 2019

Introduction[1,2]

Akynzeo® IV (fosnetupitant/palonosetron IV) was approved by the U.S. Food and Drug Administration (FDA) in April 2018 for use in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC). Akynzeo® (netupitant/ palonosetron) oral capsules were first FDA approved in 2014 for use in combination with dexamethasone in adults for the prevention of nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC. Akynzeo® IV is supplied as a single-dose vial (SDV) containing lyophilized powder for reconstitution prior to IV infusion and should be infused over 30 minutes, starting 30 minutes before chemotherapy, or 1 Akynzeo® capsule should be taken by mouth, with or without food, 1 hour before chemotherapy. The Wholesale Acquisition Cost (WAC) of Akynzeo® IV is $510 per SDV.

Cost Comparison

The following table shows a cost comparison of various oral anti-emetic medications used for chemotherapy-induced nausea and vomiting (CINV). Dronabinol oral capsules are currently available generically from multiple pharmaceutical companies. Most SoonerCare prior authorization requests for dronabinol for CINV are for twice daily dosing and most members have previously failed ondansetron for CINV prior to requesting dronabinol.

Medication	Cost Per Capsule	Cost Per Month or Per Chemotherapy Cycle
dronabinol 2.5mg capsule	$1.69	$101.40[+]
dronabinol 5mg capsule	$3.52	$211.20[+]
dronabinol 10mg capsule	$5.41	$324.60[+]
aprepitant 125mg/80mg capsule dose pack[¥]	$161.25	$483.75[¥]
Cesamet® (nabilone) 1mg capsule[Ω]	$39.20	$705.60[Ω]

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), Wholesale Acquisition Costs (WAC), or State Maximum Allowable Costs (SMAC) if NADAC unavailable.
[+]Cost per month for dronabinol capsules is based on twice daily dosing (#60 capsules for a 30-day supply).
[¥]Aprepitant dose pack includes (1) 125mg capsule and (2) 80mg capsules; aprepitant recommended dosing for CINV is 125mg on day 1 of chemotherapy cycle (1 hour prior to chemotherapy) and 80mg on days 2 and 3. Cost per chemotherapy cycle is based on 3 days of therapy (#3 capsules for a 3-day supply).
[Ω]Nabilone recommended dosing for CINV is 1 to 2mg twice daily (first dose taken 1 to 3 hours prior to chemotherapy); may administer up to 3 times daily during the entire course of each cycle of chemotherapy and continue up to 48 hours after the last dose of chemotherapy (maximum of 6mg per day in 3 divided doses). Cost per chemotherapy cycle is based on 3 days of therapy at a dose of 6mg per day (#18 capsules for a 3-day supply).

Recommendations

The College of Pharmacy recommends the prior authorization of Akynzeo® IV (fosnetupitant/palonosetron IV) with the following criteria (changes noted in red):

Akynzeo® (Netupitant/Palonosetron) and Akynzeo® IV (Fosnetupitant/Palonosetron) Approval Criteria:

1. An FDA approved indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy; and
2. For Akynzeo® oral capsules, a previously failed trial of oral aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why oral aprepitant cannot be used must be provided; and
3. For Akynzeo® IV, a previously failed trial of intravenous (IV) fosaprepitant (Emend® IV) that resulted in an inadequate response, or a patient-specific, clinically significant reason why IV fosaprepitant cannot be used must be provided; and
4. Akynzeo® IV will require a patient-specific, clinically significant reason why the oral capsule formulation cannot be used; and
5. Approval length will be based on duration of need; and
6. A quantity limit of 1 capsule or vial per chemotherapy cycle will apply; and
7. Akynzeo® oral capsules will not require prior authorization for members with cancer and claims will pay at the point of sale if the member has a reported oncology diagnosis within the past 6 months of claims history.
    a. Based on the current low net cost, Akynzeo® oral capsules will not require prior authorization for members with cancer; however, Akynzeo® oral capsules will follow the original criteria and require a previously failed trial of oral aprepitant if the net cost increases compared to other available products.

Additionally, the College of Pharmacy recommends updating the approval criteria for Marinol® (dronabinol) based on generic availability and low net cost (changes noted in red):

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

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

8. For Syndros® (dronabinol) oral solution, an age restriction of 6 years and younger will apply. Members older than 6 years of age will require a patient-specific, clinically significant reason why dronabinol oral capsules cannot be used.

[1] Helsinn News Release. Helsinn Group Announces the FDA Approval of the IV Formulation of Akynzeo® (Fosnetupitant/Palonosetron) in the United States. *GlobeNewswire*. Available online at: https://globenewswire.com/news-release/2018/04/20/1483382/0/en/Helsinn-Group-announces-the-FDA-approval-of-the-IV-formulation-of-AKYNZEO-fosnetupitant-palonosetron-in-the-United-States.html. Issued 04/20/2018. Last accessed 01/10/2019.

[2] Akynzeo® (Netupitant/Palonosetron Capsules; Fosnetupitant/Palonosetron for Injection) Prescribing Information. Helsinn Group. Available online at: https://www.akynzeo.com/hcp/assets/pdf/Prescribing_Information.pdf. Last revised 04/2018. Last accessed 01/10/2019.

Appendix M

Fiscal Year 2018 Annual Review of Anticonvulsants and 30-Day Notice to Prior Authorize Epidiolex® (Cannabidiol), Diacomit® (Stiripentol), and Sympazan™ (Clobazam Oral Film)

Oklahoma Health Care Authority
February 2019

Current Prior Authorization Criteria

1. Anticonvulsants are included in the mandatory generic plan.
    a. All brand-name anticonvulsants (with a generic equivalent) will require prior authorization.
        i. Brand-name anticonvulsants (with a generic equivalent) will be approved for all members who are currently stable on these medications and have a seizure diagnosis.
2. Prior authorization will be required for certain non-standard dosage forms of anticonvulsants when the medication is available in standard dosage forms.
    a. Members 12 years of age and older must have a documented medical reason demonstrating the need for non-standard dosage forms.
    b. Criteria for approval of extended-release formulations:
        i. Previously stabilized on the short-acting formulation; and
        ii. Dosing is not more than once daily; and
        iii. A reason why the short-acting formulation is not adequate must be provided; and
        iv. Dose packs will not be approved if standard dosage forms are available.
3. Quantity limit restrictions will be placed on lower strength tablets and capsules. The highest strengths will continue to have no quantity restrictions unless a maximum dose is specified for a particular medication.

Briviact® (Brivaracetam) Approval Criteria:

1. An FDA approved diagnosis of partial-onset seizures; and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least 3 other anticonvulsants; and
4. Members currently stable on Briviact® and who have a seizure diagnosis will be grandfathered; and
5. Approval length for Briviact® intravenous (IV) will be for a maximum of 7 days of therapy. Further approval may be granted if prescriber documents an ongoing need for Briviact® IV therapy over Briviact® oral formulations.

Carnexiv™ (Carbamazepine Injection) Approval Criteria:

1. An FDA approved indication; and
2. Initial prescription must be written by a neurologist; and
3. Member must currently be stable on oral carbamazepine; and

4. Member must have a current condition in which oral administration is temporarily not feasible and needing Carnexiv™ for replacement therapy; and
5. Approval length will be for a maximum of 7 days of therapy. Further approval may be granted if prescriber documents an ongoing need for Carnexiv™ intravenous (IV) therapy over carbamazepine oral formulations.

Aptiom® (Eslicarbazepine) Approval Criteria:

1. An FDA approved diagnosis of partial-onset seizures; and
2. Member must not currently be taking oxcarbazepine (concurrent use is contraindicated); and
3. A patient-specific, clinically significant reason why member cannot use oxcarbazepine must be provided; and
4. Members currently stable on Aptiom® and who have a seizure diagnosis will be grandfathered; and
5. A quantity limit of 30 tablets per 30 days will apply on the lower strength tablets (200mg and 400mg) and 60 tablets per 30 days on the higher strength tablets (600mg and 800mg).

Afinitor® (Everolimus) Approval Criteria [Tuberous Sclerosis Complex (TSC)-Associated Partial-Onset Seizures Diagnosis]:

1. An FDA approved diagnosis of TSC-associated partial-onset seizures; and
2. Initial prescription must be written by a neurologist or neuro-oncologist; and
3. Member must have failed therapy with at least 3 other anticonvulsants; and
4. Afinitor® must be used as adjunctive treatment; and
5. The member must not be taking any P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) concurrently with Afinitor®; and
6. The member must not be taking St. John's wort concurrently with Afinitor®; and
7. The prescriber must verify that Afinitor® trough levels and adverse reactions (e.g., non-infectious pneumonitis, stomatitis, hyperglycemia, dyslipidemia, thrombocytopenia, neutropenia, febrile neutropenia) will be monitored, and dosing changes or discontinuations will correspond with recommendations in the drug labeling; and
8. Verification from the prescriber that female members will use contraception while receiving Afinitor® therapy and for 8 weeks after the last dose of Afinitor® and that male members with female partners of reproductive potential will use contraception while receiving Afinitor® therapy and for 4 weeks after the last dose of Afinitor®; and
9. The member's recent body surface area (BSA) must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling; and
10. Members currently stable on Afinitor® and who have a seizure diagnosis will be grandfathered; and
11. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of the medication.

Felbatol® (Felbamate) Approval Criteria:

1. Initial prescription must be written by a neurologist; and

2. Member must have failed therapy with at least 3 other anticonvulsants; and
3. Members currently stable on Felbatol® and who have a seizure diagnosis will be grandfathered.

Vimpat® (Lacosamide) Approval Criteria:

1. An FDA approved diagnosis of partial-onset seizures; and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least 1* other anticonvulsant; and (*The manufacturer of Vimpat® has currently provided a supplemental rebate to require a trial with 1 other anticonvulsant; however, Vimpat® will follow the original criteria and require trials with 3 other anticonvulsants if the manufacturer chooses not to participate in supplemental rebates.); and
4. Members currently stable on Vimpat® and who have a seizure diagnosis will be grandfathered.

Spritam® (Levetiracetam) Approval Criteria:

1. An FDA approved diagnosis of partial-onset seizures, myoclonic seizures, or primary generalized tonic-clonic (PGTC) seizures; and
2. A patient-specific, clinically significant reason why the member cannot use generic formulations of levetiracetam must be provided; and
3. A quantity limit of 60 tablets per 30 days will apply.

Oxtellar XR® (Oxcarbazepine Extended-Release) Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use the short-acting formulation must be provided; and
2. A quantity limit of 30 tablets per 30 days will apply on the lower strength tablets (150mg and 300mg).

Fycompa® (Perampanel) Approval Criteria*:

1. An FDA approved indication of 1 of the following:
    a. Partial-onset seizures with or without secondarily generalized seizures; or
    b. Adjunctive therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures; and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least 1** other anticonvulsant; and (**The manufacturer of Fycompa® has currently provided a supplemental rebate to require a trial with 1 other anticonvulsant; however, Fycompa® will follow the original criteria and require trials with 3 other anticonvulsants if the manufacturer chooses not to participate in supplemental rebates.)
4. For Fycompa® oral suspension, an age restriction of 12 years and younger will apply. Members older than 12 years of age will require a patient-specific, clinically significant reason why the member cannot take the oral tablet formulation; and
5. Members currently stable on Fycompa® and who have a seizure diagnosis will be grandfathered.

(*The manufacturer of Fycompa® has currently provided a value-based agreement to make Fycompa® available without prior authorization; however, Fycompa® will follow the original prior authorization criteria if the manufacturer chooses not to participate in the value-based agreement.)

Banzel® (Rufinamide) Approval Criteria:

1. An FDA approved indication of adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS); and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least 3 other anticonvulsants; and
4. Members currently stable on Banzel® and who have a seizure diagnosis will be grandfathered.

Qudexy® XR (Topiramate Extended-Release) Approval Criteria:

1. An FDA approved indication of 1 of the following:
    a. Partial-onset or primary generalized tonic-clonic (PGTC) seizures; or
    b. Adjunctive therapy in seizures associated with Lennox-Gastaut syndrome (LGS); or
    c. Prophylaxis of migraine headaches; and
2. A patient-specific, clinically significant reason why the member cannot use the short-acting formulation, Topamax® (topiramate), must be provided; and
3. A quantity limit of 30 capsules per 30 days will apply on the lower strength capsules (25mg, 50mg, and 100mg) and 60 capsules per 30 days on the higher strength capsules (150mg and 200mg).

Trokendi XR® (Topiramate Extended-Release) Approval Criteria:

1. An FDA approved indication of 1 of the following:
    a. Partial-onset or primary generalized tonic-clonic (PGTC) seizures; or
    b. Adjunctive therapy in seizures associated with Lennox-Gastaut Syndrome (LGS); or
    c. Prophylaxis of migraine headaches; and
2. A patient-specific, clinically significant reason why the member cannot use the short-acting formulation, Topamax® (topiramate), must be provided; and
3. A quantity limit of 30 capsules per 30 days will apply on the lower strength capsules (25mg, 50mg, and 100mg) and 60 capsules per 30 days on the higher strength capsules (200mg).

Sabril® (Vigabatrin) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Refractory complex seizures in adults and pediatric patients 10 years of age or older; or
    b. Infantile spasms in children 1 month to 2 years of age; and
2. Authorization of generic vigabatrin (in place of brand Sabril®) will require a patient-specific, clinically significant reason why the member cannot use the brand formulation (brand formulation is preferred); and
3. Members with refractory complex seizures must have previous trials of at least 3 other anticonvulsants; and

4. Prescription must be written by a neurologist; and
5. Members currently stable on Sabril® will be grandfathered; and
6. Member, prescriber, and pharmacy must all register in the SABRIL REMS program and maintain enrollment throughout therapy.

Utilization of Anticonvulsants: Fiscal Year 2018

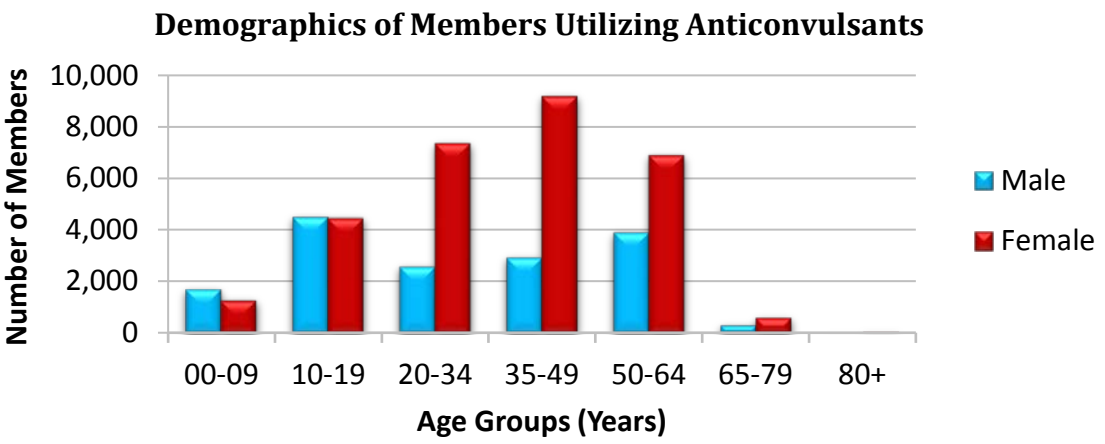
The following utilization data includes anticonvulsants used for all diagnoses and does not differentiate between epilepsy diagnoses and other diagnoses, for which use may be appropriate. Please note, the following utilization data does not include Afinitor® (everolimus) for the diagnosis of tuberous sclerosis complex (TSC)-associated partial-onset seizures; utilization data for everolimus is included in the annual review of oncology medications.

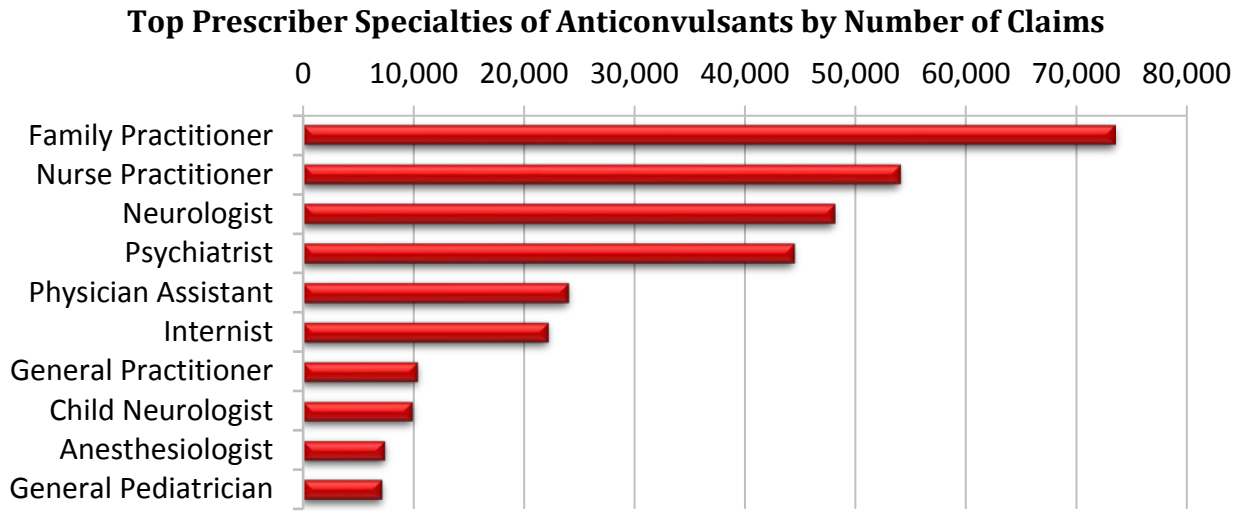
Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	46,703	332,004	$25,078,584.72	$75.54	$2.50	31,459,114	10,044,857
2018	45,800	329,439	$26,394,485.30	$80.12	$2.63	31,734,181	10,023,353
% Change	**-1.90%**	**-0.80%**	**5.20%**	**6.10%**	**5.20%**	**0.90%**	**-0.20%**
Change	**-903**	**-2,565**	**$1,315,900.58**	**$4.58**	**$0.13**	**275,067**	**-21,504**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Fiscal Year 2017 = 07/01/2016 to 06/30/2017; Fiscal Year 2018 = 07/01/2017 to 06/30/2018

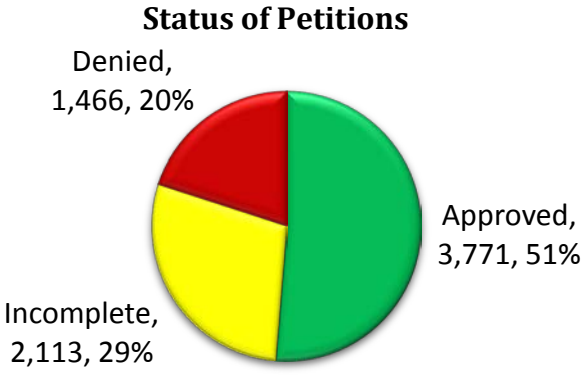
- Please note, due to new federal regulations, a new pricing methodology for pharmacy claims reimbursement was implemented by SoonerCare on January 3, 2017. Ingredient reimbursement changed from an estimated acquisition cost (EAC) to an actual acquisition cost (AAC). In addition, the professional dispensing fee increased from $3.60 in 2016 to $10.55 effective January 2017; professional dispensing fees are included in the reimbursement totals in the following report. The impact of the pricing methodology and dispensing fee change are estimated to be budget neutral. This change in reimbursement should be considered when evaluating reimbursement changes from year to year. Medications with a very low cost per claim and large volume of claims will appear to increase in price due to the increase in dispensing fee; however, these increases will be neutralized by changes in ingredient reimbursement for higher cost medications.





Prior Authorization of Anticonvulsants

There were 7,350 prior authorization requests submitted for anticonvulsants during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12]

Patent Expiration(s):

- Lyrica® [pregabalin immediate-release (IR) capsules]: June 2019
- Briviact® (brivaracetam tablets): February 2021
- Vimpat® (lacosamide tablets): March 2022
- Banzel® (rufinamide tablets): May 2023
- Sympazan™ (clobazam oral films): April 2024
- Diacomit® (stiripentol capsules): August 2025* (*Diacomit® does not have any unexpired patents; however, it does currently have exclusivity through August 2025.)
- Fycompa® (perampanel tablets): July 2026
- Oxtellar XR® [oxcarbazepine extended-release (ER) tablets]: April 2027
- Trokendi XR® (topiramate ER capsules): April 2028
- Aptiom® (eslicarbazepine tablets): August 2032
- Carnexiv™ (carbamazepine injection): February 2033
- Qudexy® XR (topiramate ER capsules): March 2033
- Spritam® (levetiracetam tablets for oral suspension): March 2034
- Epidiolex® (cannabidiol oral solution): June 2035

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

- **April 2018:** The FDA approved Afinitor Disperz® (everolimus tablets for oral suspension) for the adjunctive treatment of adult and pediatric patients ages 2 years and older with TSC-associated partial onset seizures. Afinitor Disperz® is the first approved pharmacologic therapy in the United States specifically indicated for the treatment of this condition. TSC is a rare genetic disorder, and approximately 85% of patients with TSC are affected by epilepsy. Afinitor® (everolimus tablets) was first FDA approved in 2010; Afinitor Disperz® was first FDA approved in 2012. Everolimus is indicated for several oncology diagnoses, as well as for the prophylaxis of liver and renal transplant rejection, and is reviewed annually with the oncology medications (approval criteria for the diagnosis of TSC-associated partial seizures is included in the *Current Prior Authorization Criteria* section of this report).
- **June 2018:** The FDA approved Epidiolex® [cannabidiol (CBD) oral solution] for the treatment of seizures associated with 2 rare and severe forms of epilepsy, Lennox-Gastaut syndrome (LGS) and Dravet syndrome, in patients 2 years of age and older. This is the first FDA-approved drug that contains a purified drug substance from marijuana, and it is also the first FDA approval of a drug for the treatment of patients with Dravet syndrome. CBD is a chemical component of the *Cannabis sativa* plant, more commonly known as marijuana; however, CBD does not cause intoxication or euphoria that comes from tetrahydrocannabinol (THC), which is the primary psychoactive component of marijuana. LGS begins in childhood and is characterized by multiple types of seizures. Patients with LGS begin having frequent seizures in early childhood, usually between ages 3 and 5 years, and more than 75% of patients with LGS have tonic seizures. Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent febrile seizures. Later, other types of seizures typically arise, including myoclonic seizures and status epilepticus may also occur. In September 2018, the Drug

Enforcement Administration (DEA) placed Epidiolex® in schedule V of the Controlled Substances Act (CSA), the least restrictive schedule of the CSA. The DEA was required to take some scheduling action related to CBD once the FDA approved Epidiolex® because CBD was classified as schedule I, which by definition is a substance without an accepted medical use. The DEA limited the rescheduling of CBD to a specific formulation of an FDA-approved drug product (FDA-approved drugs that contain CBD derived from cannabis and no more than 0.1% THC) and re-emphasized that except for this specific formulation, CBD remains a schedule I substance. In November 2018, GW Pharmaceuticals, along with its U.S. subsidiary, Greenwich Biosciences, announced that Epidiolex® was now available by prescription in the United States.

- **August 2018:** The FDA approved Diacomit® (stiripentol) for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. Stiripentol was previously approved for adjunctive treatment with clobazam and valproate for Dravet syndrome in 27 countries in the European Union (2007), Canada (2012), and Japan (2012). Stiripentol is a new molecular entity developed by Biocodex, an independent pharmaceutical company headquartered in France that has an American subsidiary located in Redwood City, California; Biocodex received Orphan Drug designation for stiripentol from the FDA in 2008.
- **September 2018:** The FDA expanded the indication of Fycompa® (perampanel) for the treatment of partial-onset seizures with or without secondarily generalized seizures in pediatric patients 4 years of age and older. The approval includes both the oral tablet and oral suspension formulations. Perampanel was previously FDA approved in 2017 for this indication in patients 12 years of age and older. The current approval criteria for Fycompa® oral suspension reflects this expanded indication to include an age restriction of 12 years of age and younger (see *Current Prior Authorization Criteria* section).
- **October 2018:** The FDA approved generic formulations of clobazam oral tablets and oral suspension (generic Onfi®), with multiple pharmaceutical companies receiving approval for both formulations of generic clobazam. Generic clobazam is available as 10mg and 20mg oral tablets and as a 2.5mg/mL oral suspension. The State Maximum Allowable Cost (SMAC) of clobazam 20mg oral tablets is $1.21 per tablet, resulting in a monthly cost of $72.60 at the maximum dose of 40mg per day. The Wholesale Acquisition Cost (WAC) of clobazam 2.5mg/mL oral suspension is $0.67 per mL, resulting in a monthly cost of $321.60 at the maximum dose of 40mg per day. As a result of the increased generic availability and resulting lower net cost, the prior authorization was removed from clobazam tablets and oral suspension in December 2018.
- **November 2018:** The FDA approved Sympazan™ (clobazam oral film) for the adjunctive treatment of seizures associated with LGS in patients 2 years of age and older. Sympazan™ is the first and only oral film FDA-approved to treat seizures associated with LGS. Sympazan™ oral film is available in 5mg, 10mg, and 20mg strengths. The FDA previously approved clobazam as brand name Onfi® in 2011, which is available as oral tablets (10mg and 20mg) and oral suspension (2.5mg/mL), with both formulations recently becoming available generically. The WAC of Sympazan™ 20mg is $52.00 per film, resulting in a monthly cost of $3,120.00 at the maximum dose of 40mg per day.

- **December 2018:** The FDA approved Oxtellar XR® (oxcarbazepine ER) for use as monotherapy for the treatment of partial-onset seizures in patients 6 years of age and older. Oxcarbazepine ER was first FDA approved in 2012 as adjunctive therapy for the treatment of partial-onset seizures.
- **January 2019:** The FDA approved the first generic version of vigabatrin tablets (generic Sabril®). This approval follows previous approvals of generic versions of vigabatrin oral powder for solution, with the first generic version approved in April 2017. There are currently 4 pharmaceutical companies with approvals of generic vigabatrin oral powder for solution, as well as 1 pharmaceutical company with approval of an authorized generic for vigabatrin oral powder for solution (Vigadrone™). The College of Pharmacy will continue to monitor the net costs of the generic formulations as more products become available.

Epidiolex® (CBD Oral Solution) Product Summary[13]

Indication(s): Epidiolex® (CBD oral solution) is indicated for the treatment of seizures associated with LGS or Dravet syndrome in patients 2 years of age and older.

Dosing:

- Epidiolex® is supplied as a 100mg/mL oral solution.
- The recommended starting dosage is 2.5mg/kg by mouth twice daily (5mg/kg/day). After 1 week, the dosage can be increased to a maintenance dosage of 5mg/kg by mouth twice daily (10mg/kg/day).
- Based on individual clinical response and tolerability, Epidiolex® can be increased up to a maximum recommended maintenance dosage of 10mg/kg by mouth twice daily (20mg/kg/day).
- Because of the risk of hepatocellular injury, serum transaminases (ALT and AST) and total bilirubin levels should be obtained in all patients prior to starting treatment with Epidiolex®.
- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment (*refer to Epidiolex® prescribing information for recommended dosing in patients with hepatic impairment*).
- Epidiolex® solution should be discarded 12 weeks after first opening the bottle.
- When discontinuing Epidiolex®, the dose should be decreased gradually. As with all anticonvulsants, abrupt discontinuation should be avoided when possible, to minimize the risk of increased seizure frequency and status epilepticus.

Mechanism of Action: CBD, the active ingredient in Epidiolex®, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant. The precise mechanisms by which Epidiolex® exerts its anticonvulsant effect in humans is unknown; it does not appear to exert its anticonvulsant effects through interaction with the cannabinoid receptors.

Contraindication(s): Epidiolex® is contraindicated in patients with a history of hypersensitivity to CBD or any of the ingredients in the product (inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose).

Adverse Reactions: The most common adverse reactions (incidence ≥10% and greater than placebo) in patients treated with Epidiolex® in clinical trials included: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections.

Efficacy:

- **LGS:** The effectiveness of Epidiolex® for the treatment of seizures associated with LGS was established in 2 randomized, double-blind, placebo-controlled trials in patients 2 to 55 years of age. Study 1 (N=171) compared a dose of Epidiolex® 20mg/kg/day with placebo; Study 2 (N=225) compared a 10mg/kg/day and a 20mg/kg/day dose of Epidiolex® with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least 1 anticonvulsant, with or without vagal nerve stimulation and/or ketogenic diet. Both trials had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures (≥2 drop seizures per week); the baseline period was followed by a 2-week titration period and a 12-week maintenance period. In Study 1, 94% of patients were taking at least 2 concomitant anticonvulsants; the most frequently used concomitant anticonvulsants (>25%) in Study 1 were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%). Like Study 1, 94% of patients in Study 2 were taking at least 2 concomitant anticonvulsants, with the most frequently used concomitant anticonvulsants similar to the concomitant anticonvulsants in Study 1. The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. In both studies, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for Epidiolex® than for placebo. A reduction in drop seizures was observed within 4 weeks of initiating treatment with Epidiolex®, and the effect remained generally consistent over the 14-week treatment period. The following table (Table 1) summarizes the change in drop seizure frequency in Study 1 and Study 2.

Table 1. Change in Drop Seizure Frequency in Patients with LGS during the Treatment Period (Study 1 and Study 2)

Drop Seizure Frequency*	Placebo	Epidiolex® 10mg/kg/day	Epidiolex® 20mg/kg/day
Study 1	**N=85**	**n/a**	**N=86**
Baseline Period Median	75	n/a	71
Median % Change During Treatment	-22	n/a	-44
P-Value Compared to Placebo		n/a	0.01
Study 2	**N=76**	**N=73**	**N=76**
Baseline Period Median	80	87	86
Median % Change During Treatment	-17	-37	-42
P-Value Compared to Placebo		<0.01	<0.01

LGS = Lennox-Gastaut syndrome; N = number; n/a = not applicable; % = percentage
*per 28 days

- **Dravet Syndrome:** The effectiveness of Epidiolex® for the treatment of seizures associated with Dravet syndrome was demonstrated in a single randomized, double-blind, placebo-controlled trial in 120 patients 2 to 18 years of age (Study 3). Study 3 compared a dose of Epidiolex® 20mg/kg/day with placebo. Patients had a diagnosis of treatment-resistant Dravet syndrome and were inadequately controlled on at least 1 concomitant anticonvulsant, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients were required to have at least 4 convulsive seizures while on stable anticonvulsant therapy; the baseline period was followed by a 2-week titration period and a 12-week maintenance period. In Study 3, 93% of patients were taking at least 2 concomitant anticonvulsants; the most frequently used concomitant anticonvulsants (>25%) in Study 3 were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%). The baseline median convulsive seizure frequency was 13 per 28 days for the combined groups. The primary efficacy measure was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period. The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for Epidiolex® 20mg/kg/day than for placebo. A reduction in convulsive seizures was observed within 4 weeks of initiating treatment with Epidiolex®, and the effect remained generally consistent over the 14-week treatment period. The following table (Table 2) summarizes the change in convulsive seizure frequency in Study 3.

Table 2. Change in Convulsive Seizure Frequency in Patients with Dravet Syndrome during the Treatment Period (Study 3)

Convulsive Seizure Frequency*	Placebo	Epidiolex® 20mg/kg/day
Study 3	**N=59**	**N=61**
Baseline Period Median	15	12
Median % Change During Treatment	-13	-39
P-Value Compared to Placebo		0.01

% = percentage; N = number
*per 28 days

Cost: The WAC of Epidiolex® is $12.35 per mL, resulting in a monthly cost of $1,852.50 for a patient weighing 25kg at the maximum dosage of 20mg/kg/day.

Diacomit® (Stiripentol) Product Summary[14]

Indication(s): Diacomit® (stiripentol) is indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. There are no clinical data to support the use of stiripentol as monotherapy in Dravet syndrome.

Dosing:

- Diacomit® is supplied as oral capsules and powder for oral suspension in 2 strengths: 250mg and 500mg.

- The recommended dosage of stiripentol is 50mg/kg/day, administered by mouth in 2 or 3 divided doses. If the exact dosage is not achievable by the available strengths, the dosage should be rounded to the nearest possible dosage.
- The maximum recommended total dosage of stiripentol is 3,000mg/day.
- Stiripentol capsules should be swallowed whole with a glass of water during a meal; capsules should not be broken or opened.
- Stiripentol powder for oral suspension should be mixed with a glass of water and consumed immediately after mixing; administration should occur during a meal.
- As is advisable for most anticonvulsants, if stiripentol treatment is discontinued, the drug should be withdrawn gradually to minimize the risk of increased seizure frequency and status epilepticus. In situations where rapid withdrawal of stiripentol is medically required, appropriate monitoring is recommended.

Mechanism of Action: The mechanism by which stiripentol exerts its anticonvulsant effect in humans is unknown; possible mechanisms of action include direct effects mediated through the gamma-aminobutyric acid $(GABA)_A$ receptor and indirect effects of cytochrome P450 activity, with resulting increases in blood levels of clobazam and its active metabolite.

Contraindication(s): None

Adverse Reactions: The most common adverse reactions (incidence ≥10% and greater than placebo) in patients treated with stiripentol in clinical trials included: somnolence; decreased appetite; agitation; ataxia; decreased weight; hypotonia; nausea; tremor; dysarthria; and insomnia.

Efficacy: The effectiveness of stiripentol for the treatment of seizures associated with Dravet syndrome was established in 2 multi-center, randomized, double-blind, placebo-controlled trials (Study 1 and Study 2). To be enrolled in either study, patients were required to be age 3 years to younger than 18 years of age, have a diagnosis of Dravet syndrome, and be inadequately controlled on clobazam and valproate, with at least 4 generalized clonic or tonic-clonic seizures per month despite optimized therapy. Eligible patients were enrolled in a 1-month baseline period during which they continued to receive their optimized anticonvulsant treatment; following the baseline period, patients were randomized to receive either stiripentol (fixed dose of 50mg/kg/day in divided doses with no dose titration) or placebo, added to their treatment with clobazam and valproate. The duration of the double-blind treatment was 2 months, and the frequency of generalized clonic or tonic-clonic seizures during the study was recorded in a diary by patients and/or their caregivers. The primary efficacy endpoint for both studies was the responder rate; a responder was defined as a patient who experienced a >50% decrease in the frequency (per 30 days) of generalized clonic or tonic-clonic seizures during the double-blind treatment period compared to the baseline period. In both studies, the responder rate was significantly greater for stiripentol than for placebo. The following table (Table 3) summarizes the efficacy results in Study 1 and Study 2.

Table 3. Efficacy Results in the Intent-to-Treat Population in Patients with Dravet Syndrome (Study 1 and Study 2)

Responder Analysis*	Placebo	Stiripentol
Study 1	**N=20**	**N=21**
# of Responders/Total (Responder Rate) [95% CI]	1/20 (5%) [0%-15%]	15/21 (71%) [52%-91%]
P-value		<0.0001
Study 2	**N=11**	**N=12**
# of Responders/Total (Responder Rate) [95% CI]	1/11 (9.1%) [0%-26%]	8/12 (67%) [40%-93%]
P-value		0.0094

= number; N = number; CI = confidence interval
*Responder is defined as a patient with >50% decrease in frequency per 30 days of generalized tonic-clonic or clonic seizures

Cost: Diacomit® was expected to be available in early January 2019; however, it is not yet available on the market and cost information is also not yet available.

Recommendations

The College of Pharmacy recommends the prior authorization of Epidiolex® (CBD oral solution), Diacomit® (stiripentol), and Sympazan™ (clobazam oral film) with the following criteria:

Epidiolex® (Cannabidiol Oral Solution) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
   a. Lennox-Gastaut syndrome (LGS); or
   b. Dravet syndrome; and
2. Member must be 2 years of age or older; and
3. Initial prescription must be written by, or in consultation with, a neurologist; and
4. For a diagnosis of Dravet syndrome, the member must have failed or be inadequately controlled with at least 1 anticonvulsant; or
5. For a diagnosis of LGS, the member must have failed therapy with at least 3 other anticonvulsants; and
6. Members currently stable on Epidiolex® and who have a seizure diagnosis will be grandfathered; and
7. 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; and
8. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of the medication.

Diacomit® (Stiripentol) Approval Criteria:

1. An FDA approved indication of adjunctive therapy in the treatment of seizures associated with Dravet syndrome in members 2 years of age and older; and
2. Initial prescription must be written by, or in consultation with, a neurologist; and

3. Member must have failed or be inadequately controlled with clobazam and valproate; and
4. Member must take clobazam and valproate concomitantly with Diacomit® or a reason why concomitant clobazam and valproate are not appropriate for the member must be provided; and
5. Members currently stable on Diacomit® and who have a seizure diagnosis will be grandfathered; and
6. 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; and
7. For Diacomit® powder for oral suspension, an age restriction of 12 years and younger will apply. Members older than 12 years of age will require a patient-specific, clinically significant reason why the member cannot take the oral capsule formulation; and
8. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of the medication.

Sympazan™ (Clobazam Oral Film) Approval Criteria:

1. An FDA approved indication of adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in members 2 years of age and older; and
2. Previous failure of at least 2 non-benzodiazepine anticonvulsants; and
3. Previous failure of clonazepam; and
4. A patient-specific, clinically significant reason the member cannot use clobazam oral tablets or clobazam oral suspension; and
5. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of the medication.

Additionally, the College of Pharmacy recommends updating the approval criteria for Trokendi XR® (topiramate ER) to require a reason why the member cannot use Qudexy® XR (topiramate ER) based on net cost (changes noted in red):

Trokendi XR® [Topiramate Extended-Release (ER)] Approval Criteria:

1. An FDA approved indication of 1 of the following:
    a. Partial-onset or primary generalized tonic-clonic (PGTC) seizures; or
    b. Adjunctive therapy in seizures associated with Lennox-Gastaut Syndrome (LGS); or
    c. Prophylaxis of migraine headaches; and
2. A patient-specific, clinically significant reason why the member cannot use the short-acting formulation, Topamax® (topiramate), must be provided; and
3. A patient-specific, clinically significant reason why the member cannot use Qudexy® XR (topiramate ER) must be provided; and
4. Members currently stable on Trokendi XR® (topiramate ER) and who have a seizure diagnosis will be grandfathered; and

5. A quantity limit of 30 capsules per 30 days will apply on the lower strength capsules (25mg, 50mg, and 100mg) and 60 capsules per 30 days on the higher strength capsules (200mg).

Lastly, the College of Pharmacy recommends updating the approval criteria for Briviact® (brivaracetam) to add an age restriction on the oral solution to be consistent with other anticonvulsants with special formulations (changes noted in red):

Briviact® (Brivaracetam) Approval Criteria:

1. An FDA approved diagnosis of partial-onset seizures; and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least 3 other anticonvulsants; and
4. Members currently stable on Briviact® and who have a seizure diagnosis will be grandfathered; and
5. For Briviact® oral solution, an age restriction of 12 years and younger will apply. Members older than 12 years of age will require a patient-specific, clinically significant reason why the member cannot take the oral tablet formulation; and
6. Approval length for Briviact® intravenous (IV) will be for a maximum of 7 days of therapy. Further approval may be granted if prescriber documents an ongoing need for Briviact® IV therapy over Briviact® oral formulations.

Utilization Details of Anticonvulsants: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
GABAPENTIN PRODUCTS						
GABAPENTIN CAP 300MG	36,936	10,967	$462,538.64	$12.52	3.4	1.75%
GABAPENTIN TAB 600MG	24,281	5,048	$442,554.58	$18.23	4.8	1.68%
GABAPENTIN TAB 800MG	17,394	2,929	$368,106.10	$21.16	5.9	1.39%
GABAPENTIN CAP 100MG	9,468	3,661	$105,788.99	$11.17	2.6	0.40%
GABAPENTIN CAP 400MG	6,112	1,662	$86,955.41	$14.23	3.7	0.33%
GABAPENTIN SOL 250MG/5ML	642	123	$33,509.18	$52.19	5.2	0.13%
NEURONTIN CAP 300MG	11	1	$4,859.92	$441.81	11.0	0.02%
NEURONTIN TAB 800MG	11	1	$11,070.91	$1,006.45	11.0	0.04%
GABAPENTIN SOL 300MG/6ML	1	1	$110.54	$110.54	1.0	0.00%
SUBTOTAL	**94,856**	**24,393**	**$1,515,494.27**	**$15.98**	**3.9**	**5.74%**
CLONAZEPAM PRODUCTS						
CLONAZEPAM TAB 1MG	15,470	3,267	$157,042.94	$10.15	4.7	0.59%
CLONAZEPAM TAB 0.5MG	12,440	3,318	$122,254.93	$9.83	3.7	0.46%
CLONAZEPAM TAB 2MG	4,373	828	$46,463.00	$10.62	5.3	0.18%
CLONAZEP ODT TAB 0.25MG	941	295	$34,052.56	$36.19	3.2	0.13%
CLONAZEP ODT TAB 0.5MG	511	152	$24,459.62	$47.87	3.4	0.09%
CLONAZEP ODT TAB 0.125MG	427	154	$16,735.61	$39.19	2.8	0.06%
CLONAZEP ODT TAB 1MG	241	77	$10,636.81	$44.14	3.1	0.04%
CLONAZEP ODT TAB 2MG	62	19	$2,512.00	$40.52	3.3	0.01%
KLONOPIN TAB 2MG	12	1	$2,890.66	$240.89	12.0	0.01%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
KLONOPIN TAB 1MG	4	1	$1,040.77	$260.19	4.0	0.00%
SUBTOTAL	**34,481**	**8,112**	**$418,088.90**	**$12.13**	**4.3**	**1.58%**
LEVETIRACETAM PRODUCTS						
LEVETIRACETAM SOL 100MG/ML	10,893	1,646	$226,450.81	$20.79	6.6	0.86%
LEVETIRACETAM TAB 500MG	9,308	2,005	$146,878.11	$15.78	4.6	0.56%
LEVETIRACETAM TAB 1000MG	5,538	899	$144,355.14	$26.07	6.2	0.55%
LEVETIRACETAM TAB 750MG	3,884	711	$83,527.95	$21.51	5.5	0.32%
LEVETIRACETAM TAB 250MG	1,605	394	$23,648.37	$14.73	4.1	0.09%
LEVETIRACETAM TAB 500MG ER	564	112	$16,704.49	$29.62	5.0	0.06%
LEVETIRACETAM TAB 750MG ER	539	88	$27,026.04	$50.14	6.1	0.10%
KEPPRA XR TAB 500MG	102	10	$83,533.33	$818.95	10.2	0.32%
KEPPRA XR TAB 750MG	87	8	$94,562.60	$1,086.93	10.9	0.36%
KEPPRA TAB 1000MG	59	7	$78,908.36	$1,337.43	8.4	0.30%
KEPPRA SOL 100MG/ML	57	8	$19,458.83	$341.38	7.1	0.07%
LEVETIRACETM INJ 500MG/5ML	49	2	$2,675.28	$54.60	24.5	0.01%
KEPPRA TAB 750MG	39	5	$40,747.74	$1,044.81	7.8	0.15%
KEPPRA TAB 500MG	38	4	$11,849.52	$311.83	9.5	0.04%
LEVETIRACETA SOL 500MG/5ML	9	2	$4,241.70	$471.30	4.5	0.02%
KEPPRA TAB 250MG	6	1	$5,586.90	$931.15	6.0	0.02%
SUBTOTAL	**32,777**	**5,902**	**$1,010,155.17**	**$30.82**	**5.6**	**3.83%**
TOPIRAMATE PRODUCTS						
TOPIRAMATE TAB 50MG	9,534	2,839	$115,916.45	$12.16	3.4	0.44%
TOPIRAMATE TAB 25MG	9,020	3,404	$101,738.71	$11.28	2.6	0.39%
TOPIRAMATE TAB 100MG	9,020	1,866	$118,102.53	$13.09	4.8	0.45%
TOPIRAMATE TAB 200MG	3,415	560	$51,441.55	$15.06	6.1	0.19%
TOPIRAMATE CAP 15MG	545	143	$23,530.65	$43.18	3.8	0.09%
TOPIRAMATE CAP 25MG	494	92	$31,858.00	$64.49	5.4	0.12%
TROKENDI XR CAP 200MG	141	27	$144,794.48	$1,026.91	5.2	0.55%
TROKENDI XR CAP 100MG	114	34	$74,160.31	$650.53	3.4	0.28%
TOPAMAX TAB 100MG	60	6	$50,586.85	$843.11	10.0	0.19%
TROKENDI XR CAP 50MG	59	23	$17,041.84	$288.84	2.6	0.06%
TROKENDI XR CAP 25MG	24	10	$6,173.94	$257.25	2.4	0.02%
TOPAMAX TAB 200MG	24	2	$24,229.02	$1,009.54	12.0	0.09%
TOPIRAMATE CAP ER 200MG	22	2	$10,896.31	$495.29	11.0	0.04%
TOPAMAX TAB 50MG	12	2	$1,942.15	$161.85	6.0	0.01%
TOPAMAX SPR CAP 25MG	10	1	$27,728.93	$2,772.89	10.0	0.11%
TOPAMAX TAB 25MG	10	2	$1,536.10	$153.61	5.0	0.01%
TOPIRAMATE CAP ER 100MG	6	2	$1,983.19	$330.53	3.0	0.01%
QUDEXY XR CAP 25MG/24HR	2	1	$1,262.98	$631.49	2.0	0.00%
TOPIRAMATE CAP ER 150MG	2	1	$972.98	$486.49	2.0	0.00%
TOPIRAMATE CAP ER 50MG	1	1	$162.12	$162.12	1.0	0.00%
SUBTOTAL	**32,515**	**9,018**	**$806,059.09**	**$24.79**	**3.6**	**3.05%**
DIVALPROEX, VALPROATE, AND VALPROIC ACID PRODUCTS						

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
DIVALPROEX TAB 500MG DR	8,104	1,535	$141,507.13	$17.46	5.3	0.54%
DIVALPROEX TAB 500MG ER	6,517	1,283	$247,270.09	$37.94	5.1	0.94%
DIVALPROEX TAB 250MG DR	5,669	1,278	$83,335.49	$14.70	4.4	0.32%
DIVALPROEX TAB 250MG ER	3,540	803	$130,426.99	$36.84	4.4	0.49%
VALPROIC ACD SOL 250MG/5ML	2,226	299	$45,747.81	$20.55	7.4	0.17%
DIVALPROEX CAP 125MG	1,998	315	$174,112.08	$87.14	6.3	0.66%
DIVALPROEX TAB 125MG DR	1,622	375	$21,093.22	$13.00	4.3	0.08%
VALPROIC ACD CAP 250MG	912	171	$27,492.67	$30.15	5.3	0.10%
DEPAKOTE SPR CAP 125MG	168	20	$57,343.75	$341.33	8.4	0.22%
DEPAKOTE ER TAB 500MG	74	9	$36,644.40	$495.19	8.2	0.14%
DEPAKOTE TAB 500MG DR	55	6	$38,021.91	$691.31	9.2	0.14%
DEPAKOTE ER TAB 250MG	54	5	$17,200.09	$318.52	10.8	0.07%
DEPAKOTE TAB 250MG DR	36	3	$7,298.56	$202.74	12.0	0.03%
DEPAKOTE TAB 125MG DR	12	1	$1,322.70	$110.23	12.0	0.01%
VALPROATE INJ 500MG/5ML	2	2	$39.16	$19.58	1.0	0.00%
SUBTOTAL	**30,989**	**6,105**	**$1,028,856.05**	**$33.20**	**5.1**	**3.90%**
LAMOTRIGINE PRODUCTS						
LAMOTRIGINE TAB 100MG	10,690	2,250	$126,057.84	$11.79	4.8	0.48%
LAMOTRIGINE TAB 25MG	7,399	2,587	$97,242.37	$13.14	2.9	0.37%
LAMOTRIGINE TAB 200MG	7,322	1,279	$94,902.32	$12.96	5.7	0.36%
LAMOTRIGINE TAB 150MG	3,823	761	$49,573.10	$12.97	5.0	0.19%
LAMOTRIGINE CHW 25MG	415	70	$16,656.85	$40.14	5.9	0.06%
LAMOTRIGINE TAB 200MG ER	103	18	$25,936.35	$251.81	5.7	0.10%
LAMICTAL TAB 150MG	102	9	$91,713.29	$899.15	11.3	0.35%
LAMICTAL TAB 200MG	95	11	$86,272.62	$908.13	8.6	0.33%
LAMOTRIGINE CHW 5MG	94	32	$2,590.47	$27.56	2.9	0.01%
LAMOTRIGINE TAB 300MG ER	88	15	$26,169.55	$297.38	5.9	0.10%
LAMOTRIGINE TAB 50MG ER	69	13	$10,045.88	$145.59	5.3	0.04%
LAMICTAL TAB 100MG	57	6	$53,425.37	$937.29	9.5	0.20%
LAMOTRIGINE TAB 100MG	41	7	$21,353.01	$520.81	5.9	0.08%
LAMOTRIGINE TAB 25MG ODT	41	11	$18,436.21	$449.66	3.7	0.07%
LAMOTRIGINE TAB 50MG ODT	41	6	$13,368.12	$326.05	6.8	0.05%
LAMICTAL XR TAB 200MG	34	4	$45,229.74	$1,330.29	8.5	0.17%
LAMOTRIGINE TAB 250MG ER	32	4	$27,658.82	$864.34	8.0	0.10%
LAMOTRIGINE TAB 100MG ER	31	9	$4,133.92	$133.35	3.4	0.02%
LAMICTAL ODT TAB 100MG	24	2	$8,970.00	$373.75	12.0	0.03%
LAMICTAL XR TAB 300MG	15	2	$30,958.83	$2,063.92	7.5	0.12%
LAMICTAL ODT TAB 200MG	13	1	$10,492.71	$807.13	13.0	0.04%
LAMICTAL ODT TAB 50MG	13	1	$8,230.63	$633.13	13.0	0.03%
LAMICTAL ODT TAB 25MG	12	1	$5,126.04	$427.17	12.0	0.02%
LAMOTRIGINE TAB 200MG	12	4	$2,817.83	$234.82	3.0	0.01%
LAMOTRIGINE TAB 25MG ER	11	2	$906.65	$82.42	5.5	0.00%
LAMICTAL XR TAB 250MG	10	2	$8,642.60	$864.26	5.0	0.03%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
LAMICTAL XR TAB 100MG	9	2	$6,097.50	$677.50	4.5	0.02%
LAMOTRIG ODT TAB 100MG	6	2	$2,242.50	$373.75	3.0	0.01%
LAMICTAL CHW 25MG	3	1	$4,931.20	$1,643.73	3.0	0.02%
LAMICTAL XR TAB 25MG	2	1	$556.96	$278.48	2.0	0.00%
LAMOTRIGINE STARTER KIT	1	1	$541.55	$541.55	1.0	0.00%
LAMICTAL XR TAB 50MG	1	1	$637.30	$637.30	1.0	0.00%
SUBTOTAL	**30,609**	**7,115**	**$901,918.13**	**$29.47**	**4.3**	**3.42%**
OXCARBAZEPINE PRODUCTS						
OXCARBAZEPINE TAB 300MG	10,167	2,162	$209,393.43	$20.60	4.7	0.79%
OXCARBAZEPINE TAB 600MG	8,324	1,376	$263,742.58	$31.68	6.0	1.00%
OXCARBAZEPINE TAB 150MG	6,728	1,746	$117,629.77	$17.48	3.9	0.45%
OXCARBAZEPINE SUS 300MG/5ML	2,915	462	$401,531.43	$137.75	6.3	1.52%
TRILEPTAL SUS 300MG/5ML	187	24	$116,059.92	$620.64	7.8	0.44%
OXTELLAR XR TAB 600MG	122	18	$114,571.61	$939.11	6.8	0.43%
TRILEPTAL TAB 600MG	65	9	$94,432.42	$1,452.81	7.2	0.36%
OXTELLAR XR TAB 300MG	33	7	$8,560.39	$259.41	4.7	0.03%
OXTELLAR XR TAB 150MG	25	4	$7,219.07	$288.76	6.3	0.03%
TRILEPTAL TAB 300MG	16	2	$8,144.86	$509.05	8.0	0.03%
TRILEPTAL TAB 150MG	1	1	$378.49	$378.49	1.0	0.00%
SUBTOTAL	**28,583**	**5,811**	**$1,341,663.97**	**$46.94**	**4.9**	**5.08%**
PREGABALIN PRODUCTS						
LYRICA CAP 150MG	2,815	457	$1,405,698.66	$499.36	6.2	5.33%
LYRICA CAP 100MG	1,582	303	$841,459.41	$531.90	5.2	3.19%
LYRICA CAP 75MG	1,300	313	$596,220.19	$458.63	4.2	2.26%
LYRICA CAP 300MG	1,025	143	$429,390.33	$418.92	7.2	1.63%
LYRICA CAP 200MG	744	128	$323,279.14	$434.51	5.8	1.22%
LYRICA CAP 50MG	549	157	$281,389.34	$512.55	3.5	1.07%
LYRICA CAP 225MG	264	42	$125,215.13	$474.30	6.3	0.47%
LYRICA CAP 25MG	69	19	$31,502.54	$456.56	3.6	0.12%
LYRICA SOL 20MG/ML	3	2	$3,189.15	$1,063.05	1.5	0.01%
SUBTOTAL	**8,351**	**1,564**	**$4,037,343.89**	**$483.46**	**5.3**	**15.30%**
CARBAMAZEPINE PRODUCTS						
CARBAMAZEPINE TAB 200MG	3,584	694	$180,166.98	$50.27	5.2	0.68%
CARBAMAZEPINE CHW 100MG	713	118	$37,661.19	$52.82	6.0	0.14%
CARBAMAZEPINE TAB 400MG ER	515	74	$100,256.68	$194.67	7.0	0.38%
CARBAMAZEPINE TAB 200MG ER	422	85	$42,446.09	$100.58	5.0	0.16%
CARBAMAZEPINE CAP 300MG ER	405	52	$31,250.72	$77.16	7.8	0.12%
EPITOL TAB 200MG	361	101	$17,071.02	$47.29	3.6	0.06%
CARBAMAZEPINE SUS 100MG/5ML	275	34	$28,156.51	$102.39	8.1	0.11%
CARBAMAZEPINE CAP 200MG ER	265	45	$20,769.06	$78.37	5.9	0.08%
CARBAMAZEPINE TAB 100MG ER	210	51	$12,084.96	$57.55	4.1	0.05%
CARBAMAZEPINE CAP 100MG ER	106	25	$7,091.86	$66.90	4.2	0.03%
TEGRETOL TAB 200MG	81	8	$28,720.90	$354.58	10.1	0.11%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
TEGRETOL-XR TAB 400MG	80	9	$28,488.40	$356.11	8.9	0.11%
TEGRETOL SUS 100MG/5ML	79	8	$24,809.80	$314.05	9.9	0.09%
CARBATROL CAP 200MG	51	5	$9,877.01	$193.67	10.2	0.04%
TEGRETOL-XR TAB 200MG	48	6	$15,641.23	$325.86	8.0	0.06%
CARBATROL CAP 300MG	19	2	$3,156.37	$166.12	9.5	0.01%
TEGRETOL-XR TAB 100MG	14	2	$1,290.09	$92.15	7.0	0.00%
SUBTOTAL	**7,228**	**1,319**	**$588,938.87**	**$81.48**	**5.5**	**2.23%**
LACOSAMIDE PRODUCTS						
VIMPAT TAB 200MG	2,061	249	$1,539,321.12	$746.88	8.3	5.83%
VIMPAT TAB 100MG	1,401	247	$946,529.69	$675.61	5.7	3.59%
VIMPAT TAB 150MG	848	130	$625,725.80	$737.88	6.5	2.37%
VIMPAT SOL 10MG/ML	833	120	$606,693.14	$728.32	6.9	2.30%
VIMPAT TAB 50MG	590	125	$250,722.84	$424.95	4.7	0.95%
SUBTOTAL	**5,733**	**871**	**$3,968,992.59**	**$692.31**	**6.6**	**15.04%**
PHENYTOIN AND FOSPHENYTOIN PRODUCTS						
PHENYTOIN EX CAP 100MG	4,359	680	$153,443.84	$35.20	6.4	0.58%
DILANTIN CAP 100MG	379	48	$59,971.50	$158.24	7.9	0.23%
PHENYTOIN SUS 125MG/5ML	321	38	$10,458.95	$32.58	8.4	0.04%
PHENYTOIN CHW 50MG	245	37	$9,386.83	$38.31	6.6	0.04%
PHENYTOIN EX CAP 200MG	70	22	$6,110.38	$87.29	3.2	0.02%
DILANTIN CAP 30MG	61	13	$4,203.37	$68.91	4.7	0.02%
PHENYTEK CAP 200MG	46	5	$4,769.83	$103.69	9.2	0.02%
DILANTIN CHW 50MG	41	5	$2,339.85	$57.07	8.2	0.01%
PHENYTEK CAP 300MG	26	7	$4,048.91	$155.73	3.7	0.02%
PHENYTOIN EX CAP 300MG	20	10	$1,493.41	$74.67	2.0	0.01%
DILANTIN-125 SUS 125MG/5ML	10	2	$1,326.60	$132.66	5.0	0.01%
FOSPHENYTOIN INJ 100MG/2ML	2	1	$111.10	$55.55	2.0	0.00%
CEREBYX INJ 100MG/2ML	1	1	$309.11	$309.11	1.0	0.00%
SUBTOTAL	**5,581**	**869**	**$257,973.68**	**$46.22**	**6.4**	**0.98%**
ZONISAMIDE PRODUCTS						
ZONISAMIDE CAP 100MG	3,030	439	$62,138.09	$20.51	6.9	0.24%
ZONISAMIDE CAP 50MG	915	189	$17,324.09	$18.93	4.8	0.07%
ZONISAMIDE CAP 25MG	370	96	$6,481.69	$17.52	3.9	0.02%
ZONEGRAN CAP 100MG	26	3	$49,693.14	$1,911.27	8.7	0.19%
SUBTOTAL	**4,341**	**727**	**$135,637.01**	**$31.25**	**6.0**	**0.51%**
CLOBAZAM PRODUCTS						
ONFI TAB 10MG	1,048	150	$982,717.77	$937.71	7.0	3.72%
ONFI TAB 20MG	1,018	126	$1,806,481.60	$1,774.54	8.1	6.84%
ONFI SUS 2.5MG/ML	776	115	$1,323,964.76	$1,706.14	6.7	5.02%
SUBTOTAL	**2,842**	**391**	**$4,113,164.13**	**$1,447.28**	**7.3**	**15.58%**
PHENOBARBITAL PRODUCTS						
PHENOBARB TAB 64.8MG	720	85	$31,411.63	$43.63	8.5	0.12%
PHENOBARB ELX 20MG/5ML	488	96	$33,438.11	$68.52	5.1	0.13%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
PHENOBARB TAB 32.4MG	452	66	$21,802.39	$48.24	6.8	0.08%
PHENOBARB SOL 20MG/5ML	444	104	$24,221.08	$54.55	4.3	0.09%
PHENOBARB TAB 97.2MG	222	27	$11,333.76	$51.05	8.2	0.04%
PHENOBARB TAB 30MG	138	23	$3,109.98	$22.54	6.0	0.01%
PHENOBARB TAB 60MG	99	21	$1,860.84	$18.80	4.7	0.01%
PHENOBARB TAB 16.2MG	69	12	$2,500.97	$36.25	5.8	0.01%
PHENOBARB TAB 100MG	46	8	$801.09	$17.42	5.8	0.00%
PHENOBARB TAB 15MG	17	6	$262.98	$15.47	2.8	0.00%
SUBTOTAL	**2,695**	**448**	**$130,742.83**	**$48.51**	**6.0**	**0.50%**
DIAZEPAM PRODUCTS						
DIAZEPAM GEL 10MG	1,219	762	$448,012.18	$367.52	1.6	1.70%
DIAZEPAM GEL 20MG	376	175	$193,203.37	$513.84	2.1	0.73%
DIASTAT ACDL GEL 5-10MG	135	87	$91,659.90	$678.96	1.6	0.35%
DIASTAT ACDL GEL 12.5-20MG	97	41	$62,651.98	$645.90	2.4	0.24%
DIAZEPAM GEL 2.5MG	96	76	$35,227.19	$366.95	1.3	0.13%
DIASTAT PED GEL 2.5MG	29	25	$10,011.62	$345.23	1.2	0.04%
SUBTOTAL	**1,952**	**1,166**	**$840,766.24**	**$430.72**	**1.7**	**3.19%**
ETHOSUXIMIDE PRODUCTS						
ETHOSUXIMIDE CAP 250MG	703	117	$66,513.26	$94.61	6.0	0.25%
ETHOSUXIMIDE SOL 250MG/5ML	550	99	$38,690.25	$70.35	5.6	0.15%
ZARONTIN CAP 250MG	34	3	$11,447.50	$336.69	11.3	0.04%
SUBTOTAL	**1,287**	**219**	**$116,651.01**	**$90.64**	**5.9**	**0.44%**
PRIMIDONE PRODUCTS						
PRIMIDONE TAB 50MG	614	113	$8,580.05	$13.97	5.4	0.03%
PRIMIDONE TAB 250MG	279	34	$5,307.38	$19.02	8.2	0.02%
MYSOLINE TAB 250MG	20	2	$80,334.25	$4,016.71	10.0	0.30%
SUBTOTAL	**913**	**149**	**$94,221.68**	**$103.20**	**6.1**	**0.36%**
ACETAZOLAMIDE PRODUCTS						
ACETAZOLAMIDE TAB 250MG	464	120	$54,332.20	$117.10	3.9	0.21%
ACETAZOLAMIDE CAP 500MG ER	288	93	$29,619.32	$102.84	3.1	0.11%
ACETAZOLAMIDE TAB 125MG	59	19	$6,029.19	$102.19	3.1	0.02%
SUBTOTAL	**811**	**232**	**$89,980.71**	**$110.95**	**3.5**	**0.34%**
RUFINAMIDE PRODUCTS						
BANZEL TAB 400MG	416	44	$1,055,627.95	$2,537.57	9.5	4.00%
BANZEL SUS 40MG/ML	271	39	$461,598.77	$1,703.32	6.9	1.75%
BANZEL TAB 200MG	104	13	$68,291.51	$656.65	8.0	0.26%
SUBTOTAL	**791**	**96**	**$1,585,518.23**	**$2,004.45**	**8.2**	**6.01%**
PERAMPANEL PRODUCTS						
FYCOMPA TAB 8MG	162	26	$98,172.28	$606.00	6.2	0.37%
FYCOMPA TAB 6MG	140	25	$105,599.98	$754.29	5.6	0.40%
FYCOMPA TAB 4MG	80	26	$62,123.65	$776.55	3.1	0.24%
FYCOMPA SUS 0.5MG/ML	62	10	$68,818.33	$1,109.97	6.2	0.26%
FYCOMPA TAB 2MG	58	21	$23,233.18	$400.57	2.8	0.09%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
FYCOMPA TAB 10MG	58	11	$41,281.49	$711.75	5.3	0.16%
FYCOMPA TAB 12MG	46	5	$38,967.75	$847.13	9.2	0.15%
SUBTOTAL	**606**	**124**	**$438,196.66**	**$723.10**	**4.9**	**1.66%**
BRIVARACETAM PRODUCTS						
BRIVIACT TAB 100MG	246	33	$243,301.67	$989.03	7.5	0.92%
BRIVIACT TAB 50MG	210	40	$199,829.44	$951.57	5.3	0.76%
BRIVIACT SOL 10MG/ML	39	6	$36,752.59	$942.37	6.5	0.14%
BRIVIACT TAB 75MG	37	6	$42,624.69	$1,152.02	6.2	0.16%
BRIVIACT TAB 25MG	3	1	$3,027.92	$1,009.31	3.0	0.01%
BRIVIACT TAB 10MG	1	1	$1,080.65	$1,080.65	1.0	0.00%
SUBTOTAL	**536**	**87**	**$526,616.96**	**$982.49**	**6.2**	**2.00%**
FELBAMATE PRODUCTS						
FELBAMATE TAB 600MG	269	27	$85,979.66	$319.63	10.0	0.33%
FELBAMATE SUS 600MG/5ML	115	11	$95,959.05	$834.43	10.5	0.36%
FELBAMATE TAB 400MG	82	10	$8,208.47	$100.10	8.2	0.03%
FELBATOL TAB 600MG	30	5	$44,287.49	$1,476.25	6.0	0.17%
FELBATOL TAB 400MG	26	4	$27,586.96	$1,061.04	6.5	0.10%
SUBTOTAL	**522**	**57**	**$262,021.63**	**$501.96**	**9.2**	**0.99%**
ESLICARBAZEPINE PRODUCTS						
APTIOM TAB 800MG	102	15	$116,979.53	$1,146.86	6.8	0.44%
APTIOM TAB 600MG	60	8	$107,857.11	$1,797.62	7.5	0.41%
APTIOM TAB 400MG	12	7	$10,878.86	$906.57	1.7	0.04%
APTIOM TAB 200MG	8	3	$1,605.74	$200.72	2.7	0.01%
SUBTOTAL	**182**	**33**	**$237,321.24**	**$1,303.96**	**5.5**	**0.90%**
VIGABATRIN PRODUCTS						
SABRIL POW 500MG	69	15	$1,039,726.61	$15,068.50	4.6	3.94%
VIGABATRIN PAK 500MG	56	10	$618,275.97	$11,040.64	5.6	2.34%
SABRIL TAB 500MG	24	2	$252,973.17	$10,540.55	12.0	0.96%
SUBTOTAL	**149**	**27**	**$1,910,975.75**	**$12,825.34**	**5.5**	**7.24%**
TIAGABINE PRODUCTS						
TIAGABINE TAB 4MG	36	6	$14,679.00	$407.75	6.0	0.06%
GABITRIL TAB 16MG	11	3	$2,985.62	$271.42	3.7	0.01%
GABITRIL TAB 12MG	9	2	$2,676.74	$297.42	4.5	0.01%
TIAGABINE TAB 2MG	8	2	$2,331.42	$291.43	4.0	0.01%
TIAGABINE TAB 12MG	7	2	$1,581.73	$225.96	3.5	0.01%
SUBTOTAL	**71**	**15**	**$24,254.51**	**$341.61**	**4.7**	**0.09%**
METHSUXIMIDE PRODUCTS						
CELONTIN CAP 300MG	38	3	$12,932.10	$340.32	12.7	0.05%
SUBTOTAL	**38**	**3**	**$12,932.10**	**$340.32**	**12.7**	**0.05%**
TOTAL	**329,439**	**45,800***	**$26,394,485.30**	**$80.12**	**7.2**	**100.00%**

*Total number of unduplicated members.

Costs do not reflect rebated prices or net costs.

The utilization details above include seizure medications used for all diagnoses and does not differentiate between epilepsy diagnoses and other diagnoses, for which use may be appropriate. Please note, the above utilization data does not include Afinitor® (everolimus) for the diagnosis of tuberous sclerosis complex (TSC)-associated partial-onset seizures; utilization data for everolimus is included in the annual review of oncology medications.

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Appendix N

Fiscal Year 2018 Annual Review of Anti-Migraine Medications and 30-Day Notice to Prior Authorize Aimovig™ (Erenumab-aooe), Ajovy™ (Fremanezumab-vfrm), and Emgality™ (Galcanezumab-gnlm)

Oklahoma Health Care Authority
February 2019

Current Prior Authorization Criteria

Anti-Migraine Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
eletriptan (Relpax®) – **brand only**	naratriptan (Amerge®)	almotriptan (Axert®)	dihydroergotamine injection (D.H.E. 45®)
rizatriptan (Maxalt®, Maxalt MLT®)	zolmitriptan (Zomig®, Zomig-ZMT®, Zomig® nasal spray)	frovatriptan (Frova®)	dihydroergotamine nasal spray (Migranal®)
sumatriptan (Imitrex®)			eletriptan (Relpax®) – **generic**
			sumatriptan injection (Imitrex®)
			sumatriptan injection (Sumavel® DosePro®)
			sumatriptan injection (Zembrace™ SymTouch™)
			sumatriptan nasal powder (Onzetra® Xsail®)
			sumatriptan nasal spray (Imitrex®)
			sumatriptan/naproxen (Treximet®)

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

Anti-Migraine Medications Tier-2 Approval Criteria:

1. A trial of all available Tier-1 products with inadequate response; or
2. Documented adverse effect(s) to all available Tier-1 products; or
3. Previous success with a Tier-2 product within the last 60 days.

Anti-Migraine Medications Tier-3 Approval Criteria:

1. A trial of all available Tier-1 and Tier-2 products with inadequate response; or
2. Documented adverse effect(s) to all available Tier-1 and Tier-2 products; or

3. Previous success with a Tier-3 product within the last 60 days; and
4. Use of any non-oral formulation will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation.

Anti-Migraine Medications Special Prior Authorization (PA) Approval Criteria:

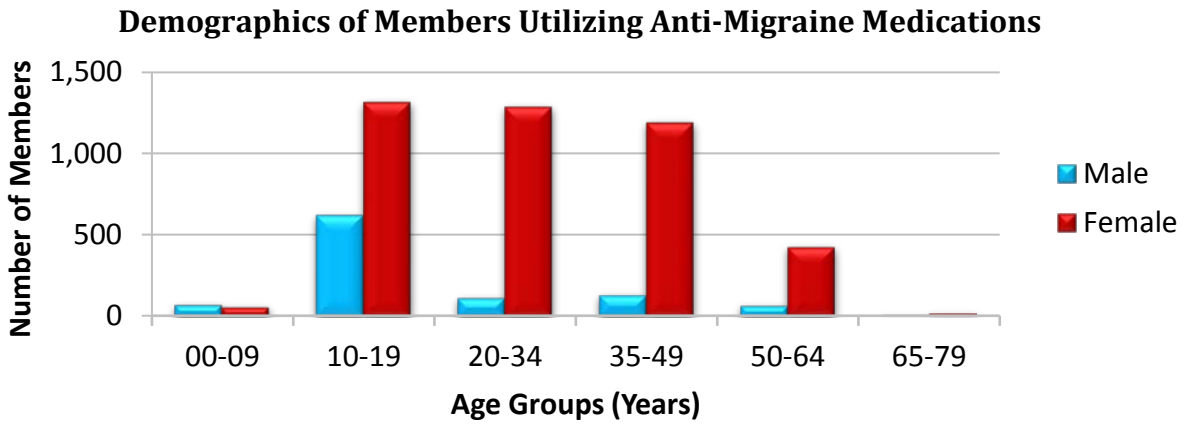
1. Use of any non-oral sumatriptan formulation will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation or lower-tiered triptan medications.
2. Use of Onzetra® Xsail® or Zembrace™ SymTouch™ will require a patient-specific, clinically significant reason why the member cannot use all available generic formulations of sumatriptan (tablets, nasal spray, and injection) or lower-tiered triptan medications.
3. Use of Treximet® (sumatriptan/naproxen) will require a patient-specific, clinically significant reason why the member cannot use the individual components separately or lower-tiered triptan medications.
4. Use of dihydroergotamine injection (D.H.E. 45®) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications.
5. Use of dihydroergotamine nasal spray (Migranal®) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications or dihydroergotamine injection (D.H.E. 45®).
6. Use of Ergomar® (ergotamine sublingual tablets) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications; and
    a. Member must not have any of the contraindications for use of Ergomar® (e.g., coadministration with a potent CYP 3A4 inhibitor, women who are or may become pregnant, peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, hypersensitivity to any of the components); and
    b. A quantity limit of 20 tablets per 28 days will apply.
7. Use of generic eletriptan will require a patient-specific, clinically significant reason why the member cannot use the brand formulation of Relpax® (brand formulation is preferred).

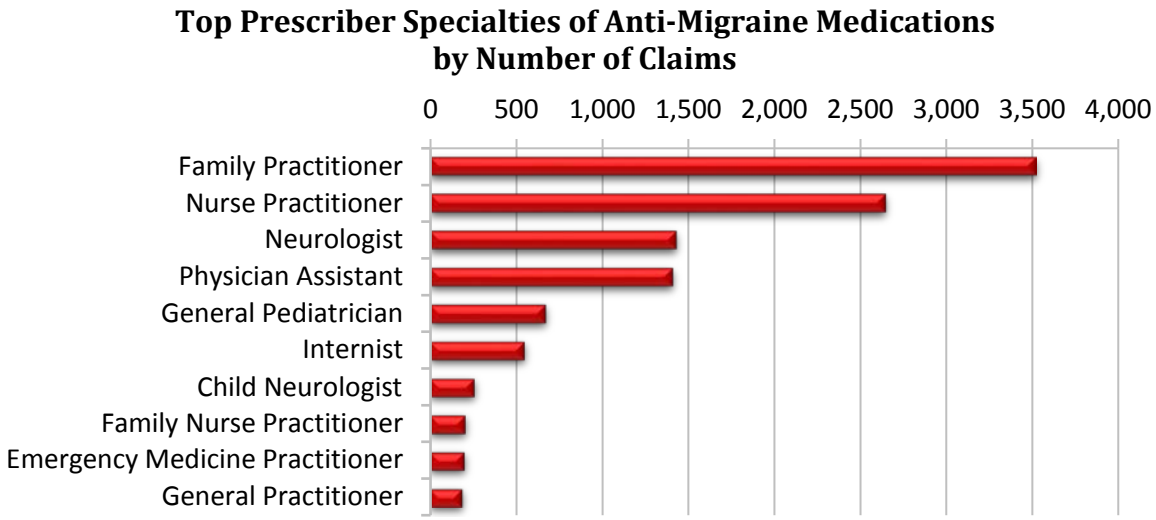
Utilization of Anti-Migraine Medications: Fiscal Year 2018

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	5,281	11,503	$263,993.38	$22.95	$1.45	123,586	182,232
2018	5,292	11,655	$289,878.37	$24.87	$1.53	125,939	189,004
% Change	**0.20%**	**1.30%**	**9.80%**	**8.40%**	**5.50%**	**1.90%**	**3.70%**
Change	**11**	**152**	**$25,884.99**	**$1.92**	**$0.08**	**2,353**	**6,772**

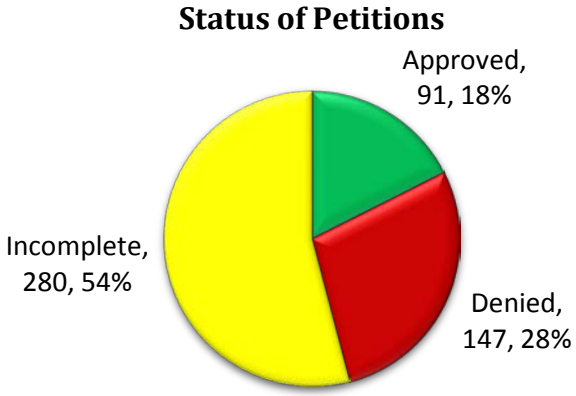
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.





Prior Authorization of Anti-Migraine Medications

There were 518 prior authorization requests submitted for anti-migraine medications during fiscal year 2018. 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 2018.



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

Anticipated Patent Expiration(s):

- Zomig® (zolmitriptan nasal spray): May 2021
- Treximet® (sumatriptan/naproxen tablets): April 2026
- Onzetra® Xsail® (sumatriptan nasal powder): October 2034

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

- **May 2018:** Novartis announced the FDA approval of Aimovig™ (erenumab-aooe) for the preventive treatment of migraine in adults.
- **September 2018:** Teva Pharmaceuticals announced the FDA approval of Ajovy™ (fremanezumab-vfrm) for migraine prevention in adults.
- **September 2018:** Eli Lilly announced the FDA approval of Emgality™ (galcanezumab-gnlm) for the prevention of migraine in adults.

Product Discontinuation(s):

- **February 2018:** Endo discontinued Sumavel® DosePro® (sumatriptan 6mg/0.5mL injection). The product discontinuation is not due to product quality, safety, or efficacy concerns.

News:

- **June 2018:** A recent study published in the *Journal of the American Medical Association (JAMA) Neurology* investigated the use of timolol eye drops as an acute migraine treatment. The study was a randomized, crossover, placebo-controlled pilot study and enrolled patients 18 years of age and older who met the International Headache Society criteria for migraine. The participants were randomized to receive timolol maleate 0.5% or artificial tears, administered as a single drop in both eyes, at onset of migraine and 30 minutes after. Patients were monitored over 4 months (5 visits total) and were crossed over at the 2-month mark with a 3-day washout period. Participants completed a data sheet to rate their migraine attacks on a scale of 0 to 3 in terms of severity. Patients were also asked to rate the effectiveness of each drop on a scale of 1 to 4. There were 10 participants in the study and a total of 198 migraine attacks assessed. Based on the results, the overall effectiveness of timolol was 2.4 compared with 1.4 with placebo. The average percentage of headaches with a severity of none or mild at 2 hours was 57% with placebo compared with 78% with timolol (a Wilcoxon match paired test was conducted to account for repeated measurements and this difference was not found to be significant, with P=0.26, as expected with a small pilot study). The authors emphasized that although this pilot study successfully explored the efficacy of timolol eye drops, further research is needed to identify patients who would benefit the most from this treatment and to determine an appropriate dosage.
- **June 2018:** Teva Pharmaceuticals announced a change in the clinical development program of fremanezumab in chronic cluster headache. The ENFORCE Phase 3 clinical development program includes a chronic cluster headache study, an episodic cluster headache study, and a long-term safety study. A pre-specified futility analysis of the chronic cluster headache study revealed that the primary endpoint of mean change

from baseline in the monthly average number of cluster headache attacks during the 12-week treatment period is unlikely to be met. Based on the study meeting the futility criteria, Teva will discontinue the trial for chronic cluster headache. The episodic cluster headache study will continue as planned.

- **July 2018:** According to research presented at the 2018 American Headache Society (AHS) Annual Scientific Meeting, treatment with fremanezumab may help reduce medication overuse and the number of days of acute medication use in individuals with chronic migraine. Medications, including opiates, triptans, ergot derivatives, and analgesic combinations, have the potential to be overused by patients with chronic migraine. Fremanezumab has indicated efficacy in previous clinical trials in reducing headache severity and frequency in chronic migraine. In a Phase 3 placebo-controlled trial, patients with chronic migraine were randomly assigned to receive quarterly fremanezumab followed by placebo injections at weeks 4 and 8; monthly fremanezumab only; or placebo over a 12-week period. Medication overuse was defined as use of acute headache medications ≥15 days, use of migraine-specific acute medication ≥10 days, or use of combination medications for headache ≥10 days over a 28-day baseline period. A greater percentage of study participants treated with fremanezumab versus placebo indicated a lack of medication overuse during the study period (quarterly fremanezumab, 55%, P=0.0389; monthly fremanezumab, 61%, P=0.0024; placebo, 46%). This drug treatment effect was noticeable beginning at week 4 (quarterly fremanezumab, 51%. P=0.0091; monthly fremanezumab, 54%, P=0.0014; placebo, 39%).
- **July 2018:** According to research reports, galcanezumab provided relief for episodic cluster headache and continued to show good efficacy against migraine. A Phase 3 trial showed that monthly injections of galcanezumab led to a significant reduction in the frequency of cluster headache attacks. During the first 3 weeks after starting treatment, weekly cluster headache attack frequency fell by 8.7 in the galcanezumab arm and by 5.2 in the placebo arm (P=0.036). At week 3, 76% of participants in the galcanezumab group and 57% in the placebo group reported at least a 50% reduction in the headache attack frequency (P=0.04). However, by week 8 the improvement rate in the placebo arm rose to about 65% while the rate in the galcanezumab group stayed the same, therefore the difference was no longer statistically significant (P=0.58). Another Phase 3 study evaluating the medication in chronic cluster headache did not see a significant difference in the reduction in headache frequency over 3 months in the galcanezumab and placebo groups (-5.4 vs. -4.6, respectively; P=0.33). The FDA has granted Breakthrough Therapy Designation to galcanezumab for the preventive treatment of episodic cluster headache.
- **July 2018:** According to results from a large, double-blind, placebo-controlled trial, Zembrace™ SymTouch™ [sumatriptan 3mg subcutaneous (sub-Q) auto-injector] is well tolerated, safe, and effective. The medication is approved by the FDA for acute treatment of episodic migraine, with or without aura. Compared with placebo and historical data for 6mg sumatriptan pen injectors, the 3mg auto-injector fared well in terms of tolerability and efficacy in both the double-blind and open-label extension periods of the multicenter Phase 3 study. The investigators are not claiming superiority

of the 3mg product over the 6mg products as the study was not a head-to-head comparison.

- **July 2018:** According to a study in *Drug, Healthcare, and Patient Safety*, a combination of opioids and selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) was found to be prescribed more frequently than co-prescriptions of opioids plus triptans in patients with a migraine diagnosis. The combination of opioids with serotonergic antidepressants and/or triptans occurred more frequently in community-based care prior to the FDA warning concerning the risk of serotonin syndrome associated with the co-prescribing of these medications. Tramadol represented the most frequently prescribed high-risk opioid medication in the opioid plus SSRI/SNRI and opioid plus triptan combination groups (18.6% vs. 21.8%, respectively). Higher-risk opioids were prescribed in up to one-fifth of all opioid co-prescribing practices. Furthermore, approximately 16.3% of visits for migraine included opioid prescribing, whereas 2.0% of visits resulted in co-prescribing of an opioid with a triptan. The investigators of this study suggest that "health care providers should consider the risks associated with opioid use, particularly when co-prescribed with other serotonergic medications."
- **July 2018:** The Institute for Clinical and Economic Review (ICER) issued the Final Evidence report and Report-at-a-Glance for the calcitonin gene-related peptide (CGRP) inhibitors as preventive treatments for patients with episodic or chronic migraine. ICER's report was reviewed at a public meeting of the California Technology Assessment Forum (CTAF) on June 14, 2018. The majority of the independent voting panel found that, when balancing the benefits and potential risk of CGRP therapy, evidence shows a net health benefit for patients with chronic migraine and no other treatment, but is currently inadequate to show a benefit in those with less frequent migraine. ICER's economic analysis found that at a net price of $5,000 the use of CGRP inhibitors in patients for who prior preventive therapy failed meets commonly accepted thresholds for cost-effectiveness of $100,000 to $150,000 per quality-adjusted life year (QALY) gained when compared to placebo. ICER did not issue an access and affordability alert at the time the report was released, as the clinical experts indicated that uptake is unlikely to exceed levels that would threaten access and affordability, as CGRP inhibitors use a novel mechanism of action with unknown long-term safety profile, are injectable, and patients who do not benefit from therapy are likely to discontinue treatment. However, given the budget impact potential, it is important for all stakeholders to closely monitor the use of CGRP inhibitors in the event that actual uptake exceeds expectations. Key policy recommendations for payers include that it is reasonable for insurers and other payers to develop prior authorization criteria to ensure prudent use of these treatments given that CGRP inhibitors have a new mechanism of action, are entering clinical use without long-term safety and efficacy data, and were labeled by the FDA using language that could suggest that all patients with migraine are eligible for treatment. Furthermore, it was noted that when responsible pricing is accomplished and the net price of CGRP inhibitors aligns with the estimated added benefit for patients, prior authorization criteria should be relatively streamlined and allow documentation of eligibility through clinical attestation rather than requiring extensive submission of

clinical documents. The CTAF panel voted that the current evidence base was inadequate to distinguish the clinical benefits among the 3 CGRP inhibitors erenumab, fremanezumab, and galcanezumab. The CTAF panel stated that payers are likely to judge that the evidence supports the option to negotiate discounts on the basis of preferential formulary placement for a single drug. However, given the different targets of the agents, it is possible that some patients may respond better to 1 agent over another. Therefore, payers should consider ways to maintain coverage for multiple CGRP inhibitors for patients who have tried and not received adequate response from the preferred agent. Potential prior authorization criteria include adult patients with migraine with 4 or more headache days per month and patients with an inadequate response to treatment with or intolerance of 2 to 3 other migraine preventive medications and a reasonable trial of triptan medications. For potential provider criteria, the report indicated that CGRP inhibitors can be covered if prescribed by any clinician or CGRP inhibitors may be covered only if prescribed by a specialist clinician with formal training in neurology or pain management. The policy roundtable members suggested that allowing broad prescribing is more appropriate in this case given important concerns that access would be too limited if restricted to specialists. It was noted that if payers do choose to limit prescribing to specialists, it is incumbent of them to evaluate potential access problems and to revisit this restriction early on as clinical experience evolves. Additional prior authorization criteria could include ongoing coverage requiring that clinicians attest to clinical improvement after some pre-specified length of treatment (e.g., 3 to 6 months). Roundtable members expressed the view that patients typically stop taking preventive therapy if it is not tolerable or ineffective, reducing the risk that CGRP inhibitors would be used for an extended time while providing no clinical benefit.

- **January 2019:** The AHS released a consensus statement on both preventive and acute strategies for clinical practice for the treatment of migraine. The AHS developed the consensus statement after reviewing existing guidelines and recent clinical trials, as well as holding discussions with various stakeholders. The statement discusses best practice for preventing migraine with oral treatments, including starting with a low dose and titrating slowly, and with newer injectable drugs, such as the CGRP drugs. Other sections discuss best practices for acute treatment of migraine with both oral and injectable treatments and strategies for using neuromodulation and biobehavioral therapy for both preventive and acute treatment. For the consensus statement, episodic migraine was defined as having <15 monthly headache days (MHDs) or monthly migraine days (MMDs). Chronic migraine was defined as having ≥15 MHDs, with at least 8 of these days being MMDs. The authors stated that “none of the currently available oral preventive treatments were designed specifically for migraine.” They also said that only 3% to 13% of patients adhere to preventive treatment because of the often high rates of adverse effects and moderate efficacy, as well as contraindications. The “recommendations for when to initiate preventive treatment are unchanged” and the situations include when migraine attacks interfere with daily routines even after acute treatment and when a patient experiences 4 or more MHDs. Preventive management should also be considered in patients with rare subtypes, including hemiplegic migraine

and migraine with prolonged aura. The cited evidence-based oral treatments include anticonvulsants and beta-blockers, as well as short-term use of frovatriptan for menstrual migraine. One important note is that the anticonvulsants valproate and topiramate should not be prescribed to women of childbearing age because of the risk of birth defects. Other treatments that are "probably effective and should be considered for migraine prevention" include certain antidepressants and candesartan, an angiotensin receptor blocker (ARB). AHS noted that the newer injectables often "work faster and may not need titration"; however, the study authors pointed out that the cost of these drugs "will almost certainly" be higher than that of oral generic preventive drugs. They wrote that in order to achieve cost-effective care, "it is important that the indications for initiating treatment with anti-CGRP mAbs are widely understood and followed closely." The position paper states for measuring efficacy of any preventive treatment, a reduction by 50% in MHDs may be useful in practice and clinical trials, but other factors should also be considered, such as pain severity, associated symptoms, functional capacity, and quality of life.

Pipeline:

- **Rimegepant:** In December 2018, Biohaven Pharmaceutical Holding Company Ltd. announced positive topline results from a randomized, controlled Phase 3 clinical trial evaluating the safety and efficacy of Zydis®, and orally disentigrating tablet (ODT) formulation of rimegepant, an oral CGRP receptor antagonist, for the acute treatment of migraine. In the study rimegepant ODT met its co-primary endpoints of pain freedom and freedom from most bothersome symptom at 2 hours after using a single dose. Patients treated with rimegepant ODT began to numerically separate from placebo on pain relief as early as 15 minutes and this difference was statistically significant at 60 minutes ($P<0.0001$). In addition, a greater percentage of patients treated with rimegepant ODT returned to normal functioning by 60 minutes as compared to placebo ($P=0.0025$). Lasting clinical benefit was observed through 48 hours after a single dose of rimegepant on freedom from pain ($P<0.0001$), pain relief ($P<0.0001$), freedom from the most bothersome symptom ($P=0.0018$), and freedom from functional disability ($P<0.0001$).
- **Eptinezumab:** New efficacy data from a Phase 3 clinical trial in patients with episodic migraine receiving eptinezumab were presented at the AHS 60th Annual Scientific Meeting. Eptinezumab is a CGRP inhibitor, and the Phase 3 data revealed that patients reported further reduction in MMDs after their third and fourth quarterly infusions of the drug. MMDs were lowered by 4.3 (baseline 8.0) for patients treated with the 300mg dose following the first infusion; compared to those treated with placebo who experienced reductions of 3.2 days ($P=0.0001$). One year after the third and fourth quarterly infusions, those administered the 300mg dose of eptinezumab reported reductions of 5.2 MMDs, compared to 4.0 for patients in the placebo group.
- **Ubrogepant:** Allergan announced it plans to file a marketing application in early 2019 for ubrogepant, an oral CGRP receptor antagonist, in the United States for the treatment of migraine following the successful completion of 2 safety studies. This follows positive efficacy data, which was released at the beginning of 2018. In 1 study,

both doses of ubrogepant showed a statistically significant greater percentage of ubrogepant-treated patients achieving pain freedom at 2 hours after initial dosing versus placebo patients (50mg, 19.2%; 100mg, 21.2%; placebo, 11.8%). A statistically significantly higher percentage of patients treated with ubrogepant achieved absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose as compared to placebo.

- **Lasmiditan:** Eli Lilly announced the submission of a New Drug Application (NDA) for lasmiditan for the acute treatment of migraine with or without aura in adults. Lasmiditan is an investigational, oral, centrally-penetrant, selective serotonin 5-HT_{1F} agonist that is structurally and mechanistically distinct from other approved migraine therapies and lacks vasoconstrictive activity.
- **Atogepant:** Allergan announced positive results from a Phase 2b/3 clinical trial evaluating the safety, efficacy, and tolerability of atogepant, an orally-administered, investigational CGRP receptor antagonist for migraine prevention. All active treatment arms of atogepant met the primary endpoint across all doses and dose regimens, with a statistically significant reduction from baseline in monthly migraine/probably migraine (MPM) headache days in patients with episodic migraine treated with atogepant compared with placebo for 12 weeks. Allergan will continue with its Phase 3 program for atogepant following discussions with regulatory authorities.

Aimovig™ (Erenumab-aooe) Product Summary[20]

Indication(s): Aimovig™ (erenumab) is a CGRP receptor antagonist indicated for the preventive treatment of migraine in adults.

Dosing:

- Aimovig™ is a sterile solution for sub-Q administration. It is supplied as a SureClick® autoinjector in packs of 1 or 2 autoinjectors and as a single-dose prefilled syringe in packs of 1 or 2 syringes.
- The recommended dosage is 70mg once monthly (QM); some patients may benefit from a dosage of 140mg QM. The 140mg dose is administered QM as 2 consecutive injections of 70mg each.
- The needle shield within the white cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe may contain dry natural rubber, which may cause allergic reactions in individuals sensitive to latex.

Contraindication(s):

- None

Adverse Reactions: The most common adverse reactions in erenumab clinical studies (occurring in at least 3% of treated patients and more often than placebo) were injection site reactions and constipation.

Use in Specific Populations:

- Pregnancy: There is no adequate data on the developmental risk associated with the use of erenumab in pregnant women. No adverse effects on offspring were observed when

pregnant monkeys were administered erenumab throughout gestation. Serum erenumab exposures in pregnant monkeys were greater than those in humans at clinical doses.

- Lactation: There is no data on the presence of erenumab in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of erenumab have not been established in pediatric patients.
- Geriatric Use: Clinical studies of erenumab did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

Efficacy: The efficacy of erenumab was evaluated as a preventive treatment of episodic or chronic migraine in 3 randomized, double-blind, placebo-controlled studies: 2 studies in patients with episodic migraine (4 to 14 MMDs) and 1 study in patients with chronic migraine (≥15 MHDs with ≥8 MMDs). The studies enrolled patients with a history of migraine, with or without aura, according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria. In each of the studies, patients were allowed to use acute headache treatments including migraine-specific medications (i.e., triptans, ergotamine derivatives) and non-steroidal anti-inflammatory drugs (NSAIDs) during the study. Patients with medication overuse headache (MOH) as well as patients with myocardial infarction (MI), stroke, transient ischemic attacks (TIA), unstable angina, coronary artery bypass grafting (CABG), or other revascularization procedures within 12 months prior to screening were excluded from all of the studies.

- **Episodic Migraine:** Study 1 was a randomized, multi-center, 6-month, placebo-controlled, double-blind study evaluating erenumab for the preventive treatment of episodic migraine. A total of 955 patients with a history of episodic migraine were randomized to receive either erenumab 70mg (N=317), erenumab 140mg (N=319), or placebo (N=319) by sub-Q injection QM for 6 months. The primary efficacy endpoint was the change from baseline in mean MMD over months 4 to 6. Secondary endpoints included the achievement of a ≥50% reduction from baseline in mean MMD over months 4 to 6 ("≥50% MMD responders"), the change from baseline in mean monthly acute migraine-specific medication days over months 4 to 6, and the change from baseline in mean Migraine Physical Function Impact Diary (MPFID) over months 4 to 6. The MPFID measures the impact of migraine on everyday activities (EA) and physical impairment (PI) using an electronic diary administered daily. Monthly MPFID scores are averaged over 28 days, including days with and without migraine; scores are scaled from 0 to 100. Higher scores indicate worse impact on EA and PI. Reductions from baseline in MPFID scores indicate improvement. A total of 858 (90%) patients completed the 6-month double-blind study. Patients had a median age of 42 years (range: 18 to 65 years of age), 85% were female, and 89% were white. In this study, 3% of patients were taking concomitant preventive treatments for migraine. The mean migraine frequency at baseline was approximately 8 MMDs and was similar across treatment groups. Erenumab treatment demonstrated statistically significant improvements for key efficacy endpoints compared to placebo ($P<0.001$).

Efficacy Endpoint	Erenumab 70mg QM (N=312)	Erenumab 140mg QM (N=318)	Placebo (N=316)
Monthly Migraine Days (MMD)			
Change from baseline	-3.2	-3.7	-1.8
Difference from placebo	-1.4	-1.9	
≥50% MMD Responders			
% responders	43.3%	50.0%	26.6%
Difference from placebo	16.7%	23.4%	
Odds ratio relative to placebo	2.1	2.8	
Monthly Acute Migraine-Specific Medication Days			
Change from baseline	-1.1	-1.6	-0.2
Difference from placebo	-0.9	-1.4	

QM = once monthly; N = number; % = percentage

Compared to placebo, patients treated with erenumab 70mg QM and 140mg QM showed greater reductions from baseline in mean monthly MPFID everyday activity scores averaged over months 4 to 6 (difference from placebo: -2.2 for 70mg and -2.6 for 140mg; P<0.001 for both).

Study 2 was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating erenumab for the preventive treatment of episodic migraine. A total of 577 patients with a history of episodic migraine were randomized to receive either erenumab 70mg (N=286) or placebo (N=291) by sub-Q injection QM for 3 months. The primary efficacy endpoint was the change from baseline in MMD at month 3. Secondary endpoints included the achievement of a ≥50% reduction from baseline in MMD ("≥50% MMD responders"), the change from baseline in monthly acute migraine-specific medication days at month 3, and the proportion of patients with at least a 5-point score reduction from baseline in MPFID at month 3. A total of 546 (95%) patients completed the 3-month double-blind study. In Study 2, 6 to 7% of patients were taking concomitant preventive migraine treatment. The mean migraine frequency at baseline was approximately 8 MMDs and was similar between treatment groups. Erenumab treatment demonstrated statistically significant improvements for key efficacy endpoints compared to placebo.

Efficacy Endpoint	Erenumab 70mg QM (N=282)	Placebo (N=288)
Monthly Migraine Days (MMD)		
Change from baseline	-2.9	-1.8
P-value	<0.001	
≥50% MMD Responders		
% responders	39.7%	29.5%
Odds ratio relative to placebo (P-value)	1.6 (P=0.010)	
Monthly Acute Migraine-Specific Medication Days		
Change from baseline	-1.2	-0.6
P-value	0.002	

QM = once monthly; N = number; % = percentage

The pre-specified analysis for the MPFID was based on at least a 5-point reduction within-patient responder definition. Erenumab 70mg QM was not significantly better than placebo for the proportion of responders for EA (difference from placebo: 4.7%; odds ratio=1.2; P=0.26).

- **Chronic Migraine:** Study 3 was a randomized, multi-center, 3-month, placebo-controlled, double-blind study evaluating erenumab as a preventive treatment of chronic migraine. A total of 667 patients with a history of chronic migraine with or without aura were randomized to receive erenumab 70mg (N=191), erenumab 140mg (N=190), or placebo (N=286) by sub-Q injections QM for 3 months. The primary efficacy endpoint was the change from baseline in monthly migraine days at month 3. Secondary endpoints included the achievement of a ≥50% reduction from baseline in MMD ("≥50% MMD responders") and change from baseline in monthly acute migraine-specific medication days at month 3. A total of 631 (95%) patients completed the 3-month double-blind study. The mean migraine frequency at baseline was approximately 18 MMDs and was similar across treatment groups. Erenumab treatment demonstrated statistically significant improvements for key efficacy outcomes compared to placebo (P<0.001).

Efficacy Endpoint	Erenumab 70mg QM (N=188)	Erenumab 140mg QM (N=187)	Placebo (N=281)
Monthly Migraine Days (MMD)			
Change from baseline	-6.6	-6.6	-4.2
≥50% MMD Responders			
% responders	39.9%	41.2%	23.5%
Odds ratio relative to placebo	2.2	2.3	
Monthly Acute Migraine-Specific Medication Days			
Change from baseline	-3.5	-4.1	-1.6

QM = once monthly; N = number; % = percentage

Ajovy™ (Fremanezumab-vfrm) Product Summary[21,22]

Indication(s): Ajovy™ (fremanezumab) is a CGRP antagonist indicated for the preventive treatment of migraine in adults.

Dosing:

- Ajovy™ is a sterile, preservative-free solution for sub-Q administration. It is supplied as a 225mg/1.5mL single-dose pre-filled syringe.
- There are 2 sub-Q dosing options:
  - 225mg QM; or
  - 675mg every 3 months (quarterly). The 675mg quarterly dosage is administered as 3 consecutive injections of 225mg each.
- Fremanezumab should be stored refrigerated in the original outer carton. After removal from the refrigerator, fremanezumab must be used within 24 hours or discarded.

Contraindication(s):

- Patients with serious hypersensitivity to fremanezumab or to any of the excipients

Warnings and Precautions:

- Hypersensitivity Reactions: Hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria were reported with fremanezumab during clinical trials. If hypersensitivity occurs, fremanezumab should be discontinued and appropriate therapy should be instituted.

Adverse Reactions: The most common adverse reaction(s) (≥5% and greater than placebo) in fremanezumab clinical studies were injection site reactions.

Use in Specific Populations:

- Pregnancy: There is no adequate data on the developmental risk associated with the use of fremanezumab in pregnant women. Fremanezumab has a long half-life (31 days) and this should be taken into consideration for women who are pregnant or plan to become pregnant while using fremanezumab. Administration of fremanezumab to rats and rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at doses resulting in plasma levels greater than those expected clinically did not result in adverse effects on development.
- Lactation: There is no data on the presence of fremanezumab in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of fremanezumab have not been established in pediatric patients.
- Geriatric Use: Clinical studies of fremanezumab did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

Efficacy: The efficacy of fremanezumab was evaluated as a preventive treatment of episodic or chronic migraine in 2 multicenter, randomized, 3-month, double-blind, placebo-controlled studies. In both studies, patients were allowed to use acute headache treatments during the study and a subset of patients (21%) was allowed to use 1 additional concomitant, preventive medication (e.g., beta-blocker, calcium channel blocker, tricyclic antidepressant, SNRI, triptan, anticonvulsant). The studies excluded patients with a history of significant cardiovascular (CV) disease, vascular ischemia, or thrombotic events, such as cerebrovascular accident (CVA), TIA, deep vein thrombosis (DVT), or pulmonary embolism (PE).

- **Episodic Migraine:** Study 1 included adults with a history of episodic migraine (patients with <15 MHDs). All patients were randomized (1:1:1) to receive sub-Q injections of either fremanezumab 675mg every 3 months (quarterly), fremanezumab 225mg QM, or placebo QM, over a 3-month treatment period. The primary efficacy endpoint was the mean change from baseline in the average number of MMDs during the 3-month treatment period. Secondary endpoints included the proportion of patients reaching ≥50% reduction in average number MMDs ("≥50% MMD responders") during the 3-month treatment period, the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 3-month treatment

period, and the mean change from baseline the number of migraine days during the first month of the treatment period. A total of 875 patients (742 females, 133 males), ranging from 18 to 70 years of age, were randomized. A total of 791 patients completed the 3-month double-blind phase. Both QM and quarterly dosing regimens demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 3-month period (P<0.001).

Efficacy Endpoint	Fremanezumab 225mg QM (N=287)	Fremanezumab 675mg Quarterly (N=288)	Placebo (N=290)
Monthly Migraine Days (MMD)			
Baseline migraine days	8.9	9.2	9.1
Change from baseline	-3.7	-3.4	-2.2
Difference from placebo	-1.5	-1.2	
≥50% MMD Responders			
% responders	47.7%	44.4%	27.9%
Difference from placebo	19.8%	16.5%	
Monthly Acute Migraine-Specific Medication Days			
Change from baseline	-3.0	-2.9	-1.6
Difference from placebo	-1.4	-1.3	

QM = once monthly; N = number; % = percentage

- **Chronic Migraine:** Study 2 included adults with a history of chronic migraine (patients with ≥15 MHDs). All patients were randomized (1:1:1) to receive sub-Q injections of either fremanezumab 675mg starting dose followed by 225mg QM, 675mg every 3 months, or placebo QM, over a 3-month treatment period. The primary efficacy endpoint was the mean change from baseline in the average number of MHDs of at least moderate severity during the 3-month treatment period. The secondary endpoints were the mean change from baseline in the average number of MMDs during the 3-month treatment period, the proportion of patients reaching ≥50% reduction in the average number of MHDs of at least moderate severity during the 3-month treatment period, the mean change from baseline in the monthly average number of days of use of any acute headache medication during the 3-month treatment period, and the mean change from baseline in the number of headache days of at least moderate severity during the first month of treatment. A total of 1,130 patients (991 females, 139 males), ranging from 18 to 70 years of age, were randomized. A total of 1,034 patients completed the 3-month double-blind phase. Both QM and quarterly dosing regimens of fremanezumab treatment demonstrated statistically significant improvement for key efficacy outcomes compared to placebo.

Efficacy Endpoint	Fremanezumab 225mg QM (N=375)*	Fremanezumab 675mg Quarterly (N=375)	Placebo (N=371)
Baseline headache days of any severity^	20.3	20.4	20.3
Baseline headache days of at least moderate severity~	12.8	13.2	13.3

Efficacy Endpoint	Fremanezumab 225mg QM (N=375)*	Fremanezumab 675mg Quarterly (N=375)	Placebo (N=371)
Δ from baseline in the avg. # of MHDs of at least moderate severity	-4.6	-4.3	-2.5
Difference from placebo	-2.1	-1.8	
Δ from baseline in the avg. # of MMDs	-5.0	-4.9	-3.2
Δ from baseline in avg. # of MHDs of at least moderate severity at 4 weeks after 1st dose	-4.6	-4.6	-2.3
% of patients with ≥50% reduction in avg. # of MHDs of at least moderate severity	40.8%	37.6%	18.1%
Δ from baseline in monthly average # of days of acute headache medication use	-4.2	-3.7	-1.9

QM = monthly; N = number; Δ = change; avg. = average; # = number; % = percentage
*Patients received a 675mg starting dose.
^Used for chronic migraine diagnosis.
~Used for primary endpoint analysis.

Emgality™ (Galcanezumab-gnlm) Product Summary[23]

Indication(s): Emgality™ (galcanezumab) is a CGRP antagonist indicated for the preventive treatment of migraine in adults.

Dosing:

- Emgality™ is a sterile, preservative-free solution for sub-Q administration. It is supplied in 120mg/mL single-dose prefilled pens and prefilled syringes.
- The recommended dose is 240mg as a loading dose (administered as 2 consecutive injections of 120mg each), followed by monthly doses of 120mg.
- Galcanezumab should be stored in the refrigerator in the original carton until use. It may be stored out of refrigeration in the original carton at temperatures up to 86°F for up to 7 days.

Contraindication(s):

- Patients with serious hypersensitivity to galcanezumab or to any of the excipients

Warnings and Precautions:

- Hypersensitivity Reactions: Hypersensitivity reactions (e.g., rash, urticaria, dyspnea) have been reported with galcanezumab in clinical studies. If a serious or severe hypersensitivity reaction occurs, galcanezumab should be discontinued and appropriate therapy initiated. Hypersensitivity reactions can occur days after administration, and may be prolonged.

Adverse Reactions: The most common adverse reaction(s) (incidence ≥2% and at least 2% greater than placebo) in galcanezumab clinical studies were injection site reactions.

Use in Specific Populations:

- Pregnancy: There is no adequate data on the developmental risk associated with the use of galcanezumab in pregnant women. Administration of galcanezumab to rats and

rabbits during the period of organogenesis or to rats throughout pregnancy and lactation at plasma exposures greater than that expected clinically did not result in adverse effects on development.

- Lactation: There is no data on the presence of galcanezumab in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of galcanezumab have not been established in pediatric patients.
- Geriatric Use: Clinical studies of galcanezumab did not include sufficient numbers of patients 65 years of age and older to determine whether they respond differently from younger patients.

Efficacy: The efficacy of galcanezumab was evaluated as a preventive treatment of episodic or chronic migraine in 3 multicenter, randomized, double-blind, placebo-controlled studies: (2) 6-month studies in patients with episodic migraine and (1) 3-month study in patients with chronic migraine. In each of the 3 studies, patients were randomized in a 1:1:2 ratio to receive QM sub-Q injections of galcanezumab 120mg, galcanezumab 240mg, or placebo. All patients in the 120mg group received an initial 240mg loading dose. Patients were allowed to use acute headache treatments, including migraine-specific medications (i.e., triptans, ergotamine derivatives), NSAIDs, and acetaminophen during the study.

- **Episodic Migraine:** In Study 1 and 2, adult patients with a history of episodic migraine (4 to 14 MMDs) were enrolled. The studies excluded patients on any other migraine preventive treatment, patients with MOH, patients with electrocardiogram (ECG) abnormalities compatible with an acute CV event, and patients with a history of stroke, MI, unstable angina, percutaneous coronary intervention (PCI), CABG, DVT, or PE within 6 months of screening. The primary efficacy endpoint was the mean change from baseline in the number of MMDs over the 6-month treatment period. Key secondary endpoints included response rates (the mean percentages of patients reaching at least 50%, 75%, and 100% reduction from baseline in the number of MMDs over the 6-month treatment period), the mean change from baseline in the number of MMDs with use of any acute headache medication during the 6-month treatment period, and the impact of migraine on daily activities, as assessed by the mean change from baseline in the average Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) Role Function-Restrictive domain score during the last 3 months of treatment (months 4 to 6). Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities. In Study 1, a total of 858 patients (718 females, 140 males) ranging in age from 18 to 65 years, were randomized. A total of 703 patients completed the 6-month double-blind phase. In Study 2, a total of 915 patients (781 female, 134 male) ranging in age from 18 to 65 years, were randomized. A total of 785 patients completed the 6-month double-blind phase. Galcanezumab 120mg demonstrated statistically significant improvements for efficacy endpoints compared to placebo over the 6-month period. Galcanezumab treatment with the 240mg QM dose showed no additional benefit over the galcanezumab 120mg QM dose.

Efficacy Endpoint	Study 1		Study 2	
	Galcanezumab 120mg QM (N=210)	Placebo (N=425)	Galcanezumab 120mg QM (N=226)	Placebo (N=450)
Monthly Migraine Headache Days (Over Months 1 to 6)				
Baseline migraine headache days	9.2	9.1	9.1	9.2
Mean change from baseline	-4.7	-2.8	-4.3	-2.3
Difference from placebo*	-1.9		-2.0	
≥50% Migraine Headache Days Responders (Over Months 1 to 6)				
% responders*	62%	39%	59%	36%
≥75% Migraine Headache Days Responders (Over Months 1 to 6)				
% responders*	39%	19%	34%	18%
≥100% Migraine Headache Days Responders (Over Months 1 to 6)				
% responders*	16%	6%	12%	6%
Monthly Migraine Headache Days that Acute Medication was Taken (Over Months 1 to 6)				
Mean change from baseline (days)*	-4.0	-2.2	-3.7	-1.9
MSQ Role Function-Restrictive Domain Score (Over Months 4 to 6)				
Baseline	51.4	52.9	52.5	51.4
Mean change from baseline^	32.4	24.7	28.5	19.7
Difference from placebo*	7.7		8.8	

QM = monthly; N = number; % = percentage; MSQ = Migraine-Specific Quality of Life Questionnaire
*P<0.001
^N = 189 for galcanezumab 120mg and N = 377 for placebo in Study 1; N = 213 for galcanezumab 120mg and N = 396 for placebo in Study 2; higher scores indicate less impact of migraine on daily activities.

- **Chronic Migraine:** Study 3 included adults with a history of chronic migraine (≥15 MHDs with ≥8 MMDs). In Study 3, a subset of patients (15%) was allowed to use a concomitant migraine preventive medication and patients with MOH were allowed to enroll. The study excluded patients with ECG abnormalities compatible with an acute CV event and patients with a history of stroke, MI, unstable angina, PCI, CABG, DVT, or PE within 6 months of screening. The primary endpoint was the mean change from baseline in the number of MMDs over the 3-month treatment period. The secondary endpoints were response rates (the mean percentages of patients reaching at least 50%, 75% and 100% reduction from baseline in the number of MMDs over the 3-month treatment period), the mean change from baseline in the number of MMDs with use of any acute headache medication during the 3-month treatment period, and the impact of migraine on daily activities as assessed by the mean change from baseline in the MSQ v2.1 Role Function-Restrictive domain score at month 3. Scores are scaled from 0 to 100, with higher scores indicating less impact of migraine on daily activities. A total of 1,113 patients (946 female, 167 male) ranging in age from 18 to 65 years were randomized. A total of 1,037 patients completed the 3-month double-blind phase. Galcanezumab 120mg demonstrated statistically significant improvement for the mean change from baseline in the number of MMDs over the 3-month treatment period, and in the mean percentage of patients reaching ≥50% reduction from baseline in the number of MMDs

over the 3-month treatment period. Galcanezumab treatment with the 240mg QM dose showed no additional benefit over the galcanezumab 120mg QM dose.

Efficacy Endpoint	Galcanezumab 120mg QM (N=273)	Placebo (N=538)
Monthly Migraine Headache Days (Over Months 1 to 3)		
Baseline migraine headache days	19.4	19.6
Mean change from baseline	-4.8	-2.7
Difference from placebo*	-2.1	
≥50% Migraine Headache Days Responders (Over Months 1 to 3)		
% Responders*	28%	15%

QM = monthly; % = percentage; N = number
*P<0.001

Cost Comparison: CGRP Antagonists

Medication	Cost Per mL	Cost Per Month	Cost Per Year
Aimovig™ (erenumab) 70mg/mL	$278.67 - $557.26^	$278.67 - $557.26^	$3,344.04 - $6,687.12^
Ajovy™ (fremanezumab) 225mg/1.5mL	$369.90	$554.85	$6,658.20
Emgality™ (galcanezumab) 120mg/mL	$575.00	$575.00*	$6,900.00*

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.
^Aimovig™ cost based on 70mg monthly dosing; some patients may benefit from 140mg QM (as 2 consecutive injections of 70mg each). Aimovig™ is currently supplied in 1 and 2 packs.
*Emgality™ cost based on maintenance dosing of 120mg QM. For initiation of therapy, a loading dose of 240mg (as 2 consecutive 120mg doses) is required.

Recommendations

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

1. Moving Treximet® (sumatriptan/naproxen) from the Special Prior Authorization (PA) Tier to Tier-1 based on net cost.
2. Updating the Onzetra® Xsail® (sumatriptan nasal powder) PA criteria as shown in the following in red.
3. Removing Sumavel® DosePro® (sumatriptan 6mg/0.5mL injection) from the Tier Chart based on product discontinuation.
4. The prior authorization of Aimovig™ (erenumab-aooe), Ajovy™ (fremanezumab-vfrm), and Emgality™ (galcanezumab-gnlm) with the following criteria. Please note, criteria may change based on supplemental rebate participation.

Proposed changes are shown in red in the following Anti-Migraine Medications Tier Chart:

Anti-Migraine Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
eletriptan (Relpax®) – **brand only**	naratriptan (Amerge®)	almotriptan (Axert®)	dihydroergotamine injection (D.H.E. 45®)

Anti-Migraine Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
rizatriptan (Maxalt®, Maxalt MLT®)	zolmitriptan (Zomig®, Zomig-ZMT®, Zomig® nasal spray)	frovatriptan (Frova®)	dihydroergotamine nasal spray (Migranal®)
sumatriptan (Imitrex®)			eletriptan (Relpax®) – **generic**
sumatriptan/naproxen (Treximet®)			sumatriptan injection (Imitrex®)
			~~**sumatriptan injection (Sumavel® DosePro®)**~~
			sumatriptan injection (Zembrace™ SymTouch™)
			sumatriptan nasal powder (Onzetra® Xsail®)
			sumatriptan nasal spray (Imitrex®)

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

Anti-Migraine Medications Tier-2 Approval Criteria:

1. A trial of all available Tier-1 products with inadequate response or a patient-specific, clinically significant reason why a Tier-1 product is not appropriate for the member; or
2. Documented adverse effect(s) to all available Tier-1 products; or
3. Previous success with a Tier-2 product within the last 60 days.

Anti-Migraine Medications Tier-3 Approval Criteria:

1. A trial of all available Tier-1 and Tier-2 products with inadequate response or a patient-specific, clinically significant reason why a lower tiered product is not appropriate for the member; or
2. Documented adverse effect(s) to all available Tier-1 and Tier-2 products; or
3. Previous success with a Tier-3 product within the last 60 days; and
4. Use of any non-oral formulation will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation.

Anti-Migraine Medications Special Prior Authorization (PA) Approval Criteria:

1. Use of any non-oral sumatriptan formulation will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation or lower-tiered triptan medications.
2. Use of ~~Onzetra® Xsail® or~~ Zembrace™ SymTouch™ will require a patient-specific, clinically significant reason why the member cannot use all available generic formulations of sumatriptan (tablets, nasal spray, and injection) or lower-tiered triptan medications.

3. ~~Use of Treximet® (sumatriptan/naproxen) will require a patient-specific, clinically significant reason why the member cannot use the individual components separately or lower-tiered triptan medications.~~
4. Use of dihydroergotamine injection (D.H.E. 45®) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications.
5. Use of dihydroergotamine nasal spray (Migranal®) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications or dihydroergotamine injection (D.H.E. 45®).
6. Use of Ergomar® (ergotamine sublingual tablets) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications; and
    a. Member must not have any of the contraindications for use of Ergomar® (e.g., coadministration with a potent CYP 3A4 inhibitor, women who are or may become pregnant, peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, hypersensitivity to any of the components); and
    b. A quantity limit of 20 tablets per 28 days will apply.
7. Use of generic eletriptan will require a patient-specific, clinically significant reason why the member cannot use the brand formulation of Relpax® (brand formulation is preferred).

Aimovig™ (Erenumab-aooe) and Ajovy™ (Fremanezumab-vfrm) Approval Criteria:

1. An FDA approved indication for the preventive treatment of migraine in adults; and
2. Member must be 18 years of age or older; and
3. Member has documented chronic migraine or episodic migraine headaches:
    a. Chronic migraine: 15 or more headache days per month with 8 or more migraine days per month; or
    b. Episodic migraine: 4 to 14 migraine days per month on average for the past 3 months; and
        i. For episodic migraine, member must have had a history of migraines for a duration of 12 months or longer; and
4. Non-migraine medical conditions known to cause headache have been ruled out and/or have been treated. This includes, but is not limited to:
    a. Increased intracranial pressure (e.g., tumor, pseudotumor cerebri, central venous thrombosis); or
    b. Decreased intracranial pressure (e.g., post-lumbar puncture headache, dural tear after trauma); and
5. Migraine headache exacerbation secondary to other medication therapies or therapies have been ruled out and/or treated. This includes, but is not limited to:
    a. Hormone replacement therapy or hormone-based contraceptives; and
    b. Chronic insomnia; and
    c. Obstructive sleep apnea; and
6. The member has failed medical migraine preventive therapy with at least 3 agents with different mechanisms of action. This includes, but is not limited to:
    a. Select antihypertensive therapy (e.g., beta-blocker therapy); or

   b. Select anticonvulsant therapy; or
   c. Select antidepressant therapy [e.g., tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI)]; and
7. Member is not frequently taking medications that are known to cause medication overuse headaches (MOH or rebound headaches) in the absence of intractable conditions known to cause chronic pain. MOH are a frequent cause of chronic headaches. A list of prescription or non-prescription medications known to cause MOH includes, but is not limited to:
   a. Decongestants (alone or in combination products) (≥10 days/month for >3 months); and
   b. Combination analgesics containing caffeine and/or butalbital (≥10 days/month for >3 months); and
   c. Opioids (≥10 days/month for >3 months); and
   d. Analgesic medications including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) (≥15 days/month for >3 months); and
   e. Ergotamine-containing medications (≥10 days/month for >3 months); and
   f. Triptans (≥10 days/month for >3 months); and
8. Member is not taking any medications that are likely to be the cause of the headaches; and
9. Member must have been evaluated within the last 6 months by a neurologist for migraine headaches and the requested medication (e.g., Aimovig™, Ajovy™) recommended as treatment (not necessarily prescribed by a neurologist); and
10. Member will not use concurrently with botulinum toxin for the prevention of migraine or with an alternative calcitonin gene-related peptide (CGRP) inhibitor; and
11. Members who smoke or use tobacco products will not be approved; and
12. Prescriber must verify that member has been counseled on appropriate use, storage of the medication, and administration technique; and
13. A patient-specific, clinically significant reason why member cannot use Emgality™ (galcanezumab-gnlm) must be provided; and*
14. Initial approvals will be for the duration of 3 months. Compliance and information regarding efficacy, such as a reduction in monthly migraine days, will be required for continued approval. Continuation approvals will be granted for the duration of 1 year; and
15. Quantity limits will apply based on FDA-approved dosing:
   a. For Aimovig™, a quantity limit of 2 syringes or autoinjectors per 30 days will apply. The autoinjector 2-pack [(2) 70mg autoinjectors] will be preferred in place of the individual autoinjector. Claims for members receiving the 70mg dose should be submitted for a 60-day supply; and
   b. For Ajovy™, a quantity limit of 1 syringe per 30 days will apply. Requests for quarterly dosing (675mg every 3 months) will be approved for a quantity limit override upon meeting Ajovy™ approval criteria.
   [*The manufacturer of Emgality™ has currently provided a supplemental rebate to be the preferred calcitonin gene-related peptide (CGRP) inhibitor; however,

Emgality™ will follow the original criteria similar to the other CGRP inhibitors if the manufacturer chooses not to participate in supplemental rebates.]

Emgality™ (Galcanezumab-gnlm) Approval Criteria:*

1. An FDA approved indication for the preventive treatment of migraine in adults; and
2. Member must be 18 years of age or older; and
3. Member has documented chronic migraine or episodic migraine headaches:
    a. Chronic migraine: 15 or more headache days per month with 8 or more migraine days per month; or
    b. Episodic migraine: 4 to 14 migraine days per month on average for the past 3 months; and
        i. For episodic migraine, member must have had a history of migraines for a duration of 12 months or longer; and
4. Non-migraine medical conditions known to cause headache have been ruled out and/or have been treated. This includes, but is not limited to:
    a. Increased intracranial pressure (e.g., tumor, pseudotumor cerebri, central venous thrombosis); or
    b. Decreased intracranial pressure (e.g., post-lumbar puncture headache, dural tear after trauma); and
5. Migraine headache exacerbation secondary to other medication therapies or therapies have been ruled out and/or treated. This includes, but is not limited to:
    a. Hormone replacement therapy or hormone-based contraceptives; and
    b. Chronic insomnia; and
    c. Obstructive sleep apnea; and
6. The member has failed medical migraine preventive therapy with at least 2* agents with different mechanisms of action. (*The manufacturer of Emgality™ has currently provided a supplemental rebate to require a trial with 2 other migraine preventative therapies; however, Emgality™ will follow the original criteria and require trials with 3 other migraine preventative therapies if the manufacturer chooses not to participate in supplemental rebates.) This includes, but is not limited to:
    a. Select antihypertensive therapy (e.g., beta-blocker therapy); or
    b. Select anticonvulsant therapy; or
    c. Select antidepressant therapy [e.g., tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI)]; and
7. Member is not frequently taking medications that are known to cause medication overuse headaches (MOH or rebound headaches) in the absence of intractable conditions known to cause chronic pain. MOH are a frequent cause of chronic headaches. A list of prescription or non-prescription medications known to cause MOH includes, but is not limited to:
    a. Decongestants (alone or in combination products) (≥10 days/month for >3 months); and
    b. Combination analgesics containing caffeine and/or butalbital (≥10 days/month for >3 months); and
    c. Opioids (≥10 days/month for >3 months); and

d. Analgesic medications including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) (≥15 days/month for >3 months); and
e. Ergotamine-containing medications (≥10 days/month for >3 months); and
f. Triptans (≥10 days/month for >3 months); and

8. Member is not taking any medications that are likely to be the cause of the headaches; and
9. Member must have been evaluated within the last 6 months by a neurologist for migraine headaches and the requested medication (e.g., Emgality™) recommended as treatment (not necessarily prescribed by a neurologist); and
10. Member will not use concurrently with botulinum toxin for the prevention of migraine or with an alternative calcitonin gene-related peptide (CGRP) inhibitor; and
11. Members who smoke or use tobacco products will not be approved; and
12. Prescriber must verify that member has been counseled on appropriate use, storage of the medication, and administration technique; and
13. Initial approvals will be for the duration of 3 months. Compliance and information regarding efficacy, such as a reduction in monthly migraine days, will be required for continued approval. Continuation approvals will be granted for the duration of 1 year; and
14. A quantity limit of 1 syringe or pen per 30 days will apply. Requests for an initial loading dose (240mg administered as 2 consecutive 120mg injections) will be approved for a quantity limit override upon meeting Emgality™ approval criteria.
[*The manufacturer of Emgality™ has currently provided a supplemental rebate to be the preferred calcitonin gene-related peptide (CGRP) inhibitor; however, Emgality™ will follow the original criteria similar to the other CGRP inhibitors if the manufacturer chooses not to participate in supplemental rebates.]

Utilization Details of Anti-Migraine Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
TIER-1 PRODUCTS						
SUMATRIPTAN TAB 100MG	3,363	1,390	$53,543.00	$1.11	$15.92	18.47%
SUMATRIPTAN TAB 50MG	3,169	1,654	$51,319.73	$1.16	$16.19	17.70%
SUMATRIPTAN TAB 25MG	2,054	1,236	$36,997.13	$1.34	$18.01	12.76%
RIZATRIPTAN TAB 10MG	1,101	525	$21,254.17	$0.84	$19.30	7.33%
RIZATRIPTAN TAB 10MG ODT	773	386	$16,433.23	$0.91	$21.26	5.67%
RIZATRIPTAN TAB 5MG	406	198	$8,442.44	$0.88	$20.79	2.91%
RIZATRIPTAN TAB 5MG ODT	368	216	$8,069.96	$0.99	$21.93	2.78%
RELPAX TAB 40MG	53	37	$27,487.13	$35.70	$518.63	9.48%
RELPAX TAB 20MG	15	11	$7,692.51	$46.62	$512.83	2.65%
TIER-1 SUBTOTAL	**11,302**	**5,653**	**$231,239.30**	**$1.27**	**$20.46**	**79.75%**
TIER-2 PRODUCTS						
NARATRIPTAN TAB 2.5MG	33	10	$1,092.03	$1.36	$33.09	0.38%
ZOMIG SPR 5MG	30	7	$11,731.93	$13.04	$391.06	4.05%
ZOLMITRIPTAN TAB 5MG	27	10	$1,212.64	$1.55	$44.91	0.42%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
ZOMIG SPR 2.5MG	14	4	$5,743.30	$13.67	$410.24	1.98%
ZOLMITRIPTAN TAB 2.5MG	10	3	$434.41	$1.45	$43.44	0.15%
ZOLMITRIPTAN TAB 5MG ODT	10	2	$502.97	$1.80	$50.30	0.17%
NARATRIPTAN TAB 1MG	6	2	$266.40	$2.90	$44.40	0.09%
ZOLMITRIPTAN TAB 2.5 MG	2	2	$106.92	$1.78	$53.46	0.04%
TIER-2 SUBTOTAL	**132**	**40**	**$21,090.60**	**$5.80**	**$159.78**	**7.28%**
TIER-3 PRODUCTS						
FROVATRIPTAN TAB 2.5MG	2	1	$596.32	$33.13	$298.16	0.21%
ALMOTRIPTAN TAB 12.5MG	2	1	$666.89	$22.23	$333.45	0.23%
TIER-3 SUBTOTAL	**4**	**2**	**$1,263.21**	**$26.32**	**$315.80**	**0.44%**
SPECIAL PRIOR AUTHORIZATION PRODUCTS						
ELETRIPTAN TAB 40MG	89	52	$9,702.21	$7.85	$109.01	3.35%
ELETRIPTAN TAB 20MG	67	36	$6,396.32	$7.98	$95.47	2.21%
SUMATRIPTAN INJ 6MG/0.5ML	28	6	$10,298.69	$27.68	$367.81	3.55%
SUMATRIPTAN SPR 20MG/ACT	12	2	$3,507.77	$12.18	$292.31	1.21%
SUMATRIPTAN INJ 6MG/0.5ML	11	1	$5,492.06	$16.64	$499.28	1.89%
SUMATRIPTAN INJ 6MG/0.5ML	9	1	$593.74	$5.40	$65.97	0.20%
SUMATRIPTAN SPR 5MG/ACT	1	1	$294.47	$18.40	$294.47	0.10%
SPECIAL PA SUBTOTAL	**217**	**99**	**$36,285.26**	**$11.50**	**$167.21**	**12.51%**
TOTAL	**11,655**	**5,292***	**$289,878.37**	**$1.53**	**$24.87**	**100%**

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

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Appendix O

30-Day Notice to Prior Authorize Gamifant® (Emapalumab-lzsg)

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3,4]

Hemophagocytic lymphohistiocytosis (HLH) is an aggressive and life-threatening syndrome of excessive immune activation that causes inflammation and tissue destruction. It most frequently affects infants from birth to 18 months of age, but the disease is also observed in children and adults of all ages. HLH can occur as a genetic disorder ("primary HLH") or as a sporadic disorder occurring secondary to another condition ("secondary HLH"). Infection is a common trigger for both primary and secondary HLH.

HLH is thought to be caused by the absence of normal downregulation by activated macrophages and lymphocytes. Most patients with HLH have impaired function of natural killer (NK) cells and cytotoxic lymphocytes (CTLs), coupled with excessive activation of macrophages. Excessive cytokine production by macrophages, NK cells, and CTLs is thought to be a primary mediator of tissue damage that is responsible for multiorgan failure and the high mortality rate of HLH. It has been shown that one of the underlying gene defects involves mutations in the gene encoding perforin (*PRF*). Perforin is secreted from CTLs and NK cells. Mutations in PRF account for 20 to 40% of all affected primary HLH patients. Other genetic mutations (e.g., *UNC13D*, *STX11*) have been shown to cause primary HLH as well. The most typical findings of HLH are fever, hepatosplenomegaly, and cytopenias. Other common findings include hypertriglyceridemia, hypofibrinogenemia, elevated levels of ferritin, and neurological symptoms. Patients with HLH can have a single episode of the disease or relapsing episodes, with relapses occurring most often in patients with primary HLH.

The incidence of primary HLH is estimated to be around 1 in 50,000 live-born children with approximately 100 patients diagnosed each year in the United States. The highest incidence is in those <3 months of age. The male-to-female ratio is close to 1:1. All forms of HLH, including cases treated adequately, may have a high mortality rate. The long-term prognosis of primary forms without treatment is poor, with a median survival of <2 months to 6 months after diagnosis. Even with treatment, only 21 to 26% are expected to survive 5 years. The course of the disease and life expectancy are not well studied in adults with primary HLH.

According to the Histiocyte Society revised HLH-2004: Diagnostic and Therapeutic Guidelines for Hemophagocytic Lymphohistiocytosis published in the journal *Pediatric Blood & Cancer*, diagnosis requires 5 of the 8 criteria to be fulfilled. The 8 diagnostic criteria include: 1) fever; 2) splenomegaly; 3) cytopenias affecting at least 2 of 3 lineages in the peripheral blood; 4) hypertriglyceridemia and/or hypofibrinogenemia; 5) hemophagocytosis in bone marrow, spleen, or lymph nodes with no malignancy; 6) low or absent NK-cell activity; 7) hyperferritinemia; and 8) high levels of soluble interleukin-2 receptor (sCD25). The guidelines

indicate that patients with a genetic diagnosis consistent with HLH do not necessarily need to fulfill the diagnostic criteria.

The current treatment guidelines suggest use of etoposide, dexamethasone, and cyclosporine (CSA) for initial therapy. Additionally, intrathecal therapy with methotrexate (MTX) and a corticosteroid is recommended for patients with signs of persistent, active central nervous system (CNS) disease and in cases of CNS reactivation. An alternative approach includes a regimen of corticosteroids, CSA, and antithymocyte globulin (ATG). Hematopoietic stem cell transplantation (HSCT) is indicated for those who do not fully recover by the end of the initial 8 weeks of induction chemotherapy. Chemotherapy is continued until a HSCT donor becomes available. HLH is refractory to treatment in some patients, and in other patients, HLH progresses as induction therapy is being tapered, while awaiting HSCT, or after having achieved remission. Relapsed, refractory, or progressive HLH may be manifested by clinical deterioration or by steadily increasing disease markers. In November 2018, the U.S. Food and Drug Administration (FDA) approved Gamifant® (emapalumab-lzsg) for the treatment of adult and pediatric patients with primary HLH with refractory, recurrent, or progressive disease or who are intolerant to conventional HLH therapy.

Gamifant® (Emapalumab-lzsg) Product Summary[5,6,7]

Indication(s): Gamifant® (emapalumab-lzsg) is an interferon gamma (IFNγ) blocking antibody indicated for the treatment of adult and pediatric (newborn and older) patients with primary HLH with refractory, recurrent, or progressive disease or who are intolerant to conventional HLH therapy.

Dosing:

- Gamifant® is available as 5mg/mL solution for intravenous (IV) infusion supplied as 10mg/2mL and 50mg/10mL single-dose vials (SDV).
- The recommended starting dose of emapalumab is 1mg/kg given as an IV infusion over 1 hour twice per week (every 3 to 4 days).
- Subsequent doses may be increased based on clinical and laboratory criteria to a maximum of 10mg/kg. Emapalumab may be titrated up if disease response is unsatisfactory. After the patient's clinical condition is stabilized, the dose should be decreased to the previous level to maintain clinical response.
- Emapalumab should be continued until HSCT is performed or unacceptable toxicity occurs.
- For patients who are not receiving baseline dexamethasone treatment, dexamethasone should be started at a daily dose of at least 5 to 10mg/m^2 the day before emapalumab treatment begins. For patients receiving baseline dexamethasone, the current dose may be continued if it is at least 5mg/m^2/day.
- During treatment with emapalumab, patients should be monitored for tuberculosis (TB), adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated.

Mechanism of Action: Emapalumab is a monoclonal antibody that binds to and neutralizes IFNγ. Nonclinical data suggest that IFNγ plays a pivotal role in the pathogenesis of HLH by being hypersecreted.

Contraindication(s): None

Warnings and Precautions:

- Infections: Emapalumab may increase the risk of fatal and serious infections involving specific pathogens favored by IFNγ neutralization including mycobacteria, herpes zoster virus, and *Histoplasma capsulatum*. In 32% of patients receiving emapalumab in clinical trials, serious infections such as sepsis, pneumonia, bacteremia, disseminated histoplasmosis, necrotizing fasciitis, viral infections, and perforated appendicitis were observed. The reported infections were viral (41%), bacterial (35%), fungal (9%), and the pathogen was not identified in 15% of cases. Patients should be evaluated for TB risk factors and tested for latent infection [purified protein derivative (PPD) testing, polymerase chain reaction (PCR), or IFNγ release assay] prior to initiating emapalumab. TB prophylaxis should be administered to patients at risk for TB or known to have a positive PPD test result. Prophylaxis for herpes zoster, *Pneumocystis jirovecii,* and fungal infection(s) should be administered to patients prior to receiving emapalumab. While receiving emapalumab patients should be closely monitored for signs or symptoms of infection.
- Increased Risk of Infection with Use of Live Vaccines: Live or live attenuated vaccines should not be administered to patients receiving emapalumab and for at least 4 weeks after the last dose of emapalumab. The safety of immunization with live vaccines during or following emapalumab therapy has not been studied.
- Infusion-Related Reactions (IRRs): IRRs including drug eruption, pyrexia, rash, erythema, and hyperhidrosis were reported with emapalumab treatment in 27% of patients. In one-third of these patients, the IRR occurred during the first infusion. All IRRs were reported as mild-to-moderate.

Adverse Reactions:

- In clinical trials, serious adverse reactions were reported in 53% of patients. The most common serious adverse reactions (≥3%) included infections, gastrointestinal (GI) hemorrhage, and multiorgan dysfunction. Fatal adverse reactions occurred in 2 (6%) patients and included septic shock and GI hemorrhage. Disseminated histoplasmosis led to drug discontinuation in 1 patient.
- The most commonly reported adverse reactions (≥20%) in clinical trials were infections, hypertension, IRRs, and pyrexia.

Use in Specific Populations:

- Pregnancy: There are no available data on emapalumab use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In an animal reproduction study, a murine surrogate anti-mouse IFNγ antibody administered to pregnant mice throughout gestation crossed the placental barrier, and no fetal harm was observed.

- Lactation: There is no information regarding the presence of emapalumab in human milk, the effects on the breastfed child, or the effects on milk production. Published data suggest that only limited amounts of therapeutic antibodies are found in breast milk and they do not enter the neonatal and infant circulations in substantial amounts.
- Pediatric Use: The safety and effectiveness of emapalumab have been established in pediatric patients, newborn and older, with primary HLH that is reactivated or refractory to conventional therapies. Use of emapalumab is supported by a single-arm trial in 27 pediatric patients with reactivated or refractory primary HLH. This study included pediatric patients in the following age groups: 5 patients newborn to 6 months of age, 10 patients 6 months to 2 years of age, and 12 patients 2 to 13 years of age.
- Geriatric Use: Clinical studies of emapalumab did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Efficacy: The efficacy of emapalumab was evaluated in a multicenter, open-label, single-arm trial in 27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy. Patients were required to fulfill the following criteria for enrollment: primary HLH based on a molecular diagnosis or family history consistent with primary HLH or 5 out of the 8 diagnostic criteria fulfilled. Patients had to have evidence of active disease as assessed by the treating physician. Patients had to fulfill 1 of the following criteria as assessed by the treating physician: having not responded, not achieved a satisfactory response, not maintained a satisfactory response to conventional HLH therapy, or intolerance to conventional HLH treatments. Patients with active infections caused by specific pathogens favored by IFNγ neutralization were excluded from the trial (e.g., mycobacteria and *Histoplasma capsulatum*). The study treatment duration was up to 8 weeks after which patients could continue treatment in the extension study. All patients received an initial starting dose of emapalumab of 1mg/kg every 3 days. Subsequent doses could be increased to a maximum of 10mg/kg based on clinical and laboratory parameters interpreted as an unsatisfactory response. A total of 44% of patients remained at a dose of 1mg/kg, 30% of patients increased to 3 to 4mg/kg, and 26% of patients increased to 6 to 10mg/kg. The median time to dose increase was 27 days (range: 3 to 31 days) with 22% of patients requiring a dose increase in the first week of treatment. Patients received emapalumab for a median of 59 days (range: 14 to 245 days), and all patients received dexamethasone as background HLH treatment with doses between 5 to 10mg/m^2/day. CSA was continued if administered prior to screening. Patients receiving MTX and corticosteroids administered intrathecally at baseline could continue these treatments. All patients received previous HLH treatments. Patients received a median of 3 prior agents before enrollment into the trial. Prior regimens included combinations of the following agents: dexamethasone, etoposide, CSA, and ATG.

The primary endpoint of the study was overall response rate (ORR) at the end of treatment, defined as achievement of either a complete or partial response or HLH improvement. ORR was evaluated using an algorithm that included the following objective clinical and laboratory

parameters: fever, splenomegaly, CNS symptoms, complete blood count, fibrinogen and/or D-dimer, ferritin, and sCD25 levels. Complete response was defined as normalization of all HLH abnormalities. Partial response was defined as normalization of ≥3 HLH abnormalities. HLH improvement was defined as ≥3 HLH abnormalities improved by at least 50% from baseline. The study achieved its primary endpoint, with 63% of patients demonstrating overall response at the end of the treatment period (P=0.013). Additionally, 70% of trial participants continued on to HSCT.

Cost: The Wholesale Acquisition Cost (WAC) of Gamifant® (emapalumab) is $3,711 per milliliter (mL). This results in a cost per dose of $7,422 and a yearly cost of $712,512 for the minimum dose of 1mg/kg twice weekly in a 10kg child. At a maximum dose of 10mg/kg in a 10kg child, the cost per dose is $74,220 and the annual cost is $7,125,120. Dosing is weight-based and may be adjusted based on patient response; therefore, pricing will vary.

Recommendations

The College of Pharmacy recommends the prior authorization of Gamifant® (emapalumab-lzsg) with the following criteria:

Gamifant® (Emapalumab-lzsg) Approval Criteria:

1. An FDA approved indication for the treatment of adult and pediatric patients with primary hemophagocytic lymphohistiocytosis (HLH) with refractory, recurrent, or progressive disease or who are intolerant to conventional HLH therapy; and
2. Diagnosis of primary HLH must be confirmed by 1 of the following:
    a. Genetic testing confirming mutation of a gene known to cause primary HLH (e.g., *PRF*, *UNC13D*, *STX11*); or
    b. Family history consistent with primary HLH; or
    c. Member meets 5 of the following 8 diagnostic criteria:
        i. Fever; or
        ii. Splenomegaly; or
        iii. Cytopenias affecting at least 2 of 3 lineages in the peripheral blood (hemoglobin <9, platelets <100 x 10^9/L, neutrophils <1 x 10^9/L); or
        iv. Hypertriglyceridemia (fasting triglycerides >3mmol/L or ≥265mg/dL) and/or hypofibrinogenemia (≤1.5g/L); or
        v. Hemophagocytosis in bone marrow, spleen, or lymph nodes with no evidence of malignancy; or
        vi. Low or absent natural killer (NK)-cell activity; or
        vii. Hyperferritinemia (ferritin ≥500mcg/L); or
        viii. High levels of soluble interleukin-2 receptor (soluble CD25 ≥2,400U/mL); and
3. Gamifant® must be prescribed by, or in consultation with, a physician who specializes in the treatment of immune deficiency disorders; and
4. Member must have at least 1 of the following:
    a. Failure of at least 1 conventional HLH treatment (e.g., etoposide, dexamethasone, cyclosporine); or

   b. Documentation of progressive disease despite conventional HLH treatment; or
   c. Patient-specific, clinically significant reason why conventional HLH treatment is not appropriate for the member; and
5. Prescriber must verify dexamethasone dosed at least 5mg/m^2/day will be used concomitantly with Gamifant®; and
6. Prescriber must verify member has received or will receive prophylaxis for herpes zoster, *Pneumocystis jirovecii,* and fungal infection(s); and
7. Prescriber must verify member will be monitored for tuberculosis (TB), adenovirus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV) every 2 weeks and as clinically indicated; and
8. 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; and
9. Approvals will be for the duration of 6 months with reauthorization granted if the prescriber documents the member is responding well to treatment, no unacceptable toxicity has occurred, and the member has not received hematopoietic stem cell transplantation (HSCT).

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Appendix P

30-Day Notice to Prior Authorize Firdapse® (Amifampridine)

Oklahoma Health Care Authority
February 2019

Introduction[1,2,3,4]

Lambert-Eaton myasthenic syndrome (LEMS) is a syndrome of weakness and fatigue due to an autoimmune process. LEMS is often associated with cancer, particularly lung cancer, but can be present in patients that never develop cancer. Symptoms of LEMS may present prior to the diagnosis of cancer and once a diagnosis of LEMS has been made, the patient should be followed for the development of cancer.

LEMS is caused by antibodies produced by the body that destroy the voltage-gated calcium channels on the motor neuron at neuromuscular junctions. These channels help regulate the amount of acetylcholine that is released. When there is not enough acetylcholine released, the muscles do not contract. Symptoms of LEMS are related to muscle weakness, primarily in the proximal legs and arms, but sometimes in the neck, and can affect swallowing, breathing, or speaking. Onset of symptoms is gradual, typically occuring over several weeks to months. Early signs include problems ascending stairs, getting up from the sitting position, and lifting arms over the head. LEMS can also impact involuntary functions causing dry mouth and impotence.

LEMS is not hereditary, and symptoms not associated with cancer usually begin in young adults, but LEMS associated with cancer tends to be associated with older adults. Approximately 1:1,000,000 people have LEMS, with 40 to 60% of those having cancer. LEMS can be diagnosed using blood tests for antibodies, Tensilon tests, or electrophysiological tests with repetitive nerve stimulation.

The most effective treatment of LEMS associated with cancer is eradication of the cancer. Symptomatic treatments include medications that increase the release or abundance of neurotransmitters for muscles to respond (e.g., amifampridine, pyridostigmine). Immunosuppressants can be taken to reduce the production of antibodies that cause the muscle to stop contracting. Other treatments include plasmapheresis and intravenous immunoglobulin (IVIG) therapy. In November 2018, the U.S. Food and Drug Administration (FDA) approved Firdapse® (amifampridine) tablets, the first FDA approved treatment for LEMS.

Market News and Updates[5,6,7,8,9,10,11,12]

Anticipated Patent Expiration(s):

- Firdapse® (amifampridine tablet): November 2023

New FDA Approval(s):

- **November 2018:** The FDA approved Catalyst Pharmaceutical's Firdapse® (amifampridine) for the treatment of LEMS. According to articles from *STAT news*, *NPR*, and *Harvard Business Review*, this approval could mean increased costs for many patients with LEMS. For the past 20 years, LEMS patients have been able to receive

amifampridine, also known as 3,4-diaminopyridine or 3,4-DAP, free of charge from Jacobus Pharmaceutical Company or from several compounding pharmacies across the United States for around $300 to $500 per month. With FDA approval, Catalyst Pharmaceuticals now has the ability to block older forms of the drug from being dispensed to patients and to set the price. Current price estimates suggest the cost of Firdapse® will be around $375,000 per year.

Pipeline:

- **January 2016:** A Phase 3, double-blind, outpatient, crossover study to evaluate the efficacy and safety of amifampridine phosphate in patients with congenital myasthenic syndromes was initiated according to the U.S. National Library of Medicine's database, *ClinicalTrials.gov*. The study includes 20 patients 2 years of age and older with certain genetic subtypes of congenital myasthenic syndromes and who demonstrated history of sustained amifampridine benefit from treatment. The primary outcome is a change from baseline in the Subject Global Impression (SGI) scale, a patient-reported impression of physical well-being. The estimated study completion date is December 2019.
- **July 2018:** An open-label, Phase 3, long-term, safety study of amifampridine in muscle-specific tyrosine kinase (MuSK) type positive and acetylcholine receptor (AChR) antibody positive myasthenia gravis started recruiting according to *ClinicalTrials.gov.* The estimated enrollment is 70 patients to be followed over 21 months to determine the safety and tolerability of amifampridine for the treatment of MuSK type positive and AChR antibody positive myasthenia gravis.

Firdapse® (Amifampridine) Product Summary[13]

Indication(s): Firdapse® (amifampridine) is a potassium channel blocker indicated for the treatment LEMS in adults.

Dosing:

- Firdapse® is supplied as off-white 10mg scored tablets.
- The recommended starting dose of amifampridine is 15 to 30mg daily by mouth in 3 to 4 divided doses.
- The dose can be increased by 5mg daily every 3 to 4 days with a maximum single dose of 20mg and a maximum daily dose of 80mg.
- The recommended starting dose for patients with renal impairment [creatinine clearance (CrCL) 15 to 90mL/min], hepatic impairment, or known N-acetyltransferase 2 (NAT2) poor metabolizers is 15mg daily, taken in 3 divided doses.

Mechanism of Action: Amifampridine is a broad-spectrum potassium channel blocker. The mechanism by which amifampridine exerts its therapeutic effect in LEMS patients is not fully known.

Contraindication(s):

- Patients with a history of seizures
- Hypersensitivity to amifampridine phosphate or another aminopyridine

Warnings and Precautions:

- Seizures: Amifampridine can cause seizures. Seizures have been observed in patients without a history of seizures taking amifampridine at the recommended doses and at various times after the initiation of treatment with an incidence of approximately 2%. Many of the patients were taking concomitant medications or had comorbidities that may have lowered the seizure threshold. Seizures may be dose-dependent, and discontinuation or dose reduction of amifampridine should be considered in patients who have a seizure while on treatment. Amifampridine is contraindicated in patients with a history of seizures.
- Hypersensitivity: In clinical trials, hypersensitivity reactions and anaphylaxis associated with amifampridine have not been reported, but there have been reported cases of anaphylaxis in patients taking another aminopyridine. If anaphylaxis does occur, administration of amifampridine should be discontinued and appropriate therapy should be initiated.

Adverse Reactions: In amifampridine clinical trials, the adverse reactions that occurred in ≥10% of newly treated patients included: paresthesia, upper respiratory tract infections, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, muscle spasms, dizziness, asthenia, muscular weakness, pain in the extremities, and cataracts.

Drug Interactions:

- Drugs that lower seizure threshold (e.g., buproprion, tramadol, amphetamines, theophylline)
- Drugs with cholinergic effects (e.g., direct or indirect cholinesterase inhibitors)

Use in Specific Populations:

- Pregnancy: There is no data on the developmental risk associated with amifampridine in pregnant women. Animal data in pregnant rats with amifampridine doses associated with lower than therapeutic plasma levels in humans showed increased stillbirths and pup death, reduced pup weight, and delayed sexual development.
- Lactation: There is no data on the presence of amifampridine in human milk, the effects on breastfed infants, or the effects on milk production. In lactating rats, amifampridine was excreted in milk and reached levels similar to those in maternal plasma.
- Pediatric Use: The safety and efficacy of amifampridine in pediatric patients have not been established.
- Geriatric Use: Clinical studies of amifampridine did not include sufficient numbers of subjects 65 years of age and older (19 of 63 patients) to determine if they respond differently compared to younger subjects. Dose selection for elderly patients should be cautious due to the greater frequency of decreased hepatic, renal, or cardiac functions and of comorbid diseases or concomitant drug therapy.
- Renal Impairment: Renal clearance is an elimination pathway for amifampridine and exposure of amifampridine is higher in subjects with renal impairment. Patients with renal impairment should start at a lower dose, and dose modification or discontinuation of amifampridine should be considered based on clinical efficacy and tolerability. The safety, efficacy, and pharmacokinetics of amifampridine have not been studied in patients with end-stage renal disease (ESRD) (CrCl <15mL/min or dialysis).

- Hepatic Impairment: The effects of amifampridine have not been studied in patients with hepatic impairment. Amifampridine is extensively metabolized by NAT2, and hepatic impairment may cause increased drug exposure. Patients with hepatic impairment should start at a lower dose, and dose modification or discontinuation of amifampridine should be considered based on clinical efficacy and tolerability.
- NAT2 Poor Metabolizers: Exposure to amifampridine is increased in patients who are known NAT2 poor metabolizers. In patients who are NAT2 poor metabolizers, amifampridine is recommended to be started at the lowest dose and patients should be monitored for adverse reactions.

Efficacy: The efficacy of amifampridine for the treatment of LEMS was demonstrated in 2 randomized, double-blind, placebo-controlled discontinuation studies. A total of 64 adults with LEMS were enrolled in both studies. The studies included patients with a confirmed diagnosis of LEMS based on either neurophysiology studies or a positive anti-P/Q-type voltage-gated calcium channel antibody test. Patients were required to be on a stable dose of amifampridine (30 to 80mg daily) prior to entering the randomized discontinuation phase. The 2 co-primary measures of efficacy were the change from baseline in the Quantitative Myasthenia Gravis (QMG) score and in the SGI score. The QMG is a 13-item physician-rated categorical scale assessing muscle weakness, and each item is assessed on a 4-point scale with 0 being no weakness. The SGI is a 7-point scale on which patients rate their global impression of the effects of the study treatment on their physical well-being with a lower score representing a lower perceived benefit. A key secondary efficacy endpoint was the Clinical Global Impression Improvement (CGI-I) score, a 7-point scale on which physicians rate the global impression of change in clinical symptoms with a higher score indicating a perceived worsening of clinical symptoms.

- Study 1: After an initial open-label, run-in phase, 38 patients were randomized in a double-blind fashion to either a continuation of therapy or a downward titration group. After a 7-day downward titration period, patients remained on either amifampridine or placebo for 7 more days. Efficacy was assessed at day 14. During the study, patients were allowed to use stable doses of peripherally acting cholinesterase inhibitors (26% vs. 36% in the amifampridine group compared to the placebo group, respectively) or oral immunosuppressants (28% amifampridine vs. 34% placebo). The QMG scores worsened in both the treatment group and the placebo group (change from baseline: 0.4 vs. 2.2, respectively) during the study period, but there was a significantly greater worsening in the placebo group (P=0.045). The SGI scores worsened in both the treatment group and the placebo group (change from baseline: -0.8 vs. -2.6, respectively) during the study period, but there was a significantly greater worsening in the placebo group (P=0.003). The CGI-I score was significantly greater (indicating a perceived worsening of symptoms) for patients randomized to placebo compared to the amifampridine group, with a mean difference of -1.1 (P=0.02).
- Study 2: A total of 26 patients stable on amifampridine were randomized in a double-blind fashion to either continued treatment (N=13) or change to placebo (N=13) for 4 days. Efficacy was assessed at the end of the double-blind discontinuation period. Patients were allowed to use stable doses of peripherally acting cholinesterase inhibitors or corticosteroids. Patients with recent use of immunomodulatory therapies,

rituximab, IVIG, and plasmapheresis were excluded from the study. From baseline to day 4, there was a significantly greater worsening in the QMG score (P=0.0004) and the SGI score (P=0.0003) in the placebo group than the amifampridine group. The CGI-I score was also significantly greater (indicating a perceived worsening of symptoms) for patients in the placebo group compared to the amifampridine group, with a mean difference of -2.7 (P=0.002).

Recommendations

The College of Pharmacy recommends the prior authorization of Firdapse® (amifampridine) with the following criteria:

Firdapse® (Amifampridine) Approval Criteria:

1. A diagnosis of Lambert-Eaton myasthenic syndrome (LEMS); and
2. Diagnosis must be confirmed by 1 of the following:
    a. A high titer anti-P/Q-type voltage-gated calcium channel (VGCC) antibody assay; or
    b. A confirmatory electrodiagnostic study [e.g., repetitive nerve stimulation (RNS), needle electromyography (EMG), single-fiber electromyography (SFEMG)]; and
3. Firdapse® must be prescribed by, or in consultation with, a neurologist or oncologist; and
4. Member must not have a history of seizures or be taking medications that lower the seizure threshold (e.g., buproprion, tramadol, amphetamines, theophylline); and
5. A quantity limit of 240 tablets per 30 days will apply; and
6. Initial approvals will be for 6 months. Continued authorization will require the prescriber to indicate that the member is responding well to treatment and continues to require treatment with Firdapse®.

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Appendix Q

Fiscal Year 2018 Annual Review of Erythropoietin Stimulating Agents (ESAs) and 30-Day Notice to Prior Authorize Retacrit™ (Epoetin Alfa-epbx)

Oklahoma Health Care Authority
February 2019

Current Prior Authorization Criteria

Aranesp® (Darbepoetin Alfa) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Anemia due to chemotherapy in patients with non-myeloid malignancies; or
    b. Anemia associated with chronic renal failure; and
        i. For the diagnosis of anemia associated with chronic renal failure: member must not be receiving dialysis [erythropoietin stimulating agents (ESAs) are included in the bundled dialysis payment if member is on any form of dialysis and cannot be billed separately]; and
2. Recent hemoglobin levels must be provided; and
3. Approvals will be for the duration of 16 weeks of therapy. Recent hemoglobin levels must be provided with continuation requests, and further approval may be granted if the member's recent hemoglobin level is <11g/dL.

Procrit® and Epogen® (Epoetin Alfa) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Anemia due to chemotherapy in patients with non-myeloid malignancies; or
    b. Anemia in zidovudine-treated Human Immunodeficiency Virus (HIV)-infected patients; or
    c. The reduction of allogeneic blood transfusion(s) in surgery patients; or
    d. Anemia associated with chronic renal failure; and
        i. For the diagnosis of anemia associated with chronic renal failure: member must not be receiving dialysis [erythropoietin stimulating agents (ESAs) are included in the bundled dialysis payment if member is on any form of dialysis and cannot be billed separately]; and
2. Recent hemoglobin levels must be provided; and
3. Approvals will be for the duration of 16 weeks of therapy. Recent hemoglobin levels must be provided with continuation requests, and further approval may be granted if the member's recent hemoglobin level is <11g/dL.

Utilization of ESAs: Fiscal Year 2018

ESA Fiscal Year Comparison: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	40	225	$160,931.25	$715.25	$36.58	535	4,399
2018	28	204	$62,745.49	$307.58	$22.68	206	2,767
% Change	**-30.00%**	**-9.30%**	**-61.00%**	**-57.00%**	**-38.00%**	**-61.50%**	**-37.10%**
Change	**-12**	**-21**	**-$98,185.76**	**-$407.67**	**-$13.90**	**-329**	**-1,632**

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

Fiscal Year 2018 Utilization of ESAs: Medical Claims

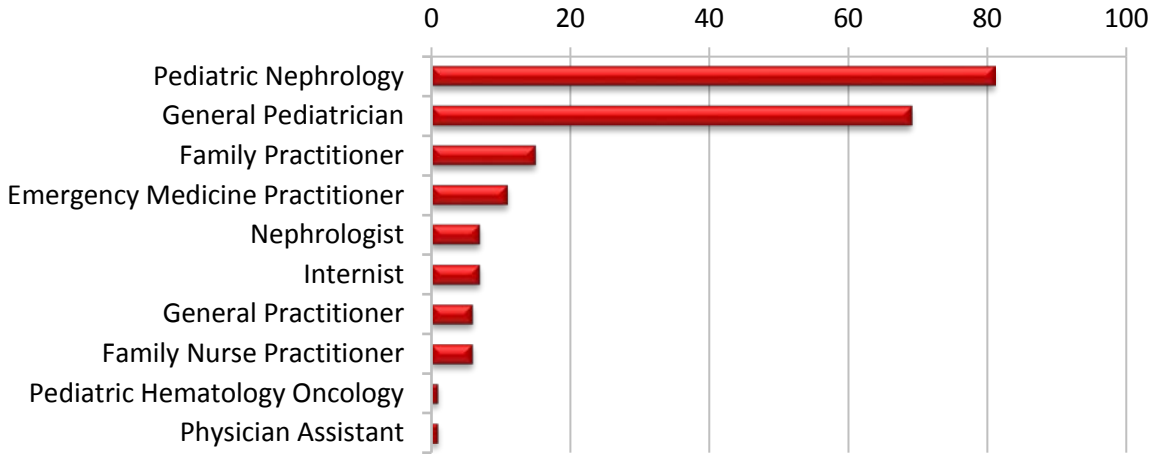
*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
39	228	$152,903.21	$670.63	56,243

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

Demographics of Members Utilizing ESAs

- Due to the limited number of members utilizaing ESAs, detailed demographic information could not be provided.

Top Prescriber Specialties of ESAs by Number of Claims



Prior Authorization of ESAs

There were 237 prior authorization requests submitted for ESAs during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions

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

Anticipated Patent Expiration(s):

- Aranesp® (darbepoetin alfa): May 2024

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

- **May 2018:** The FDA approved Retacrit™ (epoetin alfa-epbx), a biosimilar of Epogen®/Procrit® (epoetin alfa) for the treatment of anemia due to chronic kidney disease (CKD) in patients on dialysis and not on dialysis, anemia due to use of zidovudine in patients with Human Immunodeficiency Virus (HIV) infection, and anemia due to the effects of concomitant myelosuppressive chemotherapy. It is also approved for the reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery. The approval was based on comparisons of extensive structural and functional product characterization, animal data, human pharmacokinetic and pharmacodynamic data, and clinical immunogenicity between Retacrit™ and Epogen®/Procrit®, demonstrating that Retacrit™ is highly similar to Epogen®/Procrit®, and that there are no clinically meaningful differences between the products. Retacrit™ has not been shown to be interchangeable with Epogen®/Procrit®. Like Epogen®/ Procrit®, the labeling for Retacrit™ contains a *Boxed Warning* to alert health care professionals and patients about an increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.

New Indication(s):

- **June 2018:** The FDA approved Mircera® (methoxy polyethylene glycol-epoetin beta) for the treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their hemoglobin (Hb) level was stabilized with an ESA. The approval was based on data from an open-label, multiple dose, multicenter, dose-finding trial in 64 pediatric patients 5 to 17 years of age with CKD on hemodialysis and who had stable Hb levels while previously receiving another ESA (epoetin alfa/beta or darbepoetin alfa). Patients were administered Mircera® intravenously (IV) once every 4 weeks for 20 weeks, and after the first administration of Mircera®, dosage adjustments were permitted to maintain target Hb levels. Efficacy was based on maintaining Hb levels within target levels in the aforementioned clinical trial, and also from extrapolation from trials of Mircera® in adult

patients with CKD. The safety findings observed in pediatric patients were consistent with those previously reported in adults. For conversion from another ESA, Mircera® is dosed IV once every 4 weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion. Mircera® was FDA approved in November 2007 for the treatment of anemia associated with CKD in adult patients on dialysis and not on dialysis. In May 2015, Galenica entered into a supply agreement with Fresenius Medical Care North America (FMCNA) under which Galenica will supply Mircera® for FMCNA's use solely within its dialysis facilities. In September 2017, Vifor Pharma (formerly a company of Galencia) entered into an exclusive license agreement with Roche for the commercialization of its medicine Mircera® in the United States. In order to provide Vifor Pharma more flexibility to meet the ESA requirements of the United States' nephrology market, Vifor Pharma and Roche have now completed an agreement giving Vifor Pharma access to additional volume for Mircera® for the United States market in order to optimally meet the needs of new and existing partners.

Recommendations

The College of Pharmacy recommends the prior authorization of Retacrit™ (epoetin alfa-epbx). The following criteria would apply (changes noted in red):

Procrit® (Epoetin Alfa), Epogen® (Epoetin Alfa), and Retacrit™ (Epoetin Alfa-epbx) Approval Criteria:

1. An FDA approved diagnosis of 1 of the following:
    a. Anemia due to chemotherapy in patients with non-myeloid malignancies; or
    b. Anemia in zidovudine-treated Human Immunodeficiency Virus (HIV)-infected patients; or
    c. The reduction of allogeneic blood transfusion(s) in surgery patients; or
    d. An FDA approved diagnosis of anemia associated with chronic renal failure; and
        i. For the diagnosis of anemia associated with chronic renal failure: member must not be receiving dialysis [erythropoietin stimulating agents (ESAs) are included in the bundled dialysis payment if member is on any form of dialysis and cannot be billed separately]; and
2. Authorization of Retacrit™ requires a patient-specific, clinically significant reason why the member cannot use Procrit® or Epogen®; and
3. Recent hemoglobin levels must be provided; and
4. Approvals will be for the duration of 16 weeks of therapy. Recent hemoglobin levels must be provided with continuation requests, and further approval may be granted if the member's recent hemoglobin level is <11g/dL.

Utilization Details of ESAs (Pharmacy Claims): Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
DARBEPOETIN ALFA PRODUCTS						
ARANESP INJ 40MCG	8	1	$2,561.20	$22.87	$320.15	4.08%
ARANESP INJ 150MCG	7	1	$1,396.01	$7.12	$199.43	2.22%
ARANESP INJ 100MCG	1	1	$3,103.05	$110.82	$3,103.05	4.95%
SUBTOTAL	**16**	**3**	**$7,060.26**	**$21.01**	**$441.27**	**11.25%**
EPOETIN ALFA PRODUCTS						
PROCRIT INJ 20000/ML	148	13	$29,260.32	$21.64	$197.70	46.63%
PROCRIT INJ 10000/ML	15	6	$15,215.85	$25.19	$1,014.39	24.25%
EPOGEN INJ 20000/ML	12	3	$6,410.42	$38.16	$534.20	10.22%
PROCRIT INJ 3000/ML	5	1	$1,552.83	$11.09	$310.57	2.47%
EPOGEN INJ 10000/ML	2	1	$1,015.90	$72.56	$507.95	1.62%
PROCRIT INJ 2000/ML	2	1	$844.30	$14.07	$422.15	1.35%
EPOGEN INJ 2000/ML	2	1	$286.38	$5.11	$143.19	0.46%
EPOGEN INJ 4000/ML	1	1	$143.19	$20.46	$143.19	0.23%
PROCRIT INJ 40000/ML	1	1	$956.04	$31.87	$956.04	1.52%
SUBTOTAL	**188**	**28**	**$55,685.23**	**$22.91**	**$296.20**	**88.75%**
TOTAL	**204**	**28***	**$62,745.49**	**$22.68**	**$307.58**	**100%**

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

Utilization Details of ESAs (Medical Claims): Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
EPOETIN ALFA PRODUCTS					
PROCRIT INJ J0885	148	28	$61,191.42	5.28	$413.46
SUBTOTAL	**148**	**28**	**$61,191.42**	**5.28**	**$413.46**
DARBEPOETIN ALFA PRODUCTS					
ARANESP INJ J0881	80	11	$91,711.79	7.27	$1,146.40
SUBTOTAL	**80**	**11**	**$91,711.79**	**7.27**	**$1,146.40**
TOTAL	**228**	**39***	**$152,903.21**	**5.85**	**$670.63**

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

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[2] U.S. Food and Drug Administration (FDA). FDA Approves Retacrit as a Biosimilar to Epogen/Procrit. Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm607723.htm. Issued 05/15/2018. Last accessed 01/07/2019.
[3] FDA. FDA Approved Mircera for anemia associated with chronic kidney disease in pediatric patients on dialysis. Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610210.htm?utm_campaign=Oncology%206%2F7%2F18&utm_medium=email&utm_source=Eloqua&elqTrackId=cec3e3208e9b4c35ba3c9744cf320c6c&elq=3d08c8f3604740cfafac725f2e87dc68&elqaid=3829&elqat=1&elqCampaignId=2959. Issued 06/07/2018. Last accessed 01/07/2019.
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[6] Vifor Pharma. Vifor Pharma Expands Exclusive License Agreement for the Commercialization of Mircera® in the US. Available online at: http://www.viforpharma.com/~/media/Files/V/Vifor-Pharma/documents/en/media-releases/2017/27-9-2017.pdf. Issued 09/27/2017. Last accessed 01/16/2019.

Appendix R

Fiscal Year 2018 Annual Review of Parkinson's Disease (PD) Medications and 30-Day Notice to Prior Authorize Inbrija™ (Levodopa Inhalation) and Osmolex ER™ [Amantadine Extended-Release (ER)]

Oklahoma Health Care Authority
February 2019

Current Prior Authorization Criteria

Duopa™ (Carbidopa/Levodopa Enteral Suspension) Approval Criteria:

1. An FDA approved diagnosis of advanced Parkinson's disease (PD); and
2. For long-term administration, member or caregivers must be willing and able to administer Duopa™ through a percutaneous endoscopic gastrostomy; and
3. Patients must be experiencing 3 hours or more of "off" time on their current PD drug treatment and they must have demonstrated a clear responsiveness to treatment with levodopa; and
4. Approvals will be for a quantity of 1 cassette per day.

Gocovri™ [Amantadine Extended-Release (ER)] Approval Criteria:

1. An FDA approved indication for the treatment of dyskinesia in patients with Parkinson's disease (PD) receiving levodopa-based therapy; and
2. Member must use Gocovri™ concomitantly with levodopa therapy; and
3. Member must not have end-stage renal disease (ESRD) [creatinine clearance (CrCl) <15mL/min/1.73m^2]; and
4. A minimum of a 6-month trial of amantadine immediate-release (IR) that resulted in inadequate effects or intolerable adverse effects that are not expected to occur with amantadine ER; and
5. A patient-specific, clinically significant reason why amantadine IR products cannot be used must be provided; and
6. A quantity limit of (1) 68.5mg capsule or (2) 137mg capsules per day will apply.

Neupro® (Rotigotine Transdermal System) Approval Criteria:

1. For the diagnosis of Parkinson's disease (PD) the following criteria apply:
    a. An FDA approved indication for the treatment of signs and symptoms of PD; and
    b. Member must be 18 years of age or older; and
    c. Failed treatment, intolerance, or a patient-specific, clinically significant reason why the member cannot use oral dopamine agonists.
2. For the diagnosis of restless leg syndrome (RLS) the following criteria apply:
    a. An FDA approved indication of RLS; and
    b. Member must be 18 years of age or older; and
    c. Documented treatment attempts at recommended dose with at least 2 of the following that did not yield adequate relief:

i. Carbidopa/levodopa; or
ii. Pramipexole; or
iii. Ropinirole.

Nuplazid® (Pimavanserin) Approval Criteria:

1. An FDA approved diagnosis of hallucinations and delusions associated with Parkinson's disease (PD) psychosis; and
2. Member must have a concomitant diagnosis of PD; and
3. Nuplazid® will not be approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with PD psychosis; and
4. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of this medication; and
5. A quantity limit of 2 tablets daily will apply.

Requip XL® [Ropinirole Extended-Release (ER)] and Mirapex ER® (Pramipexole ER) Approval Criteria:

1. An FDA approved diagnosis of Parkinson's disease (PD); and
2. A patient-specific, clinically significant reason why the immediate-release products cannot be used must be provided.

Rytary™ [Carbidopa/Levodopa Extended-Release (ER) Capsules] Approval Criteria:

1. An FDA approved diagnosis of Parkinson's disease (PD), post-encephalitic parkinsonism, or parkinsonism that may follow carbon monoxide intoxication or manganese intoxication; and
2. A patient-specific, clinically significant reason why the member cannot use other generic carbidopa/levodopa combinations including Sinemet® CR (carbidopa/levodopa ER tablets) must be provided.

Xadago® (Safinamide) Approval Criteria:

1. An FDA approved indication as adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes; and
2. Member must be taking levodopa/carbidopa in combination with safinamide (safinamide has not been shown to be effective as monotherapy for the treatment of PD); and
3. A patient-specific, clinically significant reason why the member cannot use rasagiline or other lower cost monoamine oxidase type B (MAO-B) inhibitors must be provided; and
4. Member must not have severe hepatic impairment; and
5. Member must not be taking any of the following medications concomitantly with safinamide:
    a. Monoamine oxidase inhibitors (MAOIs); or
    b. Linezolid; or
    c. Opioid analgesics (including tramadol); or
    d. Selective norepinephrine reuptake inhibitors (SNRIs); or
    e. Tri- or tetra-cyclic or triazolopyridine antidepressants; or

f. St. John's wort; or
g. Cyclobenzaprine; or
h. Methylphenidate and its derivatives; or
i. Amphetamine and its derivatives; or
j. Dextromethorphan; and

6. Prescriber must verify member has been counseled on avoiding foods that contain a large amount of tyramine while taking safinamide; and
7. A quantity limit of 1 tablet daily will apply.

Utilization of PD Medications: Fiscal Year 2018

The following utilization data includes PD medications used for all diagnoses and does not differentiate between PD diagnoses and other diagnoses, for which use may be appropriate.

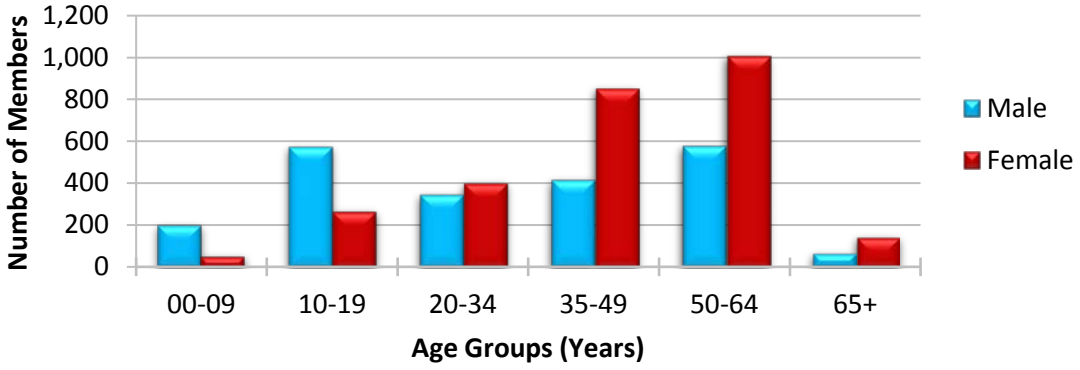
Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	4,765	25,273	$840,884.26	$33.27	$1.04	1,647,838	806,367
2018	4,913	26,190	$919,584.53	$35.11	$1.10	1,767,581	834,145
% Change	**3.10%**	**3.60%**	**9.40%**	**5.50%**	**5.80%**	**7.30%**	**3.40%**
Change	**148**	**917**	**$78,700.27**	**$1.84**	**$0.06**	**119,743**	**27,778**

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

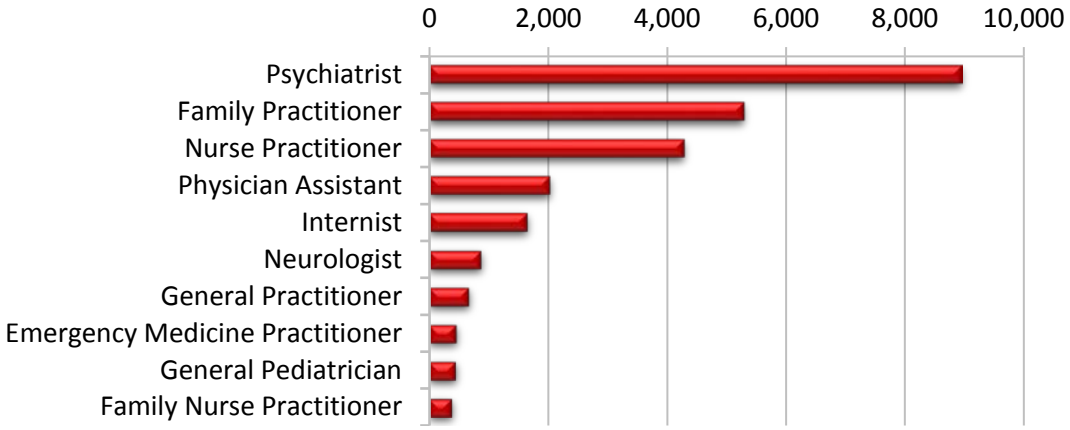
- There were no SoonerCare paid medical claims for Duopa™ (carbidopa/levodopa enteral suspension) during fiscal year 2018.

Demographics of Members Utilizing PD Medications



- The utilization data includes PD medications used for all diagnoses and does not differentiate between PD diagnoses and other diagnoses, for which use may be appropriate. Utilization of PD medications in the pediatric population can be accounted for by the inclusion of amantadine in the utilization data. Amantadine is indicated for the prophylaxis and treatment of the signs and symptoms of infection caused by various strains of the influenza A virus.

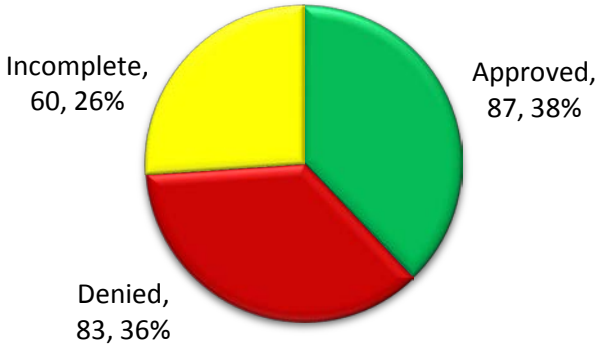
Top Prescriber Specialties of PD Medications by Number of Claims



Prior Authorization of PD Medications

There were 230 prior authorization requests submitted for PD medications during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



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

Patent Expiration(s):

- Duopa™ (carbidopa/levodopa enteral suspension): There are no unexpired patents for Duopa™ however exclusivity expiration is anticipated in January 2022
- Azilect® (rasagiline tablets): August 2027
- Nuplazid® (pimavanserin tablets): June 2028
- Rytary™ [carbidopa/levodopa extended-release (ER) capsules]: December 2028
- Xadago® (safinamide tablets): December 2028
- Osmolex ER™ (amantadine ER tablets): March 2030
- Gocovri™ (amantadine ER capsules): December 2030
- Neupro® (rotigotine transdermal patches): December 2030

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

- **February 2018:** The FDA approved Osmolex ER™ (amantadine ER tablets) for the treatment of PD and drug-induced extrapyramidal symptoms in adults. Osmolex ER™

tablets are a proprietary formulation containing a combination of immediate-release (IR) and ER amantadine using Osmotica's patented Osmodex technology. Taken once daily in the morning, the Osmolex ER™ tablet releases amantadine throughout the day.

- **June 2018:** The FDA approved a new capsule formulation and a new tablet strength for Nuplazid® (pimavanserin). The new 34mg capsule formulation will help reduce pill burden and allow patients to take the recommended once-daily dose as a single capsule versus (2) 17mg tablets. Also, the new 10mg strength tablet offers a lower dosage strength for patients who are taking concomitant strong CYP3A4 inhibitors, which can potentiate pimavanserin.
- **December 2018:** The FDA approved Inbrija™ (levodopa inhalation) for the intermittent treatment of "off" episodes in patients with PD who are being treated with carbidopa/levodopa. "Off" episodes are periods when PD symptoms return as a result of low levels of dopamine often occurring between doses of oral carbidopa/levodopa.

News:

- **Nuplazid® (pimavanserin):** A CNN investigative report explored possible medication safety issues with pimavanserin, particularly the increased risk of death found in an analysis conducted by the Institute for Safe Medication Practices (ISMP). ISMP found 244 deaths associated with pimavanserin use from April 2016 to March 2017 and concluded that "pimavanserin was FDA-approved on limited scientific evidence that its benefits outweighed its risks." ISMP also stated that the FDA "relied on a single clinical trial indicating a minimal treatment effect, used a measurement scale for symptoms that had not been validated, and succeeded only after 3 previous trials had failed to demonstrate a benefit. Further, the agency's medical reviewer recommended against approval and was overruled. He noted that although other psychiatric drugs were often approved on limited evidence of benefit, in the case of pimavanserin, treatment more than doubled the risk of death and/or serious adverse events in its pivotal trial." Acadia Pharmaceuticals, the maker of pimavanserin, along with the FDA indicated that the medication's potential benefits continue to outweigh the risks and that the medication fills a desperate need since psychosis can affect up to 50% of patients suffering from PD. Acadia also indicated that a plausible explanation for the volume of deaths reported was that patients receiving the medication are already at an increased risk of death due to advanced stages of PD. A September 2018 communication released by the FDA indicated that after a completed review of all postmarketing reports of death reported with the use of pimavanserin, the FDA did not identify any new or unexpected safety findings and that the safety findings were consistent with what is described in the drug label. The FDA concluded that the drug's benefits outweigh the risks for patients with hallucinations and delusions of PD psychosis. The FDA stated that when assessing the reports of deaths, consideration was given to the fact that patients with PD psychosis have a higher mortality rate due to their older age, advanced PD, and other medical conditions. The FDA did not identify a pattern to suggest a drug effect in the deaths. The FDA did identify "concerning prescribing patterns" of pimavanserin, particularly the concomitant use with other antipsychotic drugs or drugs that can cause potential QT prolongation. QT prolongation is noted in the *Warnings and Precautions* section of the pimavanserin product labeling, and using pimavanserin with other drugs that prolong

the QT interval can increase the risk of arrhythmias. The FDA reminded health care providers to be aware of the risks described in the pimavanserin prescribing information, and that none of the other antipsychotic medications are approved for the treatment of PD psychosis.

Pipeline:

- **Foliglurax:** In March 2018, Lundbeck announced the acquisition of foliglurax, a small molecule modulator that acts on mGluR4 glutamate receptors under investigation for the treatment of PD. Foliglurax is currently undergoing a double-blind, randomized, placebo-controlled Phase 2 clinical trial in 165 patients with PD who have previously been treated with a stable regimen of levodopa-containing therapy. The primary endpoint of the study is to evaluate the effectiveness of foliglurax in reducing levodopa-induced motor complications, also known as levodopa-induced dyskinesia. The study is expected to be completed in 2019. In preclinical studies with animal models of PD, foliglurax showed positive effects in modulating the disease course, and foliglurax was found to be safe and well tolerated in a Phase 1 clinical study with healthy volunteers.
- **Apomorphine Sublingual (SL) Film (APL-130277):** In June 2018, Sunovion Pharmaceuticals, Inc. presented positive results of its Phase 3 randomized, double-blind, placebo-controlled trial of apomorphine SL film (APL-130277) in patients with PD who experience morning “off” episodes. The results were presented at the Pan American Parkinson’s Disease and Movement Disorders Congress (MDS-PAS) in Florida. The results presented revealed that individuals with “off” episodes who received apomorphine SL film had a statistically significant treatment difference of 7.6 points in improvement of motor function in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III score from pre-dose to 30 minutes after dosing at week 12 compared with the placebo group. Apomorphine SL film was generally well-tolerated, with the majority of treatment-emergent adverse events (TEAE) being mild-to-moderate in severity, non-serious, and reversible upon treatment discontinuation. The most frequent TEAEs in the double-blind, maintenance treatment phase were nausea (27.8%), somnolence (13.0%), and dizziness (9.3%). In late January 2019, Sunovion announced that the FDA declined to approve APL-130277; Sunovion did not disclose specific reasons why the drug was not approved.
- **IRL790:** In December 2018, Integrative Research Laboratories announced that their PD investigational treatment candidate, IRL790, was safe and reduced levodopa-induced dyskinesia in a Phase 1b trial. IRL790 mainly targets the dopamine D3 receptor. The study included 15 PD patients who randomly received oral capsules of IRL790 (11 patients) or an oral placebo (4 patients) for 4 weeks. During the trial, all patients continued receiving their regular medication(s). A total of 13 patients completed the 4-week study, with IRL790 given at an average daily dose of 18mg. Overall, 14 patients (93.3%) reported 62 adverse effects. Most were reported during the first 2 weeks when the dose of IRL790 was adjusted to each patient and were mild-to-moderate. No serious adverse effects were reported in any of the groups. Patients taking IRL790 had a mean reduction of 8.2% in dyskinesia scores compared to those taking a placebo. Among patients treated with IRL790, 55.5% were assessed as having an improved global clinical condition, as compared with baseline. IRL790 is currently being tested in a Phase 2 trial,

which will assess whether the treatment can reduce dyskinesia in a larger population (74 patients). The trial will also help establish the optimal dose for further testing.

- **KW-6356:** In August 2018, Kyowa Hakko Kirin Co., Ltd. presented results of a Phase 2a randomized, placebo-controlled study of KW-6356, a selective adenosine A2A receptor antagonist under development for the treatment of patients with early PD. The study evaluated KW-6356 in patients with early PD who had not received other anti-Parkinson drugs. Participants (N=168) were randomized into a high-dose KW-6356 group, a low-dose KW-6356 group, or a placebo group at a ratio of 1:1:1, and the test drug was administered for 12 weeks. The primary efficacy endpoint was the change from baseline in MDS-UPDRS Part III scores over 12 weeks of administration. Changes from baseline in MDS-UPDRS Part III scores were -4.76 in the high-dose KW-6356 group [95% confidence interval (CI) -6.55, -2.96], -5.37 in the low-dose KW-6356 group (95% CI -7.25, -3.48), and -3.14 (95% CI -4.97,-1.30) in the placebo group, with both KW-6356 groups showing a greater reduction in score compared with the placebo group. No major safety issues were observed in any of the groups. Kyowa Hakko Kirin plans to initiate a late Phase 2 trial of KW-6356 for PD patients in Japan.
- **Prasinezumab (PRX002/RG7935):** Roche is currently conducting a randomized double-blind, placebo-controlled, 52-week, Phase 2 study of prasinezumab, an investigational, intravenous (IV) monoclonal antibody that targets α-synuclein, a protein that is believed to misfold and aggregate to form the protein structures that are implicated in PD pathology. The study enrolled 316 adult patients with early PD. The study's primary outcome measure is the change from baseline in the MDS-UPDRS Total Score at week 52. The estimated study completion date is February 2021.
- **Nuplazid® (pimavanserin):** A Phase 2 study of pimavanserin demonstrated some efficacy in Alzheimer's disease (AD) psychosis, but only in the short-term. Pimavanserin is an atypical antipsychotic currently FDA approved for the treatment of hallucinations and delusions associated with PD. Pimavanserin met the primary efficacy endpoint of reducing psychosis score after 6 weeks of treatment versus placebo (-3.76 points pimavanserin vs. -1.93 placebo; 95% CI -3.64, -0.04; P=0.045), but there was no significant treatment difference found between the groups after 12 weeks of treatment (-0.51; 95% CI -2.23, 1.21; P=0.561). Currently, there are no approved treatments specifically for psychosis in people with AD, although antipsychotics are often used. The use of antipsychotics in AD patients has been tied to adverse side effects, including a faster cognitive decline and increased risk for stroke, pulmonary embolism, bronchopneumonia, and short-term mortality. Acadia Pharmaceuticals, the maker of pimavanserin, is currently recruiting for a Phase 3 trial to assess the efficacy and prevention of relapse of dementia-related psychotic symptoms.

Inbrija™ (Levodopa Inhalation) Product Summary[17]

Indication(s): Inbrija™ (levodopa inhalation) is an aromatic amino acid indicated for the intermittent treatment of "off" episodes in patients with PD treated with carbidopa/levodopa.

Dosing:

- Inbrija™ is available as a carton containing (60) or (92) 42mg levodopa capsules for oral inhalation and 1 Inbrija™ inhaler.
- The recommended dosage of Inbrija™ is oral inhalation of the contents of (2) 42mg capsules (84mg) as needed, up to 5 times daily. The maximum dose per "off" period is 84mg, and the maximum daily dosage is 420mg.
- Inbrija™ has been shown to be effective only in combination with carbidopa/levodopa.

Mechanism of Action: Levodopa, the metabolic precursor of dopamine, crosses the blood-brain barrier and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of PD.

Contraindication(s):

- Inbrija™ is contraindicated in patients currently taking a nonselective monoamine oxidase inhibitor (MAOI) (e.g., phenelzine, tranylcypromine) or who have recently (within 2 weeks) taken a nonselective MAOI. Hypertension (HTN) can occur if these drugs are used concurrently.

Warnings and Precautions:

- Falling Asleep During Activities of Daily Living (ADL) and Somnolence: Patients treated with levodopa, the active ingredient in Inbrija™, have reported falling asleep while engaged in ADL, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence, some reported no warning signs (sleep attack) and believed that they were alert immediately prior to the event. Some of these events have been reported more than 1 year after the initiation of treatment.
- Withdrawal-Emergent Hyperpyrexia and Confusion: A symptom complex that resembles neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy.
- Hallucinations/Psychosis: In placebo-controlled trials, hallucinations were reported in <2% of patients treated with Inbrija™. Hallucinations may be responsive to reducing levodopa therapy. Hallucinations may be accompanied by confusion, insomnia, and excessive dreaming. Abnormal thinking and behavior may present with 1 or more symptoms, including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium. Because of the risk of exacerbating psychosis, patients with a major psychotic disorder should ordinarily not be treated with Inbrija™. In addition, medications that antagonize the effects of dopamine used to treat psychosis may exacerbate the symptoms of PD and may decrease the effectiveness of Inbrija™.
- Impulse Control/Compulsive Behaviors: Patients treated with Inbrija™ can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, and other intense urges, and the inability to control these urges while taking 1 or more medications that increase central dopaminergic tone.

- Dyskinesia: Inbrija™ may cause or exacerbate dyskinesias. If troublesome dyskinesias occur, prescribers may need to consider stopping treatment with Inbrija™ or adjusting the patient's daily medications for the treatment of PD. In a double-blind study, 4% of patients treated with Inbrija™ 84mg reported dyskinesia, compared with 1% for patients on placebo.
- Bronchospasm in Patients with Lung Disease: Because of the risk of bronchospasm, use of Inbrija™ in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended. In a double-blind, placebo-controlled, crossover clinical study, 25 otherwise healthy subjects with mild or moderate asthma on a stable regimen of asthma medication(s) received placebo or Inbrija™ 84mg every 4 hours for a total of 3 doses. Following administration of Inbrija™, 10 subjects (40%) had temporary reductions from baseline (between 15 and 59%) forced expiratory volume in 1 second (FEV_1); 4 of these subjects also had a reduction in FEV_1 following administration of placebo.
- Glaucoma: Inbrija™ may cause increased intraocular pressure in patients with glaucoma.
- Laboratory Test Abnormalities: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactic dehydrogenase (LDH), and bilirubin. Abnormalities in blood urea nitrogen (BUN), hemolytic anemia, and positive direct antibody tests have also been reported.

Drug Interactions:

- MAOIs: The use of nonselective MAOIs with Inbrija™ is contraindicated. Nonselective MAOIs should be discontinued at least 2 weeks prior to initiating Inbrija™.
- Dopamine D2 Receptor Antagonists and Isoniazid: Dopamine D2 receptor antagonists (e.g., phenothiazines, butyrophenones, risperidone, metoclopramide) and isoniazid may reduce the effectiveness of levodopa.
- Iron Salts: Iron salts or multivitamins containing iron salts can form chelates with levodopa and consequently reduce the bioavailability of levodopa.

Adverse Reactions: The most common adverse reactions (≥5% and greater than placebo) reported during Inbrija™ clinical trials were cough, nausea, upper respiratory tract infection, and discolored sputum.

Efficacy: The efficacy and safety of Inbrija™ for the treatment of "off" episodes in patients with PD treated with oral carbidopa/levodopa were evaluated in a 12-week, randomized, placebo-controlled, double-blind study. A total of 114 patients were treated with Inbrija™ 84mg, and 112 patients received placebo. Study medication could be administered up to 5 times daily. At baseline, patients had at least 2 hours of "off" time per day, and carbidopa/levodopa doses did not exceed 1,600mg levodopa per day. The mean UPDRS Part III scores at screening in the "on" state were 14.9 for patients randomized to Inbrija™ and 16.1 for patients randomized to placebo. The UPDRS Part III motor score is designed to assess the severity of the cardinal motor findings (e.g., tremor, rigidity, bradykinesia, postural instability) in patients with PD. The primary endpoint was the change in UPDRS Part III motor score from pre-dose "off" state to 30 minutes post-dose, measured at week 12. The average use of Inbrija™ or placebo was

approximately 2 doses per day. At week 12, the reduction in UPDRS Part III motor score for Inbrija™, compared to placebo at 30 minutes post-dose, were -9.8 and -5.9 (P=0.009), respectively. The proportion of patients who returned to an "on" state and sustained that "on" through 60 minutes post-dose was 58% for Inbrija™ and 36% for placebo (P=0.003).

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month	Cost Per Year
Inbrija™ (levodopa) 42mg capsule	**Not Available**	**Not Available**	**Not Available**
selegiline 5mg tablet	$1.09	$65.40*	$784.80*
Apokyn® (apomorphine) 30mg/3mL injection	$331.67	$5,970.06[+]	$71,640.72[+]

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.
Unit = capsule, tablet, or mL
*Dosing based on adjunctive therapy in patients taking concomitant levodopa (5mg twice daily).
[+]Dosing based on FDA recommended starting dose of 2mg three times daily.

Osmolex ER™ (Amantadine ER) Product Summary[18]

Indication(s): Osmolex ER™ (amantadine ER) is indicated for the treatment of PD and for the treatment of drug-induced extrapyramidal reactions in adult patients.

Dosing:

- Osmolex ER™ is available as 129mg, 193mg, and 258mg ER oral tablets.
- The recommended initial dosage of Osmolex ER™ is 129mg administered by mouth once daily in the morning. The dosage may be increased in weekly intervals to a maximum daily dose of 322mg (administered as a 129mg and 193mg tablet), taken in the morning.
- Osmolex ER™ is not interchangeable with other amantadine IR or ER products.
- For patients unable to tolerate more than 100mg per day of IR amantadine, there is no equivalent dose or dosing regimen of Osmolex ER™.
- There are no modifications for the recommended initial and maximum dosage in patients with renal impairment; however, modifications are recommended for the titration interval and frequency of dosing in patients with moderate and severe renal impairment (*see Osmolex ER™ prescribing information for detailed dosing recommendations*).
- Osmolex ER™ should be swallowed whole, and can be taken with or without food.
- Osmolex ER™ should not be discontinued abruptly. The dose should be reduced gradually from higher doses to 129mg daily for 1 to 2 weeks before discontinuing.

Mechanism of Action: The mechanism by which amantadine exerts efficacy in the treatment of PD and drug-induced extrapyramidal reactions is unknown. Amantadine is a weak uncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor; however, it exhibits anticholinergic-like side effects such as dry mouth, urinary retention, and constipation in humans. Amantadine may have direct and indirect effects on dopamine neurons; it exerts dopaminergic-like side effects such as hallucinations and dizziness in humans.

Contraindication(s):

- Osmolex ER™ is contraindicated in patients with end-stage renal disease (ESRD) [i.e., creatinine clearance (CrCl) <15mL/min/1.73m^2].

Warnings and Precautions:

- Falling Asleep During ADL and Somnolence: Patients treated with amantadine, the active ingredient in Osmolex ER™, have reported falling asleep while engaged in ADL, including the operation of motor vehicles, which sometimes has resulted in accidents. Patients may not perceive warning signs, such as excessive drowsiness, or they may report feeling alert immediately prior to the event.
- Suicidality and Depression: Suicide, suicide attempts, and suicidal ideation have been reported in patients with and without prior history of psychiatric illness while treated with amantadine. Amantadine can exacerbate psychiatric symptoms in patients with a history of psychiatric disorders or substance abuse.
- Hallucinations/Psychotic Behavior: Patients with a major psychotic disorder should ordinarily not be treated with Osmolex ER™ because of the risk of exacerbating psychosis. Treatment with amantadine or abrupt withdrawal can cause confusion, psychosis, personality changes, agitation, aggressive behavior, hallucinations, paranoia, or other psychotic or paranoia reactions.
- Dizziness and Orthostatic Hypotension: Dizziness and orthostatic hypotension can occur with Osmolex ER™. Patients should be monitored for these adverse reactions, especially after starting Osmolex ER™ or increasing the dose. Concomitant use of alcohol when using Osmolex ER™ is not recommended.
- Withdrawal-Emergent Hyperprexia and Confusion: A symptom complex resembling neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in drugs that increase central dopaminergic tone.
- Impulse Control/Compulsive Behaviors: Patients can experience intense urges to gamble, increased sexual urges, intense urges to spend money, binge eating, or other intense urges, and the inability to control these urges while taking 1 or more of the medications that increase central dopaminergic tone, including Osmolex ER™.

Drug Interactions:

- Other Anticholinergic Drugs: Products with anticholinergic properties may potentiate the anticholinergic-like side effects of amantadine. The dose of anticholinergic drugs or of Osmolex ER™ should be reduced if atropine-like effects appear when these drugs are used concurrently.
- Drugs Affecting Urinary pH: The pH of urine has been reported to influence the excretion rate of amantadine. Urine pH is altered by diet, drugs (e.g., carbonic anhydrase inhibitors, sodium bicarbonate), and the clinical state of the patient (e.g., renal tubular acidosis, severe infections of the urinary tract). Since the excretion rate of amantadine increases rapidly when the urine is acidic, the administration of urine acidifying drugs may increase the elimination of the drug from the body. Alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a

possible increase in adverse reactions. It is recommended to monitor patients for efficacy or adverse reactions under conditions that alter the urine pH to more acidic or alkaline, respectively.

- Live Attenuated Influenza Vaccines: Because of its antiviral properties, amantadine may interfere with the efficacy of live attenuated influenza vaccines. Therefore, live vaccines are not recommended during treatment with Osmolex ER™. Inactivated influenza vaccines may be used.
- Alcohol: Concomitant use with alcohol is not recommended, as it may increase the potential for central nervous system (CNS) effects such as dizziness, confusion, lightheadedness, and orthostatic hypotension.

Adverse Reactions: The most common adverse reactions (≥5%) reported during pooled clinical studies of amantadine IR clinical trials were nausea, dizziness/lightheadedness, and insomnia.

Efficacy: The efficacy of Osmolex ER™ is based upon bioavailability studies comparing Osmolex ER™ to amantadine IR.

Cost Comparison:

Medication	Cost Per Unit	Cost Per Month*	Cost Per Year*
Osmolex ER™ (amantadine ER) 129mg, 193mg, and 258mg tablet	**$15.00**	**$900.00**	**$10,800.00**
amantadine 100mg capsule	$0.49	$29.40	$352.80
amantadine 100mg tablet	$1.00	$60.00	$720.00
amantadine 50mg/5mL oral syrup	$0.21	$126.00	$1,512.00
Gocovri™ (amantadine ER) 68.5mg and 137mg capsule	$39.58	$2,374.80	$28,497.60

Unit = capsule, tablet, or mL
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.
*Dosing based on adjunctive therapy in patients taking concomitant levodopa.

Recommendations

The College of Pharmacy recommends the prior authorization of Inbrija™ (levodopa inhalation) and Osmolex ER™ (amantadine ER) with the following criteria:

Inbrija™ (Levodopa Inhalation) Approval Criteria:

1. An FDA approved indication for the treatment of "off" episodes in patients with Parkinson's disease (PD) treated with carbidopa/levodopa; and
2. Member must be taking levodopa/carbidopa in combination with Inbrija™. Inbrija™ has been shown to be effective only in combination with carbidopa/levodopa; and
3. The member must be experiencing motor fluctuations with a minimum of 2 hours of "off" time and demonstrate levodopa responsiveness; and
4. Member must not be taking nonselective monoamine oxidase inhibitors (MAOIs) concomitantly with Inbrija™ or within 2 weeks prior to initiating Inbrija™; and
5. A quantity limit of 10 capsules for inhalation per day will apply.

Osmolex ER™ [Amantadine Extended-Release (ER)] Approval Criteria:

1. An FDA approved indication for the treatment of Parkinson's disease (PD) or drug-induced extrapyramidal reactions in adults patients; and
2. Member must not have end-stage renal disease (ESRD) [creatinine clearance (CrCl) <15mL/min/1.73m^2]; and
3. A minimum of a 6-month trial of amantadine immediate-release (IR) that resulted in inadequate effects or intolerable adverse effects that are not expected to occur with amantadine ER; and
4. A patient-specific, clinically significant reason why amantadine IR products cannot be used must be provided; and
5. A quantity limit will apply based on FDA approved dosing regimen(s).

Additionally, the College of Pharmacy recommends updating the Nuplazid® (pimavanserin) prior authorization criteria based on recent FDA safety warnings regarding concomitant therapy. The following criteria would apply (changes noted in red):

Nuplazid® (Pimavanserin) Approval Criteria:

1. An FDA approved diagnosis of hallucinations and delusions associated with Parkinson's disease (PD) psychosis; and
2. Member must have a concomitant diagnosis of PD; and
3. Member must not be taking concomitant medications known to prolong the QT interval including Class 1A antiarrhythmics (e.g., quinidine, procainamide) or Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibiotics (e.g., gatifloxacin, moxifloxacin); and
4. The member must not have a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval; and
5. Nuplazid® will not be approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with PD psychosis; and
6. Initial approvals will be for the duration of 3 months. For continuation, the prescriber must include information regarding improved response/effectiveness of this medication; and
7. A quantity limit of 2 tablets daily will apply.

Lastly, the College of Pharmacy recommends updating the Gocovri™ (amantadine ER) criteria based on net cost compared to other amantadine ER products. The following criteria would apply (changes noted in red):

Gocovri™ [Amantadine Extended-Release (ER)] Approval Criteria:

1. An FDA approved indication for the treatment of dyskinesia in patients with Parkinson's disease (PD) receiving levodopa-based therapy; and
2. Member must use Gocovri™ concomitantly with levodopa therapy; and

3. Member must not have end-stage renal disease (ESRD) [creatinine clearance (CrCl) <15mL/min/1.73m^2]; and
4. A minimum of a 6-month trial of amantadine immediate-release (IR) that resulted in inadequate effects or intolerable adverse effects that are not expected to occur with amantadine ER; and
5. A patient-specific, clinically significant reason why amantadine IR products cannot be used must be provided; and
6. A patient-specific, clinically significant reason why Osmolex ER™ (amantadine ER) cannot be used must be provided; and
7. A quantity limit of (1) 68.5mg capsule or (2) 137mg capsules per day will apply.

Utilization Details of PD Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
AMANTADINE PRODUCTS						
AMANTADINE CAP 100MG	3,673	804	$186,201.96	4.57	$1.74	$50.69
AMANTADINE TAB 100MG	1,471	496	$128,999.36	2.97	$3.07	$87.70
AMANTADINE SYP 50MG/5ML	222	67	$3,995.14	3.31	$0.67	$18.00
SUBTOTAL	**5,366**	**1,158**	**$319,196.46**	**4.63**	**$2.06**	**$59.48**
BENZTROPINE PRODUCTS						
BENZTROPINE TAB 1MG	5,564	1,137	$78,675.37	4.89	$0.46	$14.14
BENZTROPINE TAB 2MG	2,303	419	$34,138.67	5.5	$0.48	$14.82
BENZTROPINE TAB 0.5MG	1,749	349	$23,723.27	5.01	$0.45	$13.56
SUBTOTAL	**9,616**	**1,734**	**$136,537.31**	**5.55**	**$0.46**	**$14.20**
ROPINIROLE PRODUCTS						
ROPINIROLE TAB 1MG	1,525	427	$18,831.31	3.57	$0.33	$12.35
ROPINIROLE TAB 0.5MG	1,146	326	$14,539.05	3.52	$0.35	$12.69
ROPINIROLE TAB 2MG	945	234	$12,218.56	4.04	$0.33	$12.93
ROPINIROLE TAB 0.25MG	654	222	$8,636.35	2.95	$0.38	$13.21
ROPINIROLE TAB 3MG	292	65	$4,121.21	4.49	$0.36	$14.11
ROPINIROLE TAB 4MG	264	60	$3,913.89	4.4	$0.38	$14.83
ROPINIROLE TAB 5MG	99	22	$1,691.56	4.5	$0.52	$17.09
SUBTOTAL	**4,925**	**1,166**	**$63,951.93**	**4.22**	**$0.35**	**$12.99**
TRIHEXYPHENIDYL PRODUCTS						
TRIHEXYPHEN TAB 2MG	1,364	308	$14,811.53	4.43	$0.36	$10.86
TRIHEXYPHEN TAB 5MG	1,291	238	$19,027.65	5.42	$0.48	$14.74
TRIHEXYPHEN ELX 0.4MG/ML	134	20	$3,903.53	6.7	$0.99	$29.13
SUBTOTAL	**2,789**	**519**	**$37,742.71**	**5.37**	**$0.45**	**$13.53**
CARBIDOPA/LEVODOPA PRODUCTS						
CARB/LEVO TAB 25-100MG	798	161	$13,814.42	4.96	$0.57	$17.31
CARB/LEVO TAB 25-250MG	249	32	$6,819.16	7.78	$0.95	$27.39
CARB/LEVO TAB 10-100MG	177	42	$3,583.21	4.21	$0.62	$20.24
CARB/LEVO ER TAB 50-200MG	99	17	$4,157.39	5.82	$1.17	$41.99
CARB/LEVO ER TAB 25-100MG	39	14	$1,325.36	2.79	$1.06	$33.98

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
CARB/LEVO TAB 10-100MG	15	2	$529.50	7.5	$1.20	$35.30
RYTARY CAP 195MG	10	1	$5,527.27	10	$18.42	$552.73
CARB/LEVO TAB 25-100MG	6	2	$832.80	3	$5.63	$138.80
RYTARY CAP 245MG	2	1	$1,046.20	2	$23.78	$523.10
SUBTOTAL	**1,395**	**245**	**$37,635.31**	**5.69**	**$0.87**	**$26.98**
CARBIDOPA/LEVODOPA/ENTACAPONE PRODUCTS						
CARB/LEVO/ENTACA TAB 37.5/150/200MG	12	1	$1,706.21	12	$4.74	$142.18
CARB/LEVO/ENTACA TAB 50/200/200MG	11	1	$1,653.41	11	$5.01	$150.31
CARB/LEVO/ENTACA TAB 12.5/50/200MG	8	1	$1,064.10	8	$4.43	$133.01
CARB/LEVO/ENTACA TAB 25/100/200MG	6	1	$805.98	6	$4.48	$134.33
SUBTOTAL	**37**	**4**	**$5,229.70**	**9.25**	**$4.71**	**$141.34**
CARBIDOPA PRODUCTS						
CARBIDOPA TAB 25MG	6	3	$1,312.04	2	$8.75	$218.67
SUBTOTAL	**6**	**3**	**$1,312.04**	**2**	**$8.75**	**$218.67**
PRAMIPEXOLE PRODUCTS						
PRAMIPEXOLE TAB 0.5MG	445	110	$5,206.06	4.05	$0.32	$11.70
PRAMIPEXOLE TAB 0.125MG	358	103	$4,399.19	3.48	$0.35	$12.29
PRAMIPEXOLE TAB 0.25MG	296	88	$3,447.10	3.36	$0.31	$11.65
PRAMIPEXOLE TAB 1MG	241	59	$3,148.09	4.08	$0.33	$13.06
PRAMIPEXOLE TAB 1.5MG	73	16	$852.43	4.56	$0.27	$11.68
PRAMIPEXOLE TAB 0.75MG	23	9	$309.88	2.56	$0.31	$13.47
SUBTOTAL	**1,436**	**337**	**$17,362.75**	**4.26**	**$0.32**	**$12.09**
BROMOCRIPTINE PRODUCTS						
BROMOCRIPTIN TAB 2.5MG	338	83	$40,276.54	4.07	$3.86	$119.16
BROMOCRIPTIN CAP 5MG	117	30	$40,439.38	3.9	$11.63	$345.64
SUBTOTAL	**455**	**100**	**$80,715.92**	**4.55**	**$5.80**	**$177.40**
ENTACAPONE PRODUCTS						
ENTACAPONE TAB 200MG	25	4	$5,831.96	6.25	$7.78	$233.28
SUBTOTAL	**25**	**4**	**$5,831.96**	**6.25**	**$7.78**	**$233.28**
RASAGILINE PRODUCTS						
RASAGILINE TAB 1MG	18	4	$5,981.73	4.5	$11.08	$332.32
RASAGILINE TAB 0.5MG	12	1	$3,984.60	12	$11.07	$332.05
SUBTOTAL	**30**	**5**	**$9,966.33**	**6**	**$11.07**	**$332.21**
ROTIGOTINE PRODUCTS						
NEUPRO DIS 8MG/24HR	7	1	$4,334.81	7	$20.64	$619.26
SUBTOTAL	**7**	**1**	**$4,334.81**	**7**	**$20.64**	**$619.26**
SELEGILINE PRODUCTS						
SELEGILINE TAB 5MG	11	3	$591.90	3.67	$2.04	$53.81
SUBTOTAL	**11**	**3**	**$591.90**	**3.67**	**$2.04**	**$53.81**
PIMAVANSERIN PRODUCTS						
NUPLAZID TAB 17MG	92	15	$199,175.40	6.13	$76.84	$2,164.95
SUBTOTAL	**92**	**15**	**$199,175.40**	**6.13**	**$76.84**	**$2,164.95**
TOTAL	**26,190**	**4,913***	**$919,584.53**	**5.33**	**$1.10**	**$35.11**

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

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Appendix S

Industry News and Updates

Oklahoma Health Care Authority
February 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[1,2,3]

News:

- **Heroin Vaccine:** Researchers at Upstate Medical University and the Walter Reed Army Institute of Research in Maryland have received a grant to conduct clinical trials on an experimental heroin vaccine. The vaccine was developed by researchers at the National Institute on Drug Abuse and Walter Reed's Military HIV Research Program. During preclinical studies conducted in mice and rats, the vaccine produced antibodies that stopped heroin from entering the brain for up to 3 months. The experimental vaccine may be tested in human volunteers starting in late 2020.
- **Smartphones:** The U.S. Food and Drug Administration (FDA) is expected to formally propose a plan that would limit the need for patients to obtain a prescription for certain drugs that have prescription-only status. The plan would permit patients to use their smartphone to answer a set of questions to determine their medical need for certain medications. This self-selection process would ideally determine whether the use of an over-the-counter (OTC) medication is appropriate for the patient. If the medication is deemed appropriate, the patient would provide a code or ticket to use to pick up the medication at the pharmacy. FDA Commissioner Scott Gottlieb sees smartphones and other technologies as ways to boost OTC drug utilization and facilitate switches from prescription-only medications to OTC drugs. The FDA has said that more switched products could reduce health care costs while facilitating access.
- **Hepatitis C:** Louisiana is on track to become the first state to adopt a new process for obtaining hepatitis C medications in an effort health officials hope will ultimately help the state eradicate the disease. State officials announced in January that the state has begun the process of formally seeking a pharmaceutical partner for an innovative "subscription" model for obtaining hepatitis C medications. The state hopes to have a contract in place by July. The state plans to take the money that it currently spends toward hepatitis C treatment in Medicaid and the prison system, and find a drug manufacturer that will agree to be paid that amount for unlimited access to the medication over a 5-year period. Due to the high cost of the medications, only 384 Louisiana Medicaid patients were treated for hepatitis C last year; however, nearly 35,000 people in Louisiana's Medicaid program have the hepatitis C virus.

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Appendix T

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

New Drug Class Employs Novel Mechanism for Migraine Treatment and Prevention

The FDA has recently approved members of a new class of drugs specifically designed to treat migraine by targeting calcitonin gene-related peptide (CGRP), a substance that is elevated in blood serum during migraine attacks. Designed to decrease the number of migraine attacks, the new class of migraine drugs is metabolized differently and has fewer adverse reactions observed in clinical trials, as well as fewer warnings and precautions, compared to other approved migraine therapeutics. The three new FDA-approved drugs are Aimovig™ (erenumab-aooe), Ajovy™ (fremanezumab-vfrm), and Emgality™ (galcanezumab-gnlm).

A migraine can cause severe, debilitating, and persistent pain that can last for hours or days. Migraine symptoms may also include nausea, vomiting, and extreme sensitivity to light and sound, with some migraine sufferers reporting visual disturbances, called an aura, such as light flashes, spots, or vision loss.

Although several therapeutics are available to stop migraine attacks after they are already underway and some drugs include migraine prevention among several approved indications, the new class of CGRP-targeted drugs is the first to be specifically designed for the preventive treatment of migraine, marking a significant new era of migraine therapeutics.

Understanding the Role of CGRP and the Trigeminal Pain System in Migraine

Migraine is a neurovascular disorder associated with dysfunction of the cerebral nerve cells and blood vessels. Although scientists initially believed that migraine attacks originated in the cerebral blood vessels, more recent research suggests that migraine probably results from primary dysfunction in the brainstem centers that regulate vascular tone and pain sensation. The migraine attack often begins when triggers, such as stress, certain foods, or hormonal changes, set off dysfunctional reactions in the brain, causing excessive relaxation or dilation of cranial blood vessels.

These dilated blood vessels then mechanically activate sensory fibers from the trigeminal nerve located in the vessel wall, which then convey pain impulses to the brainstem and from there to higher brain centers. These impulses prompt the nerve fibers to release vasoactive peptides such as CGRP, which intensify dilation of the cranial blood vessels and cause “neurogenic” inflammation. This chain of events results in increased leakiness of blood vessels and the release of toxic compounds from mast cells, a type of white blood cell found in connective tissue. These events further increase the activation of the sensory fibers and perpetuate the release of vasoactive peptides, including CGRP. Scientists believe that as the migraine attack progresses, the brainstem and spinal cord centers that are the first to receive the pain impulses from the trigeminal nerves amplify the headache pain and increase sensitivity to environmental and other stimuli affecting visual and auditory sensation.

How the New Drug Class Uses CGRP-Targeted Monoclonal Antibodies to Prevent Migraine

In the new class of migraine therapeutics, the primary mechanism of action is the blocking of the effects of CGRP. These specialized monoclonal antibodies that are designed to treat migraine are cloned subclasses of immunoglobulin G (IgG), the most common type of antibody circulating in the blood, and are designed to have little potential to interact with other drugs. They act as antagonists, sometimes called blockers or inhibitors.

In the case of the drug erenumab-aooe, the antagonist selectively targets and binds to the CGRP receptor, blocking CGRP from interacting with the receptor. In contrast, fremanezumab-vfrm and galcanezumab-gnlm block the ability of CGRP to bind to the CGRP receptor.

Previously approved migraine preventive treatments were first approved for other conditions, and were later found to be effective in reducing the frequency of migraine attacks. The mechanism of action for earlier migraine therapeutics is less clear than that of CGRP antagonists, which were developed based on the knowledge that blocking the role of CGRP in the cascade of events that lead to a migraine attack may be an effective mechanism for migraine treatment.

Safety Announcements

Tris Pharma, Inc. Expands Its Voluntary Nationwide Retail Recall of Ibuprofen Oral Suspension Drops, USP, 50mg per 1.25mL, Due to Higher Concentration of Ibuprofen

[01/29/2019] Monmouth Junction, NJ, Tris Pharma, Inc. is expanding the scope of its November 2018 recall by adding) additional lots of Ibuprofen Oral Suspension Drops, USP, 50mg per 1.25mL, to the retail (pharmacy) level. Some units from these batches have been found to have higher levels of Ibuprofen concentration.

Infants already susceptible to the adverse effects of ibuprofen may be at a slightly higher risk if they receive medication from an impacted bottle. There is a remote probability that infants, who may be more susceptible to a higher potency level of drug, may be more vulnerable to permanent NSAID-associated renal injury. Some units from these 6 lots have been found to contain Ibuprofen as high as 10% above the specified limit. Studies have shown that safety issues or toxicity is generally accepted to be a concern in infants at doses in excess of 700% of the recommended dose. To date, no serious adverse events have been reported related to this recall. The product is used as a pain reliever/fever reducer and is packaged in ½ oz. and 1 oz. bottles.

Tris Pharma, Inc. manufactures Ibuprofen Oral Suspension Drops, USP for a single customer, who markets and distributes the product to retailers. The retailers should stop further distribution of the affected lots, which are being recalled. Tris Pharma, Inc. has notified its customer by urgent recall notice and has arranged for the return of recalled products from retailers and distributors.

Consumers with questions regarding this recall may contact Tris Customer Service by 732-940-0358 (Monday through Friday, 8:00 AM ET- 5:00 PM PT) or via email at micc_tris@vigilarebp.com. Consumers, who may be concerned, should contact their physician or health care provider if they have experienced any problems that may be related to taking or using this drug product.

Safety Announcements

Lupin Pharmaceuticals, Inc. Issues Voluntary Recall of Ceftriaxone for Injection USP, 250mg, 500mg, 1g, and 2g

[01-05-2019] Lupin Pharmaceuticals, Inc. is voluntarily recalling 5 lots of Ceftriaxone for Injection, USP, 250mg, 10 lots of Ceftriaxone for Injection, USP, 500mg, 24 lots of Ceftriaxone for Injection, USP, 1g, and 3 lots of Ceftriaxone for Injection, USP 2g, to the hospital/physician level. The products have been found to contain visual grey particulate matter in reconstituted vials.

Improper piercing and use of a needle greater than 21 gauge (larger internal diameter), while reconstituting the vial, can push rubber flecks into the solution. There were no grey flecks seen prior to the reconstitution of the vials and the issue was identified upon standard visual inspection prior to patient administration.

If injected, this product (containing rubber particulate matter from the stopper) could cause vein irritation/phlebitis or pulmonary embolic events that could result in permanent impairment of body function or damage to body structures, such as the lungs and vascular system. In addition, as ceftriaxone can be administered intramuscularly, the use of the product may result in local muscle inflammation and/or abscesses.

Ceftriaxone for Injection, USP, is used as a sterile, semi-synthetic, broad-spectrum cephalosporin antibiotic for intravenous or intramuscular administration. It is used to reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftriaxone sodium and other antibacterial drugs.

Ceftriaxone for Injection, USP, should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. To date, the Company has not received any reports of adverse events related to the recalled lots.

Ceftriaxone for Injection, USP, is packaged in a glass vial, in pack of 10, containing 10 vials in a carton, with NDC 68180-611-10, 68180-622-10, 68180-633-10, 68180-644-10, and as single pack containing one glass vial in a carton with NDC 68180-611-01, 68180-622-01, 68180-633-01.

Ceftriaxone for Injection, USP, 250mg, Ceftriaxone for Injection, USP, 500mg, Ceftriaxone for Injection, USP, 1g, and Ceftriaxone for Injection, USP, 2g were distributed Nationwide to Wholesalers/Drug chains.

Lupin Pharmaceuticals, Inc. is notifying its distributors by phone and through recall notification and is arranging for return of all recalled product lots.

Hospitals/prescribers that have Ceftriaxone for Injection, USP, which are being recalled should stop using and return to Genco Pharmaceuticals Services “a subsidiary of FedEx Supply Chain” 6101 North 64th Street, Milwaukee, WI 53218, Tel: (855) 838-5786.

Questions regarding this recall can be made by contacting GENCO Pharmaceutical Services at 1-855-838-5786 Monday – Friday 7:30 am to 6:00 pm EST. For reimbursement, the recalled lots should be returned to GENCO, the lot number can be found on the side of the vial. Consumers should contact their physician or health care provider if they have experienced any problems that may be related to taking or using this drug product.

Current Drug Shortages Index (as of February 1st, 2019):

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

Abciximab (ReoPro) Injection	***Currently in Shortage***
Amino Acids	***Currently in Shortage***
Aminophylline Injection, USP	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Azithromycin (Azasite) Ophthalmic Solution 1%	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Belladonna and Opium Suppository	***Currently in Shortage***
Bisoprolol Fumarate Tablets	***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***
Calcium Gluconate Injection	***Currently in Shortage***
Carbidopa and Levodopa Extended Release Tablets	***Currently in Shortage***
Cefazolin Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cycloserine Capsules, USP	***Currently in Shortage***
Deferoxamine Mesylate for Injection, USP	***Currently in Shortage***
Dexrazoxane Injection	***Currently in Shortage***
Dextrose 5% Injection Bags	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Diazepam Injection, USP	***Currently in Shortage***
Diltiazem Hydrochloride	***Currently in Shortage***
Diltiazem Hydrochloride ER (Twice-a-Day) Capsules	***Currently in Shortage***
Diphenhydramine Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Dobutamine Hydrochloride Injection	***Currently in Shortage***
Dopamine Hydrochloride Injection	***Currently in Shortage***
Dorzolamide Hydrochloride and Timolol Maleate (Cosopt) Ophthalmic Solution	***Currently in Shortage***
Dorzolamide Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Eflornithine Hydrochloride (Vaniqa) Cream	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Epinephrine Injection, Auto-Injector	***Currently in Shortage***
Erythromycin Lactobionate for Injection, USP	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***

Fludrocortisone Acetate Tablets	***Currently in Shortage***
Fluorescein Injection	***Currently in Shortage***
Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Fluorescein Strips	***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***
Hydroxyprogesterone Caproate Injection	***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***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Letermovir (Prevymis) Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Leuprolide Acetate Injection	***Currently in Shortage***
Lidocaine Hydrochloride (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***
Magnesium Sulfate Injection	***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 (QUILLICHEW ER) Extended-Release Chewable Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLIVANT XR) for Extended-Release Oral Suspension	***Currently in Shortage***
Metoclopramide Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Molindone Hydrochloride Tablets	***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***
Nelarabine (Arranon) Injection	***Currently in Shortage***
Nystatin Oral Suspension	***Currently in Shortage***
Ondansetron Hydrochloride Injection	***Currently in Shortage***
Penicillamine (Depen) Titratable Tablets	***Currently in Shortage***
Penicillin G Procaine Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Phenytoin Sodium Injection, USP	***Currently in Shortage***
Phosphate Injection Products	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Progesterone 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***
Sacrosidase (Sucraid) Oral Solution	***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***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Sterile Water	***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***
Trifluoperazine Hydrochloride Tablets	***Currently in Shortage***
Valsartan Tablets	***Currently in Shortage***