Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday, January 9, 2019

No live January meeting. January is a packet only meeting.

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 Packet – January 9, 2019

DATE: December 24th, 2018

Enclosed are the following items related to the January meeting.
Material is arranged in order of the agenda.
No live January meeting. January is a packet only meeting.

DUR Board Meeting Minutes – Appendix A

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

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

Annual Review of Glaucoma Medications and 30-Day Notice to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion) – Appendix D

30-Day Notice to Prior Authorize Revcovi™ (Elapegademase-lvlr) – Appendix E

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 – Appendix F

Annual Review of Mepsevii™ (Vestronidase Alfa-vjbk) – Appendix G

Annual Review of Nuedexta® (Dextromethorphan/Quinidine) – Appendix H

Annual Review of Zilretta® [Triamcinolone Acetonide Extended-Release (ER) Injection] – Appendix I

Industry News and Updates – Appendix J

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

Future Business

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
January 9, 2019
No live January meeting. January is a packet only meeting.

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. DUR Board Meeting Minutes – See Appendix A

A. December 12, 2018 DUR Minutes
B. December 12, 2018 DUR Recommendations Memorandum

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

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

A. Medication Coverage Activity for December 2018
B. Pharmacy Helpdesk Activity for December 2018
C. FDA Safety Alerts

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

3. Annual Review of Injectable and Vaginal Progesterone Products and 30-Day Notice to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector] – See Appendix C

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

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

4. Annual Review of Glaucoma Medications and 30-Day Notice to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion) – See Appendix D

A. Current Prior Authorization Criteria
B. Utilization of Glaucoma Medications
C. Prior Authorization of Glaucoma Medications
D. Market News and Updates
E. Xelpros™ (Latanoprost 0.005% Emulsion) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Glaucoma Medications

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

5. 30-Day Notice to Prior Authorize Revcovi™ (Elapegademase-lvlr) – See Appendix E

A. Introduction
B. Market News and Updates
C. Revcovi™ (Elapegademase-lvlr) Product Summary
D. College of Pharmacy Recommendations

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

6. 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 – See Appendix F

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Hyperkalemia Medications
D. Prior Authorization of Hyperkalemia Medications
E. Market News and Updates
F. Lokelma™ (Sodium Zirconium Cyclosilicate) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Hyperkalemia Medications

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

7. Annual Review of Mepsevii™ (Vestronidase Alfa-vjbk) – See Appendix G

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Mepsevii™ (Vestronidase Alfa-vjbk)
D. Prior Authorization of Mepsevii™ (Vestronidase Alfa-vjbk)
E. Market News and Updates
F. College of Pharmacy Recommendations

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

8. Annual Review of Nuedexta® (Dextromethorphan/Quinidine) – See Appendix H

A. Current Prior Authorization Criteria
B. Utilization of Nuedexta® (Dextromethorphan/Quinidine)
C. Prior Authorization of Nuedexta® (Dextromethorphan/Quinidine)
D. Market News and Updates
E. College of Pharmacy Recommendations

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

9. Annual Review of Zilretta® [Triamcinolone Acetonide Extended-Release (ER) Injection] – See Appendix I

A. Current Prior Authorization Criteria
B. Utilization of Zilretta® (Triamcinolone Acetonide ER Injection)
C. Prior Authorization of Zilretta® (Triamcinolone Acetonide ER Injection)
D. Market News and Updates
E. College of Pharmacy Recommendations

Non-Presentation; Questions Only:

10. Industry News and Updates – See Appendix J

A. Introduction
B. News and Updates

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

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

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

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

A. Parkinson's Disease Medications
B. Antiepileptic Medications
C. Anti-Migraine Medications
D. Gamifant® (Emapalumab)
E. Firdapse® (Amifampridine)

**Future business subject to change.*

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 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 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.

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)

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).
    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 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

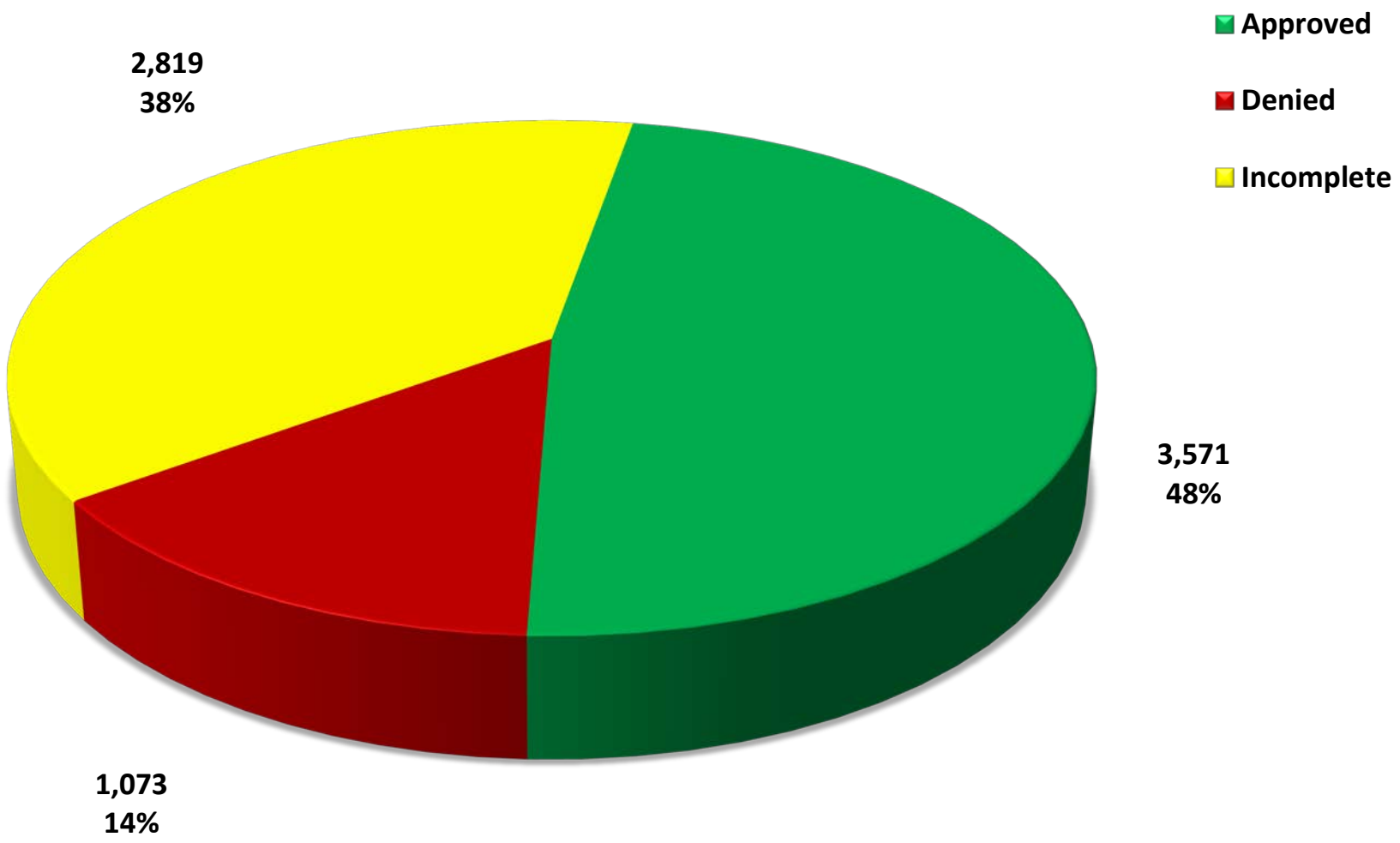
NO ACTION REQUIRED.

Recommendation 15: Future Business

NO ACTION REQUIRED.

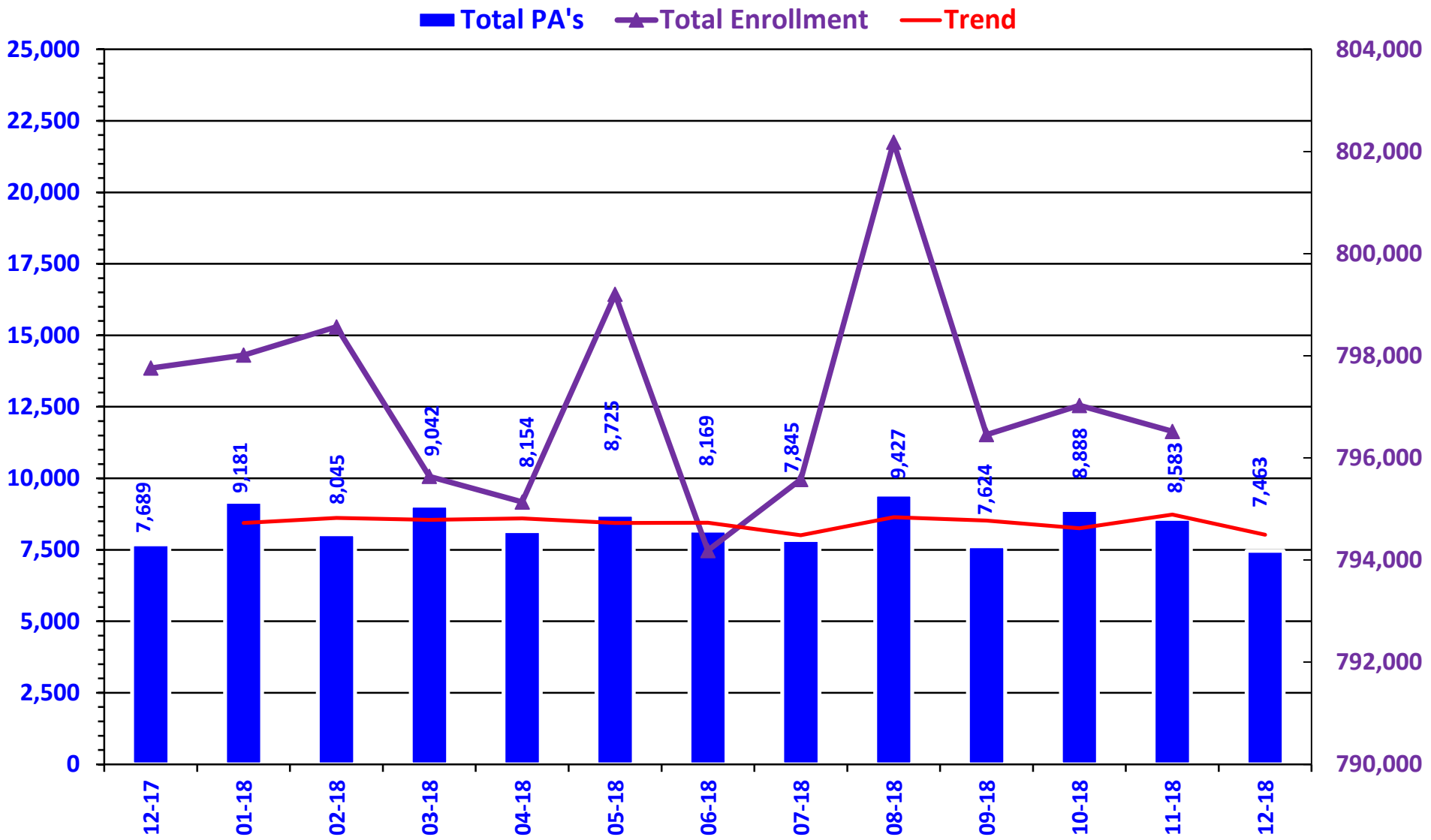
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: DECEMBER 2018



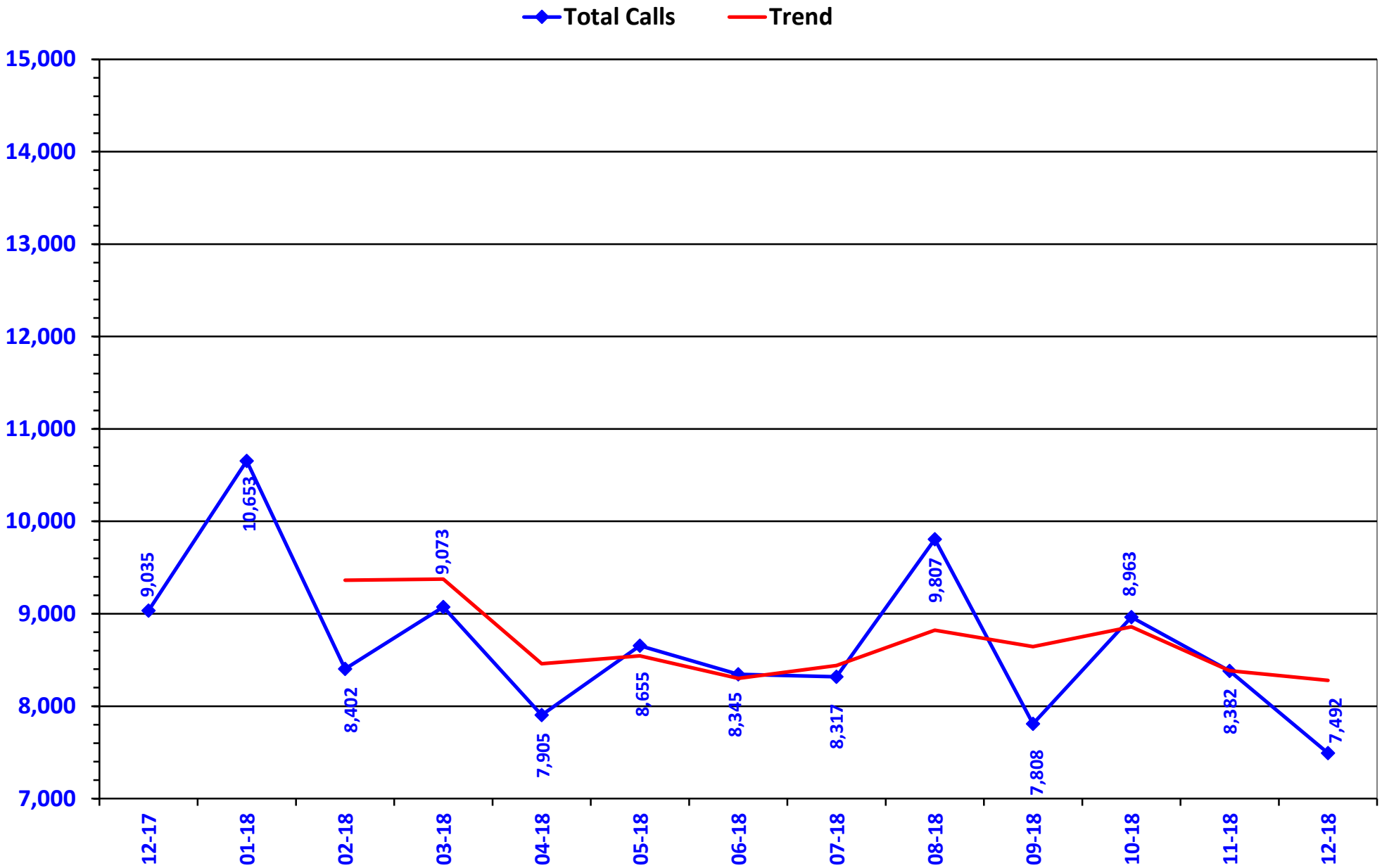
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: DECEMBER 2017 – DECEMBER 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
DECEMBER 2017 – DECEMBER 2018



Prior Authorization Activity

12/1/2018 Through 12/31/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	79	10	18	51	324
Analgesic - NonNarcotic	14	0	0	14	0
Analgesic - Narcotic	343	156	42	145	155
Angiotensin Receptor Antagonist	11	1	4	6	358
Antiasthma	67	15	15	37	268
Antibiotic	34	22	1	11	299
Anticonvulsant	162	64	16	82	254
Antidepressant	123	34	21	68	315
Antidiabetic	212	77	34	101	354
Antihistamine	17	3	4	10	267
Antimigraine	110	10	41	59	162
Antineoplastic	71	50	2	19	139
Antiparasitic	12	3	3	6	7
Antiulcers	141	39	50	52	137
Anxiolytic	29	10	4	15	203
Atypical Antipsychotics	195	109	19	67	356
Biologics	107	59	11	37	286
Bladder Control	64	22	14	28	284
Blood Thinners	266	147	16	103	315
Botox	44	29	6	9	320
Buprenorphine Medications	412	286	19	107	77
Calcium Channel Blockers	10	0	1	9	0
Cardiovascular	112	53	14	45	332
Chronic Obstructive Pulmonary Disease	145	29	34	82	315
Constipation/Diarrhea Medications	122	20	43	59	273
Contraceptive	28	24	1	3	358
Corticosteroid	10	0	4	6	0
Dermatological	143	22	61	60	187
Diabetic Supplies	450	267	10	173	244
Endocrine & Metabolic Drugs	151	79	18	54	142
Erythropoietin Stimulating Agents	29	19	2	8	109
Fibric Acid Derivatives	11	1	2	8	358
Fibromyalgia	189	86	50	53	65
Gastrointestinal Agents	83	20	21	42	190
Glaucoma	10	5	0	5	128
Growth Hormones	76	53	10	13	137
Hematopoietic Agents	12	5	2	5	152
Hepatitis C	143	84	13	46	8
HFA Rescue Inhalers	40	0	9	31	0
Insomnia	40	3	18	19	287
Insulin	110	31	12	67	330
Miscellaneous Antibiotics	21	4	1	16	55
Multiple Sclerosis	40	21	3	16	201
Muscle Relaxant	31	3	11	17	136
Nasal Allergy	56	7	23	26	205
Neurological Agents	98	34	28	36	240
NSAIDs	83	36	16	31	87
Ocular Allergy	19	1	6	12	84
Ophthalmic Anti-infectives	16	4	4	8	11
Osteoporosis	2	1	1	0	359

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Other*	263	50	56	157	268
Otic Antibiotic	17	1	4	12	26
Respiratory Agents	23	18	0	5	193
Stimulant	630	300	64	266	340
Synagis	104	49	29	26	102
Testosterone	54	12	13	29	337
Thyroid	10	2	1	7	74
Topical Antifungal	20	3	4	13	15
Topical Corticosteroids	65	1	41	23	9
Vitamin	85	16	32	37	230
Pharmacotherapy	85	74	0	11	300
Emergency PAs	0	0	0	0	
Total	**6,149**	**2,584**	**1,002**	**2,563**	
Overrides					
Brand	28	21	1	6	220
Compound	20	17	0	3	15
Diabetic Supplies	8	7	0	1	88
Dosage Change	271	255	1	15	12
High Dose	1	1	0	0	5
IHS-Brand	1	1	0	0	17
Ingredient Duplication	8	7	0	1	7
Lost/Broken Rx	87	82	3	2	12
NDC vs Age	244	156	23	65	290
Nursing Home Issue	61	42	8	11	14
Opioid Quantity	41	29	5	7	157
Other*	35	29	2	4	17
Quantity vs. Days Supply	444	298	26	120	235
STBS/STBSM	14	6	1	7	54
Stolen	8	6	0	2	14
Temporary Unlock	1	1	0	0	8
Third Brand Request	42	29	1	12	37
Overrides Total	**1,314**	**987**	**71**	**256**	
Total Regular PAs + Overrides	**7,463**	**3,571**	**1,073**	**2,819**	

Denial Reasons	
Unable to verify required trials.	2,323
Does not meet established criteria.	1,083
Lack required information to process request.	465
Other PA Activity	
Duplicate Requests	462
Letters	9,353
No Process	17
Changes to existing PAs	595
Helpdesk Initiated Prior Authorizations	528
PAs Missing Information	37

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

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

Oklahoma Health Care Authority
January 2019

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

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

Date	Drug	Issue
02/01/2018	**Obeticholic Acid (Ocaliva®)**	**Incorrect dosing daily instead of weekly in patients with advanced disease**
Issue Details: The FDA issued a warning regarding the incorrect dosing of obeticholic acid in some patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment. The label indicates that patients with Child-Pugh Class B or C hepatic impairment or patients with a prior decompensation event should be initiated at a dose of 5mg once weekly rather than daily, with increases to no more than 10mg twice weekly. Excessive dosing can lead to an increased risk of serious liver injury and death. Obeticholic acid is FDA approved for PBC and is taken with ursodeoxycholic acid (UDCA) unless UDCA is not tolerated. Since FDA approval in May 2016, 19 deaths and 11 cases of serious liver injury have been reported, most of which occurred during obeticholic acid use. **FDA Recommendation(s):** The FDA required the addition of a *Boxed Warning* and clarification in the label regarding dosing. Prescribers should evaluate baseline liver function before initiating obeticholic acid. Patients should be advised to report new or worsening severe skin itching, in addition to worsening gastrointestinal (GI) complaints, fatigue, and vague behavior changes. Prescribers are encouraged to report side effects to the FDA MedWatch program. **Pharmacy Claims Evaluation:** Since obeticholic acid was FDA approved in May 2016, only 1 SoonerCare member has had paid claims for this medication. The College of Pharmacy did confirm with the prescriber that this member was receiving appropriate dosing based on the member's liver status. **SoonerCare Action:** All prior authorization requests are reviewed under the clarified dosing recommendations. Requests not specifying the member's liver status will not be approved without further information.		

Date	Drug	Issue
02/22/2018	**Clarithromycin (Biaxin®)**	**Increased risk of heart problems**
Issue Details: Prescribers should exercise caution before prescribing clarithromycin to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. In a large clinical trial, an unexpected increase in deaths among patients with coronary heart disease who received a 2-week course of clarithromycin became apparent		

after patients had been followed for 1 year or longer. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. Of the 6 observational studies published to date in patients with or without coronary artery disease, 2 found evidence of long-term risks from clarithromycin, and 4 did not. There are no prospective, randomized, and controlled trials with prespecified long-term safety outcome measures following clarithromycin treatment in patients who do not have heart disease.

FDA Recommendation(s): The FDA is requiring that a *Warning* be added to clarithromycin labels regarding the increased risk of death in patients with heart disease. In addition, the FDA is advising prescribers to consider using other antibiotics in place of clarithromycin in patients with heart disease.

Pharmacy Claims Evaluation: During fiscal year (FY) 2018, a total of 1,738 members had paid claims for clarithromycin tablets or suspension. The average number of claims per member was 1.12 and the percentage of members with more than 1 paid claim was 8.2%. A comparison of April 2017 to April 2018 revealed a 25.0% decrease in claims for clarithromycin tablets and suspension.

SoonerCare Action: An update regarding recent antibiotic safety issues, including the increased risk of heart-related problems associated with clarithromycin use, will be included in the SoonerCare provider newsletter.

Date	Drug	Issue
04/25/2018	**Lamotrigine (Lamictal®)**	**Risk of serious immune system reaction(s)**

Issue Details: The FDA issued a Safety Communication regarding the risk of hemophagocytic lymphohistocytosis (HLH), an uncontrolled response by the immune system, in patients taking lamotrigine. Symptoms of HLH include fever, rash, enlarged spleen, cytopenias, elevated triglycerides, high levels of ferritin, hemophagocytosis, decreased natural killer (NK) cell activity, and elevated blood levels of CD25 showing prolonged immune cell activation. In the 24 years since lamotrigine's 1994 FDA approval, the FDA identified 8 cases of confirmed or suspected HLH associated with lamotrigine. The patients in these cases required hospitalization and received drug and other medical treatments, with 1 patient dying. All cases had a plausible temporal relationship with lamotrigine, occurring within 24 days of starting lamotrigine treatment. Doses ranged from 25mg every other day to 250mg once daily in the 6 cases that reported this information.

FDA Recommendation(s): The FDA is requiring that a *Warning* be added to lamotrigine labels regarding the increased risk of HLH. The FDA is also encouraging health care professionals to be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated because early signs and symptoms such as fever and rash are not specific. HLH may also be confused with other serious immune-related adverse reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Patients should be advised to seek immediate medical attention if they experience symptoms of HLH during lamotrigine treatment.

Pharmacy Claims Evaluation: During FY 2018, a total of 5,293 members accounted for 30,623 paid claims for lamotrigine-containing products. None of the members utilizing lamotrigine-containing products had a diagnosis of HLH in their diagnosis claims history during that time.

Date	Drug	Issue
05/18/2018	**Pembrolizumab (Keytruda®) and Atezolizumab (Tecentriq®)**	**Decreased survival when used as monotherapy**

Issue Details: The FDA issued a warning regarding decreased survival associated with the use of pembrolizumab or atezolizumab when used as monotherapy to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1). In 2 clinical trials, the FDA's early reviews found that patients in the monotherapy arms of both trials with low PD-L1 status had decreased survival compared to patients who received cisplatin- or carboplatin-based chemotherapy. Health care professionals should be aware that the populations enrolled in the clinical trials were eligible for platinum-containing chemotherapy, and therefore differ from those enrolled in the trials that led to the accelerated approvals of both pembrolizumab and atezolizumab in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.
FDA Recommendation(s): The FDA required an update to the prescribing information of both pembrolizumab and atezolizumab restricting the indication for use to patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy. In addition, the FDA required an update to the prescribing information for both medications to require the use of a companion diagnostic test to determine PD-L1 levels in tumor tissue from patients with locally advanced or metastatic urothelial cancer who are cisplatin-ineligible.
Pharmacy Claims Evaluation: During FY 2018, 38 SoonerCare members accounted for 168 paid claims for pembrolizumab and no claims for atezolizumab.
SoonerCare Action: The current SoonerCare prior authorization criteria for both medications follows the FDA's recommendations regarding use of pembrolizumab or atezolizumab as monotherapy in cisplatin-ineligible patients. Requests not following the FDA's recommendations will not be approved.

Date	Drug	Issue
05/18/2018	**Dolutegravir (Tivicay®), Dolutegravir/Rilpivirine (Juluca®), and Abacavir/ Dolutegravir/Lamivudine (Triumeq®)**	**Risk of neural tube birth defects**

Issue Details: Serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women treated with dolutegravir used for the treatment of human immunodeficiency virus (HIV). Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir-containing medications at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.
FDA Recommendation(s): The FDA is advising health care professionals to inform women of childbearing age about the potential risk of neural tube defects when a dolutegravir-containing regimen is used at the time of conception and early in pregnancy. In addition, health care professionals should weigh the benefits and the risks of dolutegravir when

prescribing antiretroviral medicines to women of childbearing age. If the decision is made to use dolutegravir in women of childbearing age, health care professionals should reinforce the consistent use of effective birth control. The FDA is continuing to monitor the observational study in Botswana. Additional birth outcomes are projected from pregnant women who were exposed to dolutegravir at the time of becoming pregnant. The FDA will conduct a comprehensive review of the results and any other data that becomes available.
Pharmacy Claims Evaluation: During FY 2018, a total of 37 females 15 to 45 years of age had paid claims for a dolutegravir-containing medication. Of those 37 females, a small number did have a pregnancy diagnosis during the same timeframe; all members with pregnancy diagnoses were being followed by an infectious disease specialist.
SoonerCare Action: The College of Pharmacy will continue to monitor the FDA recommendations following the conclusion of the Botswana observational study. Additional action may be taken following the FDA's final recommendations.

Date	Drug	Issue
05/23/2018	**Oral Over-The-Counter (OTC) Benzocaine Products**	**Risk of serious and potentially fatal blood disorder**

Issue Details: The FDA issued a Drug Safety Communication regarding the increased risk of methemoglobinemia, a life-threatening condition in which the amount of oxygen carried through the blood cells is greatly reduced, in patients younger than 2 years of age who use OTC oral drug products containing benzocaine to treat teething pain.
FDA Recommendation(s): The FDA has instructed manufacturers to stop marketing OTC oral drug products for treating teething in infants and children younger than 2 years of age. They have also required label changes to all OTC oral drug products containing benzocaine including the addition of a *Warning* about methemoglobinemia and revising the directions to instruct caregivers not to use the product in children younger than 2 years of age.
Pharmacy Claims Evaluation: SoonerCare does not cover oral OTC benzocaine products.
SoonerCare Action: Details regarding this warning were included in the Summer 2018 provider newsletter.

Date	Drug	Issue
8/29/2018	**Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors**	**Risk of serious infection in the genital area**

Issue Details: The FDA issued a Drug Safety Communication regarding the risk of necrotizing fasciitis or Fournier's gangrene, a rare but serious infection, in the genital area in patients who use SGLT2 inhibitors. First FDA approved in 2013, medications in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Fournier's gangrene is an extremely rare but life-threatening bacterial infection of the tissue under the skin that surrounds muscles, nerves, fat, and blood vessels of the perineum. The bacteria usually get into the body through a cut or break in the skin, where they quickly spread and destroy the tissue they infect. Having diabetes is a risk factor for developing Fournier's gangrene; however,

this condition is still rare among diabetic patients. Publications report that Fournier's gangrene occurs in 1.6 out of 100,000 males annually, and most frequently occurs in males 50 to 79 years of age (3.3 out of 100,000). From March 2013 to May 2018, the FDA identified 12 cases of Fournier's gangrene in patients taking an SGLT2 inhibitor. Although most cases of Fournier's gangrene have previously been reported in men, the FDA found that of the 12 cases included, 7 were men and 5 were women. Fournier's gangrene developed within several months of the patients starting an SGLT2 inhibitor and the drug was stopped in most cases. All 12 patients were hospitalized and required surgery. Some patients required multiple disfiguring surgeries, some developed complications, and 1 patient died. In comparison, only 6 cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years.

FDA Recommendation(s): Health care professionals should assess patients for Fournier's gangrene if they present with the symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4°F. If suspected, patients should be started on treatment immediately with broad-spectrum antibiotics and surgical debridement if necessary. The SGLT2 inhibitor should be discontinued.

Pharmacy Claims Evaluation: During FY 2018, 625 SoonerCare members had paid claims for SGLT2-containing medications, none of whom had a diagnosis of necrotizing fasciitis in their diagnosis claims history during the same timeframe.

SoonerCare Action: SGLT2 inhibitor medications require prior authorization by SoonerCare, moving between Tier-2 and Tier-3 of the Antidiabetic Product Based Prior Authorization (PBPA) category, based on rebate agreements. The College of Pharmacy will monitor claims and diagnosis codes and present data to the DUR Board where appropriate.

Date	Drug	Issue
11/20/2018	**Fingolimod (Gilenya®)**	**Worsening of multiple sclerosis (MS) after medication discontinuation**

Issue Details: The FDA is warning that when fingolimod is discontinued, the patient's MS can become worse than before the medication was initiated. The worsening is rare but can result in permanent disability. The FDA identified 35 cases of severely increased disability accompanied by the presence of multiple new lesions on magnetic resonance imaging (MRI) that occurred 2 to 24 weeks after fingolimod was stopped in the 8 years since fingolimod was FDA approved. Most patients experienced this worsening in the first 12 weeks after stopping. The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state. Several patients who were able to walk without assistance prior to discontinuing fingolimod progressed to needing wheelchairs or becoming totally bedbound. In patients experiencing worsening of disability after stopping fingolimod, recovery varied. A total of 17 patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during fingolimod treatment.

FDA Recommendation(s): The FDA is requiring that a warning about disability progression after fingolimod discontinuation be added to *Warnings and Precautions* section of the medication label. Health care professionals should inform patients before starting treatment

about the potential risk of severe increase in disability after stopping fingolimod. When fingolimod is discontinued, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately.
Pharmacy Claims Evaluation: During FY 2018, a total of 23 SoonerCare members had paid claims for fingolimod, all of whom were being followed by a neurologist.

[1] U.S. Food and Drug Administration (FDA). 2018 Safety Alerts for Human Medical Products. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm590808.htm. Last revised 11/20/2018. Last accessed 12/10/2018.
[2] FDA. Ocaliva (obeticholic acid): Drug Safety Communication - Boxed Warning Added To Highlight Correct Dosing. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm594901.htm. Issued 02/01/2018. Last accessed 12/10/2018.
[3] Ocaliva® Prescribing Information. Intercept Pharmaceuticals, Inc. Available online at: http://www.ocaliva.com/pdf/ocaliva-us-package-insert.pdf. Last revised 02/2018. Last accessed 12/19/2018.
[4] FDA. FDA Drug Safety Communication: FDA review finds additional data supports the potential for increased long-term risks with antibiotic clarithromycin (Biaxin) in patients with heart disease. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm597289.htm. Issued 02/22/2018. Last accessed 12/10/2018.
[5] FDA. FDA Drug Safety Communication: FDA warns of serious immune system reaction with seizure and mental health medicine lamotrigine (Lamictal). Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm605470.htm. Issued 04/25/2018. Last accessed 12/10/2018.
[6] FDA. FDA Alerts Health Care Professionals and Oncology Clinical Investigators about an Efficacy Issue Identified in Clinical Trials for Some Patients Taking Keytruda (pembrolizumab) or Tecentriq (atezolizumab) as Monotherapy to Treat Urothelial Cancer with Low Expression of PD-L1. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm608075.htm. Last revised 08/16/2018. Last accessed 12/12/2018.
[7] FDA. Juluca, Tivicay, Triumeq (dolutegravir): FDA to Evaluate - Potential Risk of Neural Tube Birth Defects. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608168.htm. Issued 05/18/2018. Last accessed 12/12/2018.
[8] FDA. Oral Over-the-Counter Benzocaine Products: Drug Safety Communication - Risk of Serious and Potentially Fatal Blood Disorder. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608612.htm. Issued 05/23/2018. Last accessed 12/12/2018.
[9] FDA. FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm617360.htm. Issued 08/29/2018. Last accessed 12/12/2018.
[10] FDA. FDA warns about severe worsening of multiple sclerosis after stopping the medicine Gilenya (fingolimod). Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm626095.htm. Issued 11/20/2018. Last accessed 12/12/2018.

Appendix C

Fiscal Year 2018 Annual Review of Injectable and Vaginal Progesterone Products and 30-Day Notice to Prior Authorize Makena® [Hydroxyprogesterone Caproate Subcutaneous (Sub-Q) Auto-Injector]

Oklahoma Health Care Authority
January 2019

Current Prior Authorization Criteria

Crinone® (Progesterone Vaginal Gel) Approval Criteria:

1. Current singleton pregnancy; and
2. Member must not have history of previous singleton spontaneous preterm delivery (SPTD); and
3. Cervical length of ≤20mm; and
4. Gestational age between 20 weeks, 0 days and 26 weeks, 6 days of gestation; and
5. A patient-specific, clinically significant reason why the member cannot use Endometrin® (progesterone vaginal insert); and
6. Authorizations will be given for treatment through 36 weeks, 6 days of gestation; and
7. Crinone® will not be covered for use with assisted reproductive technology (ART) for female infertility.

Endometrin® (Progesterone Vaginal Insert) Approval Criteria:

1. Current singleton pregnancy; and
2. Member must not have history of previous singleton spontaneous preterm delivery (SPTD); and
3. Cervical length of ≤20mm; and
4. Gestational age between 20 weeks, 0 days and 26 weeks, 6 days of gestation; and
5. Authorizations will be given for treatment through 36 weeks, 6 days of gestation; and
6. Endometrin® will not be covered for use with assisted reproductive technology (ART) for female infertility.

Hydroxyprogesterone Caproate 250mg/mL Injection (Generic Delalutin®) Approval Criteria:

1. An FDA approved indication of one of the following in non-pregnant women:
    a. For the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); or
    b. For the management of amenorrhea (primary and secondary) or abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; or
    c. As a test for endogenous estrogen production or for the production of secretory endometrium and desquamation; and
2. The quantity approved will be patient-specific depending on patient diagnosis, maximum recommended dosage, and manufacturer packaging.

3. Requests for the prevention of preterm birth in pregnant women with a history of previous singleton spontaneous preterm delivery (SPTD) prior to 37 weeks gestation will not be approved for generic Delalutin® and should be resubmitted for authorization of Makena® (hydroxyprogesterone caproate injection).

Makena® (Hydroxyprogesterone Caproate Injection) 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 a week administration by a health care professional through 36 weeks, 6 days of gestation.

When it is determined to be appropriate to use the compounded hydroxyprogesterone caproate product, this product is covered through SoonerCare as a medical-only benefit without a prior authorization requirement.

Utilization of Injectable and Vaginal Progesterone Products: Fiscal Year 2018

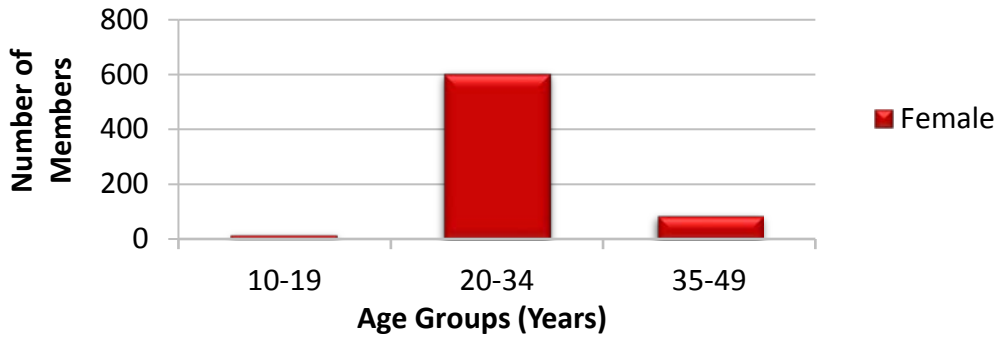
Please note, the compounded hydroxyprogesterone caproate product is billed by medical claims only and not reflected in the following pharmacy claims data. Fiscal year 2018 medical claim utilization details for the compounded hydroxyprogesterone caproate product can be found at the end of this report. The following utilization details include pharmacy claims data only.

Comparison of Fiscal Years: Pharmacy Claims

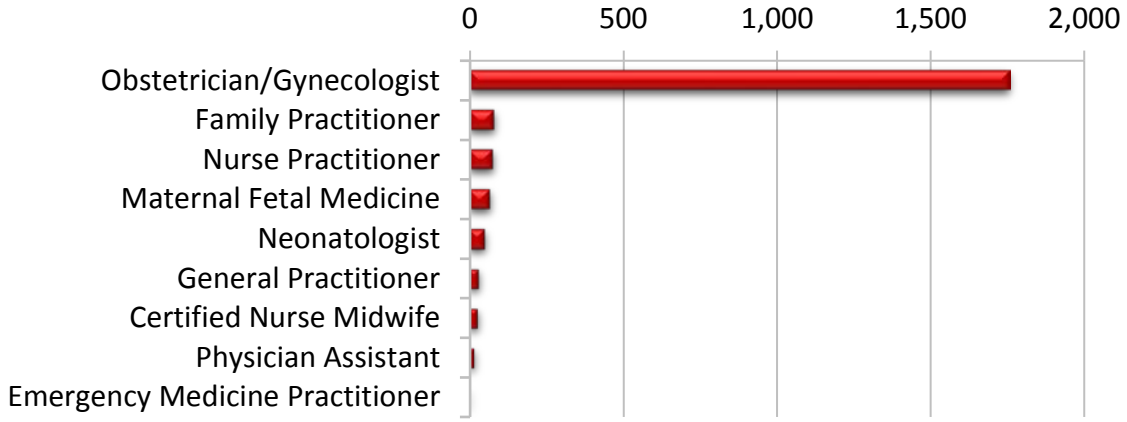
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	659	1,895	$5,947,034.65	$3,138.28	$105.67	8,296	56,278
2018	707	2,112	$6,652,170.24	$3,149.70	$109.43	8,923	60,787
% Change	**7.30%**	**11.50%**	**11.90%**	**0.40%**	**3.60%**	**7.60%**	**8.00%**
Change	**48**	**217**	**$705,135.59**	**$11.42**	**$3.76**	**627**	**4,509**

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

Demographics of Members Utilizing Injectable and Vaginal Progesterone Products: Pharmacy Claims



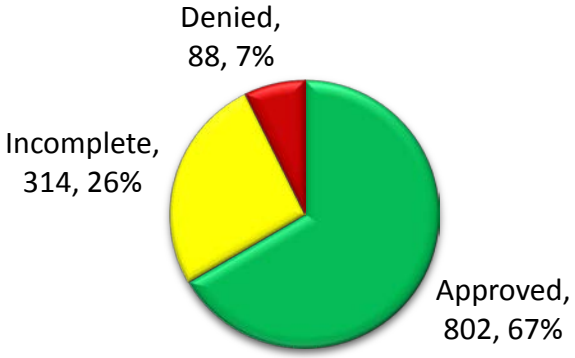
Top Prescriber Specialties of Injectable and Vaginal Progesterone Products by Number of Claims: Pharmacy Claims



Prior Authorization of Injectable and Vaginal Progesterone Products

There were 1,204 prior authorization requests submitted for injectable and vaginal progesterone products 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):

- Endometrin® (progesterone vaginal insert): September 2019

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

- **February 2018:** The FDA approved Makena® (hydroxyprogesterone caproate sub-Q auto-injector) to reduce the risk of preterm birth in women pregnant with a single baby who have a history of singleton spontaneous preterm delivery (SPTD). 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 at <37 weeks of gestation compared to placebo. 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 singleton SPTD, and it 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.

- **June 2018:** The FDA approved the first preservative-free, AP-rated, generic alternative to Makena® (hydroxyprogesterone caproate) IM injection. Generic hydroxyprogesterone caproate IM injection is available as a 250mg/mL, 1mL SDV and a 250mg/mL, 5mL MDV, and the WAC of generic hydroxyprogesterone caproate IM injection is $682.55 per 1mL SDV.

News:

- **February 2018:** The FDA denied a citizen petition seeking to withdrawal approval for Makena® (hydroxyprogesterone caproate injection) as a drug used in pregnancy pending fetal germline impact assessment. The patients' rights group emphasized the unequivocal drug vulnerabilities of fetal germline to intentional, high-dose, persistent endocrine disrupting chemical (EDC) exposures, such as hydroxyprogesterone caproate. They also argued that Makena® is ineffective at reducing preterm birth, increases the risk of maternal diabetes in the exposed mother, and causes long-term adverse neurodevelopmental effects in offspring. The group noted that a safer alternative to Makena® is readily available. The group called for the FDA to withdrawal approval for Makena® based on the health and welfare of 3 generations being at stake: the exposed mother, the exposed offspring, and the exposed fetal germ cells. The FDA denied the petition to withdraw approval of Makena®, noting that the data presented do not demonstrate a connection, or the possibility of a connection, between Makena® and autism spectrum disorder (ASD) in subsequent generations. The FDA found no evidence in the petition, or through the FDA's independent research, that would cause the FDA to reevaluate its prior determination that Makena® is safe and effective for its indicated use or to withdrawal approval of Makena®. However, the FDA will continue to monitor available evidence concerning the epigenetic effects of products indicated for use in pregnancy, including Makena®. The FDA also notes that Makena® is currently being further evaluated through the confirmatory clinical trials required as a condition of its approval, which were designed to evaluate a potential signal for early pregnancy loss, as

well as to conduct developmental assessments (and where indicated, neurological evaluations) of infants born to women treated with Makena®.

Pipeline:

- **LPCN 1107:** Lipocine, Inc. is currently developing LPCN 1107, an oral product candidate of 17-alpha hydroxyprogesterone caproate, for the indication of prevention of recurrent preterm birth. LPCN 1107 has the potential to become the first oral hydroxyprogesterone caproate product for the prevention of preterm birth in women with a prior history of at least one preterm birth. Potential benefits of this oral product candidate relative to current injectable products include the elimination of pain and injection site reactions associated with weekly injections, as well as the elimination of weekly doctor visits or visits from the nurse to administer the weekly injections. A multi-dose pharmacokinetics (PK) dose selection study in pregnant women has been completed; the objective of this study was to assess hydroxyprogesterone caproate blood levels in order to identify the appropriate LPCN 1107 Phase 3 dose. This study was an open-label, 4-period, 4-treatment, randomized, single and multiple dose, PK study in pregnant women of 3 dose levels of LPCN 1107 and hydroxyprogesterone caproate IM injection (Makena®). The study enrolled 12 healthy pregnant women with a gestational age of approximately 16 to 19 weeks. Patients received 3 dose levels of oral LPCN 1107 [400mg twice daily (BID), 600mg BID, or 800mg BID] in a randomized, crossover manner during the first 3 treatment periods and then received 5 weekly injections of hydroxyprogesterone caproate during the fourth treatment period. Results from this study demonstrated that average steady state hydroxyprogesterone caproate levels were comparable or higher for all 3 oral LPCN 1107 doses than for injectable hydroxyprogesterone caproate. Lipocine is working with the FDA to define a Phase 3 development plan for LPCN 1107, and the FDA has granted Orphan Drug designation to LPCN 1107 based on a major contribution to patient care.

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 a week 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.)

Utilization Details of Injectable and Vaginal Progesterone Products: Fiscal Year 2018

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
HYDROXYPROGESTERONE INJECTABLE PRODUCTS						
MAKENA INJ 250MG/ML	2,061	675	$6,529,085.35	$3,167.92	3.05	98.15%
MAKENA INJ 275MG/1.1ML	41	30	$120,109.97	$2,929.51	1.37	1.81%
SUBTOTAL	**2,102**	**705**	**$6,649,195.32**	**$3,163.27**	**2.98**	**99.96%**
PROGESTERONE VAGINAL PRODUCTS						
ENDOMETRIN SUP 100MG	10	6	$2,974.92	$297.49	1.67	0.04%
SUBTOTAL	**10**	**6**	**$2,974.92**	**$297.49**	**1.67**	**0.04%**
TOTAL	**2,112**	**707***	**$6,652,170.24**	**$3,149.70**	**2.99**	**100%**

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

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER
HYDROXYPROGESTERONE CAPROATE INJ S5000	16	11	$164.64	$10.29	1.45
TOTAL	**16**	**11***	**$164.64**	**$10.29**	**1.45**

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

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[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 10/2018. Last accessed 12/12/2018.
[2] 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 12/19/2018.
[3] 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 12/19/2018.
[4] American Regent News Release. American Regent Announces the FDA Approval of Hydroxyprogesterone Caproate Injection, USP; the First Preservative Free, AP Rated Generic to Makena®. *PR Newswire*. Available online at: https://www.prnewswire.com/news-releases/american-regent-announces-the-fda-approval-of-hydroxyprogesterone-caproate-injection-usp-the-first-preservative-free-ap-rated-generic-to-makena1-300673943.html. Issued 06/28/2018. Last accessed 12/20/2018.
[5] Germline Exposures News Release. Third Letter to FDA re Citizens Petition to Withdraw Approval for the Synthetic Progestin 17-OHPC ("Makena") as a Drug Used in Pregnancy. Available online at: http://www.germlineexposures.org/blog/third-letter-to-fda-re-citizens-petition-to-withdraw-approval-for-the-synthetic-progestin-17-ohpc-makena-as-a-drug-used-in-pregnancy. Issued 02/05/2018. Last accessed 12/19/2018.
[6] Lipocine, Inc. Lipocine Pipeline: LPCN 1107. Available online at: https://www.lipocine.com/pipeline/lpcn-1107/. Last accessed 12/20/2018.

Appendix D

Fiscal Year 2018 Annual Review of Glaucoma Medications and 30-Day Notice to Prior Authorize Xelpros™ (Latanoprost 0.005% Emulsion)

Oklahoma Health Care Authority
January 2019

Current Prior Authorization Criteria

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%)		
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%)		
brinzolamide/brimonidine (Simbrinza® 0.2%/1%)		
dorzolamide (Trusopt® 2%)		
dorzolamide/timolol (Cosopt® 22.3mg/mL/6.8mg/mL)		
methazolamide (Neptazane® 25mg, 50mg tabs)+		
Cholinergic Agonists/Cholinesterase Inhibitors		
echothiophate iodide (Phospholine Iodide® 0.125%)	pilocarpine (Isopto® Carpine 1%, 2%, 4%)	

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
Prostaglandin Analogs		
latanoprost (Xalatan® 0.005%)	bimatoprost (Lumigan® 0.01%, 0.03%)	latanoprostene bunod (Vyzulta® 0.024%)
travoprost (Travatan-Z® 0.004%)	tafluprost (Zioptan® 0.0015%)	
	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

Glaucoma Medications Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and
2. The member must have documented, recent (within the last 120 days) trials with at least 3 Tier-1 medications for a minimum of 4 weeks duration each. Tier-1 trials may be from any pharmacologic class; or
3. Approvals may be granted if there is a documented adverse effect, drug interaction, or contraindication to all Tier-1 medications; or
4. Approvals may be granted if there is a unique FDA approved indication not covered by all Tier-1 medications; and
5. The member must have had a comprehensive, dilated eye exam within the last 365-day period as recommended by the National Institutes of Health; and
6. Approvals will be for the duration of 1 year.

Glaucoma Medications Special Prior Authorization (PA) Approval Criteria:

1. An FDA approved diagnosis; and
2. A patient-specific, clinically significant reason why a special formulation is needed over a Tier-1 or Tier-2 medication; or
3. Approvals may be granted if there is a documented adverse effect, drug interaction, or contraindication to all Tier-1 and Tier-2 medications; or
4. Approvals may be granted if there is a unique FDA approved indication not covered by all Tier-1 and Tier-2 medications; and
5. The member must have had a comprehensive, dilated eye exam within the last 365-day period as recommended by the National Institutes of Health; and
6. Approvals will be for the duration of 1 year.

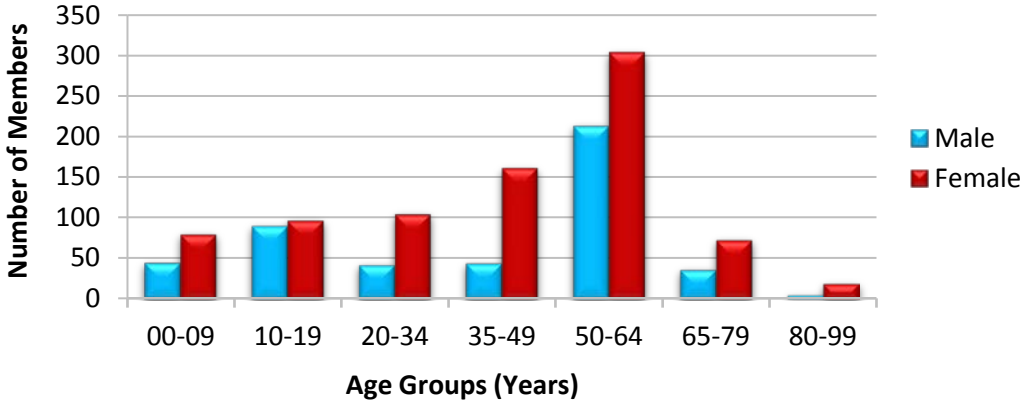
Utilization of Glaucoma Medications: Fiscal Year 2018

Comparison of Fiscal Years

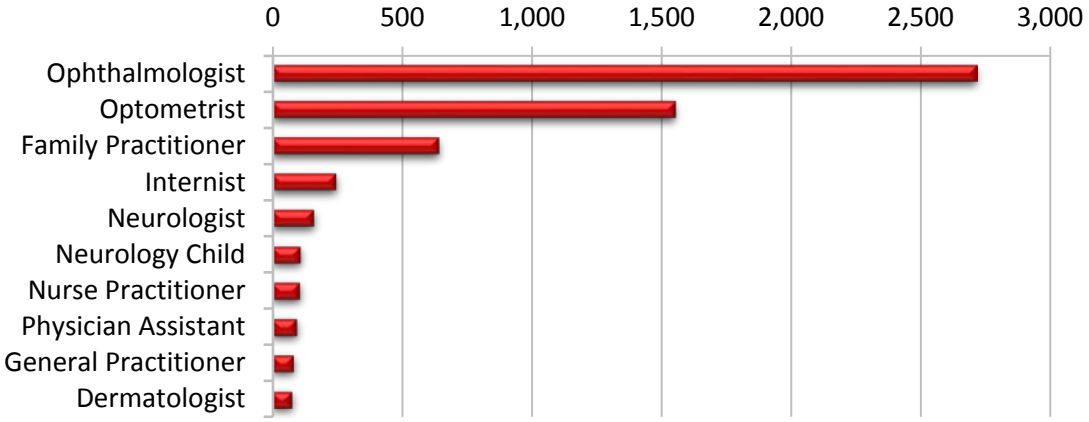
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	1,290	6,106	$556,059.34	$91.07	$2.70	101,331	205,981
2018	1,314	6,177	$568,069.74	$91.97	$2.67	93,518	212,899
% Change	**1.90%**	**1.20%**	**2.20%**	**1.00%**	**-1.10%**	**-7.70%**	**3.40%**
Change	**24**	**71**	**$12,010.40**	**$0.90**	**-$0.03**	**-7,813**	**6,918**

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

Demographics of Members Utilizing Glaucoma Medications

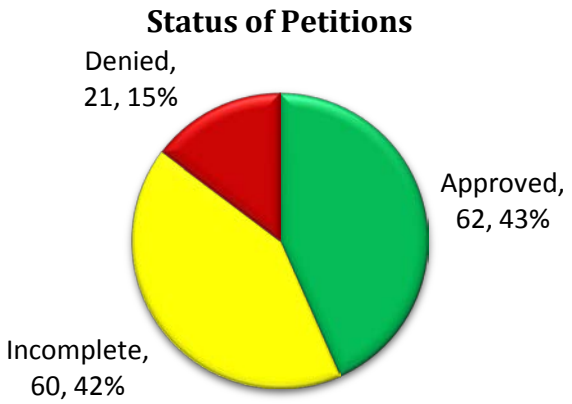


Top Prescriber Specialties of Glaucoma Medications by Number of Claims



Prior Authorization of Glaucoma Medications

There were 143 prior authorization requests submitted for glaucoma medications during fiscal year 2018. Computer edits are in place to detect lower tiered medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions for fiscal year 2018.



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

Anticipated Patent Expiration(s):

- Combigan® (brimonidine/timolol 0.2%/0.5%): January 2023
- Alphagan-P® (brimonidine 0.1%): March 2024
- Vyzulta® (latanoprostene bunod 0.024%): October 2025
- Lumigan® (bimatoprost 0.01%): June 2027
- Zioptan® (tafluprost 0.0015%): May 2029
- Simbrinza® (brinzolamide/brimonidine 0.2%/1%): October 2030
- Rhopressa® (netarsudil 0.02%): March 2034

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

- **September 2018:** In a joint press release, Sun Pharmaceutical Industries, Ltd. and Sun Pharma Advanced Research Company, Ltd. (SPARC) announced the FDA approval of Xelpros™ (latanoprost 0.005% ophthalmic emulsion), indicated for reducing elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (OHT). Xelpros™ is the only FDA-approved benzalkonium chloride (BAK)-free version of latanoprost. It joins 3 other FDA-approved topical glaucoma medications completely free of preservatives: Zioptan® (tafluprost 0.0015% ophthalmic solution), Cosopt® PF (dorzolamide/timolol 2%/0.5% ophthalmic solution), and Timoptic® in Ocudose (timolol maleate 0.25% and 0.5% ophthalmic solution). Xelpros™ was developed using SPARC's proprietary Swollen Micelle Microemulsion (SMM) technology, which helps to solubilize ophthalmic drugs that have limited water solubility or no solubility thus eliminating the need for BAK.

News:

- **January 2017:** Inotek Pharmaceuticals announced topline results of MATrX-1, the first pivotal Phase 3 trial of trabodenoson for the treatment of primary open-angle glaucoma

(POAG) or OHT. The trial did not achieve its primary endpoint of superiority in reduction of IOP compared with placebo at all 12 time points. The primary endpoint of the MATrX-1 trial was the IOP reduction of trabodenoson compared to that of placebo on days 28, 42, and 84 and at 4 time points during each of these days: 8am, 10am, 12pm, and 4pm. The 8am time point did not achieve statistical separation with any trabodenoson dose; this was primarily due to an unexpectedly high placebo response compared to that observed in Phase 2. Trabodenoson is a first-in-class, highly selective adenosine mimetic targeting the A_1 subreceptor. Trabodenoson lowers IOP by augmenting the eye's natural function of the trabecular meshwork, the primary outflow pathway for the aqueous humor and a site of pathology in glaucoma.

- **January 2018:** A pooled analysis that included the results of the APOLLO and LUNAR Phase 3, randomized, multicenter trials and their open-label safety extension phases showed results favoring latanoprostene bunod (LBN) 0.024% over timolol maleate 0.5%. LBN 0.024% instilled once a day in the evening was superior to timolol 0.5% instilled twice a day over the 3 months of the controlled comparison, and this effect lasted through the 12 months of the open-label phases. A significantly greater proportion of LBN-treated patients achieved IOP ≤18mmHg and had an IOP reduction ≥25% from baseline versus timolol-treated patients ($P<0.001$). The mean reduction of IOP with LBN was 32%, compared to 27.6% with timolol. Patients initially randomized to timolol and who switched to LBN in the open-label phases had an additional significant diurnal IOP decrease of 1.2mmHg ($P\leq0.009$).
- **July 2018:** Aerie Pharmaceuticals, Inc. reported that the FDA completed its initial 60-day review of the New Drug Application (NDA) for Roclatan™ (netarsudil/latanoprost ophthalmic solution 0.02%/0.005%). The FDA determined that the application is sufficiently complete to permit a substantive review. The Prescription Drug User Fee Act (PDUFA) goal date for the completion of the FDA's review of the Roclatan™ NDA is set for March 14, 2019. Roclatan™ is a once-daily eye drop designed to reduce IOP in patients with glaucoma or OHT. It is a fixed dose combination of Aerie's Rhopressa® (netarsudil ophthalmic solution 0.02%), which is currently available in the United States, and the widely prescribed prostaglandin analog, latanoprost.

Discontinued Medication(s):

- **Travatan® (travoprost 0.004%):** Based on the FDA website, Travatan® has been discontinued. The information provided indicates it was not discontinued or withdrawn for safety or efficacy reasons. Travatan-Z® (travaprost 0.004%) has replaced the discontinued product.

Xelpros™ (Latanoprost 0.005% Emulsion) Product Summary[7,8,9,10]

Indication(s): Xelpros™ (latanoprost 0.005% emulsion) is a prostaglandin $F_{2\alpha}$ analog indicated for reduction of elevated IOP in patients with open-angle glaucoma or OHT.

Dosing:

- Xelpros™ is supplied as an off-white to pale yellow, translucent, isotonic, sterile, buffered emulsion of latanoprost 0.005% (50mcg/mL) in a 2.5mL bottle with a dropper tip.
- The recommended dosage is one drop in the affected eye(s) once daily in the evening.
- The dosage of Xelpros™ should not exceed once daily; the combined use of 2 or more prostaglandins or prostaglandin analogs, including Xelpros™, is not recommended.
- It has been shown that administration of prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.
- Xelpros™ may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart. Contact lenses should be removed prior to the administration of Xelpros™ and may be reinserted 15 minutes after administration.

Mechanism of Action: Latanoprost is a prostaglandin $F_{2\alpha}$ analog believed to reduce the IOP by increasing the outflow of the aqueous humor. Human and animal studies suggest that the main mechanism of action of latanoprost is increased uveoscleral outflow.

Warnings and Precautions:

- Pigmentation: Topical latanoprost ophthalmic products, including Xelpros™, have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.
- Eyelash Changes: Latanoprost ophthalmic products, including Xelpros™, may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, pigmentation, number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.
- Intraocular Inflammation: Xelpros™ should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation because inflammation may be exacerbated.
- Macular Edema: Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost ophthalmic products, including Xelpros™. Xelpros™ should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.
- Herpetic Keratitis: Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. Xelpros™ should be used with caution in patients with a history of herpetic keratitis. Xelpros™ should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

- Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures to prevent contamination by common bacteria known to cause ocular infections.

Contraindication(s): Known hypersensitivity to latanoprost or any other ingredients in Xelpros™.

Adverse Reactions: The most frequently reported ocular adverse reactions reported in Xelpros™ clinical studies were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of Xelpros™-treated patients, respectively. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia. Other adverse reactions reported by ≥5% of patients receiving Xelpros™ during clinical studies included conjunctival hyperemia, eye discharge, growth of eyelashes, eyelash thickening, and ocular Itching.

Use in Specific Populations:

- Pregnancy: Reproduction studies have been performed in rats and rabbits. In pregnant rabbits, an incidence of 4 out of 16 had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies of Xelpros™ in pregnant women.
- Lactation: It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Xelpros™ is administered to a nursing woman.
- Pediatric Use: The safety and effectiveness of Xelpros™ in pediatric patients have not been established.
- Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly patients and younger patients using Xelpros™.

Efficacy: The efficacy of preservative-free latanoprost in reducing IOP was tested in a non-inferiority Phase 3 study comparing preservative-free (PF) latanoprost to BAK-preserved latanoprost (BPL, Xalatan®). This trial was a prospective, international, multicenter, randomized, investigator-masked, parallel–group study in adults 18 years of age and older already managed by BPL monotherapy for at least 9 months as defined by stable IOP (≤18mmHg) and stable visual field. The modified intent-to-treat set consisted of 353 patients (189 in the PF latanoprost group and 164 in the BPL group). Primary exclusion criteria included any secondary OHT, severe glaucoma (defined by advanced cupping and/or severe visual loss, notably an absolute defect in the 10° central point), corrected visual acuity ≤1/10, filtration or laser surgery for glaucoma (within the last 12 months), other intraocular surgery, and abnormalities preventing accurate IOP assessment. After a wash-out period, POAG or OHT patients, previously managed by BPL monotherapy, randomly received PF latanoprost or BPL [1 drop into the affected eye(s)] once daily from day 0 (D0) to day 84 (D84). Change in IOP was measured at 09:00 (±1h) from D0 to D84 in the worse eye. Mean IOP reduction (D0-to-D84) was

−8.6 ± 2.6mmHg (−36%) with PF latanoprost and −9.0 ± 2.4mmHg (−38%) with BPL, confirming non-inferiority of PF latanoprost to BPL. Non-inferiority of PF latanoprost was observed from day 15.

Tolerance: A prospective, open-label, single-arm, multicenter, 8-week study in patients with POAG or OHT using BAK-containing latanoprost for ≥12 months was performed to evaluate the efficacy and safety of BAK-free latanoprost. BAK, included as a preservative in many topical treatments for glaucoma, induces significant toxicity and alters tear breakup time (TBUT). TBUT is recorded as the number of seconds that elapse between the last blink and the appearance of the first dry spot in the tear film. A TBUT under 10 seconds is considered abnormal. In this study, patients were switched to BAK-free latanoprost ophthalmic solution 0.005% administered once daily, and eyes were assessed after 28 and 56 days of treatment. Primary efficacy and safety variables were TBUT and treatment-emergent adverse events (AEs), respectively. At day 56, 40 eyes were evaluable. Mean TBUT increased significantly from baseline (3.67 ± 1.60 seconds) to 5.03 ± 2.64 and 6.06 ± 3.39 seconds after 28 and 56 days of treatment with BAK-free latanoprost, respectively (P<0.0001). A reduction in conjunctival hyperemia IOP was observed at both time points. No treatment-related serious AEs were evident. BAK-free latanoprost appears to be effective in protecting ocular surface integrity in glaucoma patients but further studies are needed to confirm this beneficial effect.

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.
3. Updating the Glaucoma Medications tier chart to remove Travatan® (travoprost 0.004%) based on product discontinuation.

Proposed changes are shown in 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		

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
(Combigan® 0.2%/0.5%)		
brinzolamide/brimonidine (Simbrinza® 0.2%/1%)		
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

Utilization Details of Glaucoma Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
TIER-1 PRODUCTS					
ALPHA-2 ADRENERGIC AGONISTS					
COMBIGAN SOL 0.2/0.5%	316	77	$65,045.65	$5.80	$205.84
BRIMONIDINE SOL 0.2%	278	113	$3,972.42	$0.40	$14.29
SIMBRINZA SUS 1-0.2%	276	71	$40,692.16	$4.18	$147.44
ALPHAGAN P SOL 0.1%	120	37	$28,343.78	$6.04	$236.20
SUBTOTAL	**990**	**298**	**$138,054.01**	**$3.88**	**$139.45**
BETA-BLOCKERS					
TIMOLOL MAL SOL 0.5%	612	256	$6,769.20	$0.27	$11.06
DORZOL/TIMOL 22.3-6.8MG	346	132	$6,174.08	$0.37	$17.84
TIMOLOL MAL SOL 0.25%	53	30	$553.82	$0.25	$10.45
LEVOBUNOLOL SOL 0.5%	6	3	$139.31	$0.43	$23.22
SUBTOTAL	**1,017**	**421**	**$13,636.41**	**$0.31**	**$13.41**
CARBONIC ANHYDRASE INHIBITORS					
ACETAZOLAMID TAB 250MG	472	126	$54,802.88	$3.79	$116.11
ACETAZOLAMID CAP 500MG	288	93	$29,619.32	$3.35	$102.84
DORZOLAMIDE SOL 2%	131	60	$2,611.22	$0.45	$19.93
AZOPT SUS 1%	93	43	$26,583.55	$5.84	$285.84
ACETAZOLAMID TAB 125MG	62	21	$7,313.72	$4.23	$117.96
METHAZOLAMID TAB 50MG	24	3	$8,370.53	$11.25	$348.77
SUBTOTAL	**1,070**	**346**	**$129,301.22**	**$3.58**	**$120.84**
CHOLINERGIC AGONISTS/CHOLINESTERASE INHIBITORS					
PHOSPHOLINE 0.125%	1	1	$99.22	$7.09	$99.22
SUBTOTAL	**1**	**1**	**$99.22**	**$7.09**	**$99.22**
PROSTAGLANDIN ANALOGS					
LATANOPROST SOL 0.005%	1,930	461	$26,353.46	$0.48	$13.65
TRAVATAN Z DRO 0.004%	837	235	$199,052.60	$6.57	$237.82
SUBTOTAL	**2,767**	**696**	**$225,406.06**	**$2.63**	**$81.46**
RHO KINASE INHIBITORS					
RHOPRESSA SOL 0.02%	1	1	$239.55	$7.99	$239.55
SUBTOTAL	**1**	**1**	**$239.55**	**$7.99**	**$239.55**
TIER-1 SUBTOTAL	**5,846**	**1,763**	**$506,736.47**	**$2.52**	**$86.68**
TIER-2 PRODUCTS					
BETA-BLOCKERS					
BETOPTIC-S SUS 0.25%	1	1	$295.18	$3.28	$295.18
SUBTOTAL	**1**	**1**	**$295.18**	**$3.28**	**$295.18**
CHOLINERGIC AGONISTS/CHOLINESTERASE INHIBITORS					
PILOCARPINE SOL 1%	7	3	$466.17	$1.94	$66.60
PILOCARPINE SOL 4%	4	1	$328.02	$2.73	$82.01
PILOCARPINE SOL 2%	3	2	$195.08	$0.96	$65.03
SUBTOTAL	**14**	**6**	**$989.27**	**$1.76**	**$70.66**

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
PROSTAGLANDIN ANALOGS					
LUMIGAN SOL 0.01%	121	29	$30,113.43	$7.30	$248.87
ZIOPTAN DRO 0.0015%	2	1	$371.70	$6.20	$185.85
BIMATOPROST SOL 0.03%	1	1	$99.91	$3.33	$99.91
SUBTOTAL	**124**	**31**	**$30,585.04**	**$7.26**	**$246.65**
TIER-2 SUBTOTAL	**139**	**38**	**$31,869.49**	**$6.55**	**$229.28**
SPECIAL PA PRODUCTS					
ALPHA-2 ADRENERGIC AGONISTS					
BRIMONIDINE SOL 0.15%	61	14	$12,669.19	$5.37	$207.69
ALPHAGAN P SOL 0.15%	13	2	$3,840.63	$9.14	$295.43
SUBTOTAL	**74**	16	**$16,509.82**	**$5.94**	$223.11
BETA-BLOCKERS					
TIMOLOL GEL SOL 0.5%	114	47	$12,345.24	$3.10	$108.29
COSOPT PF SOL 2%/0.5%	3	2	$493.50	$5.48	$164.50
TIMOLOL GEL SOL 0.25%	1	1	$115.22	$3.84	$115.22
SUBTOTAL	**118**	**50**	**$12,953.96**	**$3.15**	**$109.78**
SPECIAL PA SUBTOTAL	**192**	**66**	**$29,463.78**	**$4.28**	**$153.46**
TOTAL	**6,177**	**1,314***	**$568,069.74**	**$2.67**	**$91.97**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Please note, utilization details for combination products are only listed in one pharmaceutical class/subcategory, although they are listed in both applicable pharmaceutical classes in the tier chart.

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[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 11/2018. Last accessed 12/17/2018.
[2] Sun Pharmaceutical Industries, Ltd. and Sun Pharma Advanced Research Company, Ltd. (SPARC). FDA Approves Preservative-Free Xelpros™ for Open-Angle Glaucoma. *New Glaucoma Treatments*. Available online at: http://new-glaucoma-treatments.com/fda-approves-preservative-free-xelpros-for-open-angle-glaucoma/. Issued 09/17/2018. Last accessed 12/19/2018.
[3] Inotek Pharmaceuticals. Inotek Fails Phase 3 Trial of Trabodenoson for Glaucoma. *Eyewire*. Available online at: https://eyewire.news/articles/inotek-announces-top-line-results-for-matrx-1-first-phase-3-trial-of-trabodenoson-for-glaucoma/. Issued 01/03/2017. Last accessed 12/18/2018.
[4] Weinreb RN, Liebmann JM, Martin KR, et al. Latanoprostene Bunod 0.024% in Subjects With Open-angle Glaucoma or Ocular Hypertension: Pooled Phase 3 Study Findings. *J Glaucoma* 2018; 27(1):7-15.
[5] Cimberle M. Latanoprostene bunod shows efficacy greater than timolol. *Healio*. Available online at: https://www.healio.com/optometry/glaucoma/news/online/%7B16b16bbf-cfa9-45ae-bbd9-043e293789cf%7D/latanoprostene-bunod-shows-efficacy-greater-than-timolol. Issued 03/22/2018. Last accessed 12/19/2018.
[6] Aerie Pharmaceuticals, Inc. Aerie Pharmaceuticals Announces Early Notification of FDA Acceptance of NDA Submission for Roclatan™ (netarsudil/latanoprost ophthalmic solution) 0.02%/0.005% with PDUFA Date Set for March 14, 2019. *Business Wire*. Available online at: http://investors.aeriepharma.com/news-releases/news-release-details/aerie-pharmaceuticals-announces-early-notification-fda. Issued 07/23/2018. Last accessed 12/18/2018.
[7] Xelpros™ Prescribing Information. Sun Pharmaceutical Industries, Inc. Available online at: https://myxelpros.com/pdf/XelprosPI.pdf. Last revised 09/2018. Last accessed 12/19/2018.
[8] 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.
[9] 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.
[10] Vislisel, J. Tear breakup time (TBUT). Available online at: https://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/TBUT/index.htm. Last revised 06/02/2015. Last accessed 12/19/2018.

Appendix E

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

Oklahoma Health Care Authority
January 2019

Introduction[1,2,3]

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. There are currently 2 U.S. Food and Drug Administration (FDA) approved ERTs indicated for the treatment of ADA-SCID: Adagen® (pegademase bovine) and Revcovi™ (elapegademase-lvlr).

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.

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

New FDA Approval(s):

- **October 2018:** The FDA approved Revcovi™ (elapegademase-lvlr) 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.

News:

- **March 2018:** The Dutch Pharmaceutical Accountability Foundation announced that it will request that the Netherlands Authority for Consumers and Markets investigate Leadiant Biosciences, the maker of Revcovi™ and Adagen®, for the price hike of chenodeoxycholic acid (CDCA). CDCA is used for the treatment of cerebrotendinous xanthomatosis (CTX), a rare genetic metabolic disease that affects around 60 people in the Netherlands. The price of CDCA increased more than 500-fold from 300 euros per patient per year to 153,300 euros per patient per year.

Pipeline:

- **ADA-SCID Gene Therapy:** Strimvelis®, an autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence, is a one-time gene therapy that replaces the defective gene coding for ADA. Strimvelis® has been available in Europe since 2016 for ADA-SCID patients who cannot be treated by a bone marrow transplant, but is currently only delivered at a single facility in Italy and has had limited uptake since launch. Orchard Therapeutics, the manufacturer of Strimvelis®, says it is planning to build a manufacturing plant for the therapy and expand the roll-out of the drug to other clinical centers in Europe. The benefits of Strimvelis® have been shown in 1 study involving 12 patients from 6 months to 6 years of age with ADA-SCID. Patients in the study had no appropriate bone marrow donor and alternative treatments had failed or were not available. All patients were treated with Strimvelis® and were still alive 3 years after treatment. The rate of severe infections declined after treatment and continued to decline with longer-term follow-up

beyond 3 years. Orchard is also developing another gene therapy, OTL-101, for ADA-SCID, in development for both the European and United States markets. The FDA granted Orchard Rare Pediatric Disease designation for OTL-101. To be granted Rare Pediatric Disease designation, a drug must be designed for the treatment of a serious or life-threatening disease which affects less than 200,000 patients in the United States and which primarily includes patients between 0 and 18 years of age. Due to this designation the company may qualify for a Pediatric Priority Review voucher at the time the drug gets approved for this indication. That voucher could then be redeemed to receive priority review of a subsequent marketing application for a different product or be transferable to other company. More than 40 ADA-SCID patients have been treated with OTL-101. All patients have survived up to 5 years after treatment, and OTL-101 has restored patients' immune function with a favorable safety profile.

Revcovi™ (Elapegademase-lvlr) Product Summary[10]

Indication(s): Revcovi™ (elapegademase-lvlr) is a recombinant ADA indicated for the treatment of ADA-SCID in pediatric and adult patients.

Dosing:

- 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 Adagen® (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 dAXP level, and/or on the treating physician's medical assessment of the patient's clinical status.

Therapeutic Monitoring:

- 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.
- ADA Activity: Once treatment with elapegademase has been initiated, a target trough plasma ADA activity should be ≥30mmol/hr/L. In order to determine an effective dose of elapegademase, trough plasma ADA activity (pre-injection) should be determined every 2 weeks for pegademase bovine-naïve patients and every 4 weeks for patients previously receiving pegademase bovine therapy during the first 8 to 12 weeks of treatment and every 3 to 6 months thereafter. A decrease of ADA activity <30mmol/hr/L suggests noncompliance to treatment or a development of antibodies (anti-drug, anti-PEG, and neutralizing antibodies). In such patients, testing for antibodies to elapegademase should be performed. If antibodies to elapegademase are found to be the cause of a persistent fall in trough plasma ADA activity, then adjustment in the

dosage of elapegademase and other measures may be taken to induce tolerance and restore adequate ADA enzyme activity.

- Erythrocyte dAXP: Trough erythrocyte dAXP levels should be maintained <0.02mmol/L and monitored at least twice a year.
- Immune Function: The degree of immune function may vary from patient to patient. Each patient will require appropriate monitoring consistent with immunologic status. Total and subset lymphocytes should be monitored every 4 to 8 weeks for up to 1 year and every 3 to 6 months thereafter in pegademase bovine-naïve patients and every 3 to 6 months in patients previously receiving pegademase bovine therapy.
    - Immune function, including the ability to produce antibodies, generally improves after 2 to 6 months of therapy and matures over a longer period. In general, there is a lag between the correction of the metabolic abnormalities and improved immune function. Improvement in the general clinical status of the patient may be gradual (as evidenced by improvement in various clinical parameters), but should be apparent by the end of the first year of therapy.
- Immunogenicity: As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity results from clinical studies suggest that patients who previously received pegademase bovine may present an immunologic response to elapegademase. Therefore, monitoring for changes in ADA levels during elapegademase treatment is recommended.

Mechanism of Action: The ADA enzyme is involved in purine metabolism, catalyzing the irreversible hydrolytic deamination of adenosine or dAXP to inosine or deoxyinosine, respectively, as well as several naturally occurring methylated adenosine compounds. Maintaining a low level of 2'-dAXP and adenosine is crucial for proper number and function of immune cells as well as decreasing the frequency of opportunistic infections. Elevated adenosine levels, as occurring in ADA deficiency, contribute to apoptosis and a block in the differentiation of thymocytes, causing severe T-lymphopenia. Elapegademase provides an exogenous source of ADA enzyme that is associated with a decrease in toxic adenosine and dAXP nucleotides levels as well as an increase in lymphocyte number.

Contraindication(s): None

Warnings and Precautions:

- Injection Site Bleeding in Patients with Thrombocytopenia: Since elapegademase is administered by IM injection, it should be used with caution in patients with thrombocytopenia and should not be used if thrombocytopenia is severe.
- Delay in Improvement of Immune Function: Precautions should be maintained to protect immune deficient patients from infections until improvement in immune function has been achieved. The timing and degree of improvement in immune function may vary from patient to patient.

Adverse Reactions: The most common adverse reactions experienced in a clinical study (N=6) of elapegademase were cough (3/6 patients) and vomiting (2/6 patients). Other adverse reactions that were reported in 1 patient each were: upper abdominal pain, arthralgia, asthenia, cerumen impaction, conjunctivitis, convulsion, dental caries, diarrhea, ear canal

irritation, ear lobe infection, epistaxis, fatigue, fungal skin infection, gait disturbance, gastrointestinal infection, groin abscess, hematochezia, haemophilus infection (pulmonary), hemoptysis, influenza, injection site discomfort, laceration, lymphadenopathy, migraine, nasal edema, nausea, nephrolithiasis, oral candidiasis, oropharyngeal pain, otitis externa, productive cough, rash, stoma site infection, swelling face, tooth abscess, tooth extraction, and upper respiratory tract infection, regardless of investigator causality assessment.

Use in Specific Populations:

- Pregnancy: Adequate and well-controlled studies with elapegademase have not been conducted in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted with elapegademase. It is not known whether elapegademase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.
- Lactation: Human or animal lactation studies have not been conducted to assess the presence of elapegademase in breast milk, the effects on the breastfed infant, or the effects on milk production for the mother.
- Pediatric Use: The safety and efficacy of elapegademase have been established in pediatric patients as young as 3.4 months of age.
- Geriatric Use: Elapegademase was not studied in patients 65 years of age or older.

Efficacy: Elapegademase was administered IM in 2 prospective, open-label, single-arm, multi-center studies to evaluate the efficacy, safety, tolerability, and pharmacokinetics in patients with ADA-SCID: Study 1 and Study 2.

- Study 1 was conducted in the United States and is an ongoing Phase 3, open-label, multicenter, single-arm, one-way crossover study. The study treatment consists of 3 phases: pegademase bovine lead-in phase (minimum of 3 weeks), elapegademase treatment phase (through week 21), and then followed by the elapegademase maintenance phase. A total of 6 ADA-SCID patients 8 to 37 years of age were treated. Weekly elapegademase doses ranged from 0.188mg/kg to 0.292mg/kg. The efficacy endpoints assessed included: trough dAXP level (metabolic detoxification was defined as a trough erythrocyte dAXP concentration ≤0.02mmol/L); trough plasma ADA activity (adequate trough plasma ADA activity was defined as trough plasma ADA activity ≥15mmol/hr/L); and immune status [lymphocyte and B-, T-, and NK-lymphocyte subset counts as well as quantitative immunoglobulin (Ig) concentration (IgG, IgA, IgM)].
    - A total of 5 of 6 patients reached the 21-week endpoint of the treatment phase, and 3 of 6 patients received treatment with elapegademase for over 135 weeks. These patients (except for 1 value in a patient at treatment week 47) had erythrocyte dAXP concentration ≤0.02mmol/L and had trough plasma ADA activity ≥15mmol/hr/L at 88/89 time points and maintained metabolic detoxification for at least 2 years on elapegademase treatment. Patients achieved trough plasma ADA activity >30mmol/hr/L by week 5, except for 1 patient who achieved this level at week 1. The mean trough plasma ADA activity for patients receiving elapegademase at a normalized dose of 0.2mg/kg/week were 34.3 ± 6.6mmol/hr/L. The same patients had a mean trough plasma ADA activity of 14.2 ±

5.1mmol/hr/L when treated with pegademase bovine during the lead-in phase of the study.

- Lymphocyte and subset counts during elapegademase treatment increased above levels observed during the pegademase bovine lead-in phase: maximum increases of approximately 3-fold at weeks 60 to 73 for 1 patient, maximum increases of approximately 2- to 3-fold at weeks 73 to 99 for 1 patient, and increases of approximately 1.5- to 3-fold for the third patient at several time points. For these 3 patients who completed the primary endpoint (21 weeks of treatment) and received elapegademase for over 135 weeks, a positive trend between high trough plasma ADA activity and increased total lymphocyte counts was observed. Observations for the other 3 patients in the study indicate that these patients also achieved complete detoxification based on trough dAXP level and trough plasma ADA activity, and show stable or slightly increased lymphocyte counts during elapegademase treatment relative to values recorded during the pegademase bovine lead-in phase.

- Study 2 was conducted in Japan and is a single-arm clinical study made up of 2 phases: 1) evaluation, consisting of a dose adjustment period (5 weeks) and a dose maintenance period (16 weeks); and 2) continuous administration (extension) phase, to be continued until the end of the study. A total of 4 patients were enrolled in the study: 2 males (age 25 years and 3.4 months) and 2 females (age 16 years and 4.3 months). Of the 4 patients in the study, 2 were on pegademase bovine treatment within 4 weeks before entering the study. Over the dose adjustment phase of the study, the dose was titrated to meet criteria for dAXP level (≤0.02mmol/L) and adequate trough ADA activity (≥15mmol/hr/L).
    - All 4 of the patients in Study 2 achieved and maintained detoxification [trough dAXP (erythrocyte or blood) ≤0.02mmol/L] throughout their participation in the treatment phase of 21 weeks. Serum ADA activity increased after administering elapegademase for all 4 patients, with 3 patients achieving ADA activity level >15mmol/hr/L during the dose maintenance period. Total lymphocyte counts and B-/T-/NK-lymphocyte subset counts for 3 patients increased from screening to day 15 during dose adjustment and were stable or increasing during the maintenance period.

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. Revocvi™ must be prescribed by or in consultation with a physician 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.

[1] Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol* 2018; pii: S0091-6749(18)31268-5. doi: 10.1016/j.jaci.2018.08.024.

[2] Rubinstein A. Adenosine deaminase deficiency: treatment. *UpToDate*. Available online at: https://www.uptodate.com/contents/adenosine-deaminase-deficiency-pathogenesis-clinical-manifestations-and-diagnosis?topicRef=3955&source=see_link. Last revised 08/29/2017. Last accessed 12/18/2018.

[3] Rubinstein A. Adenosine deaminase deficiency: Pathogenesis, clinical manifestations, and diagnosis. *UpToDate*. Available online at: https://www.uptodate.com/contents/adenosine-deaminase-deficiency-pathogenesis-clinical-manifestations-and-diagnosis?search=ada%20scid&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Last revised 11/07/2016. Last accessed 12/18/2018.

[4] 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 12/13/2018.

[5] Leadiant Biosciences, Inc. What is Adagen? Available online at: http://www.adagen.com/what_is_adagen.html. Last accessed 12/18/2018.

[6] 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 12/13/2018.

[7] Pharma Letter Staff. BRIEF—Dutch group to address 'unreasonably high pricing'. *The Pharma Letter*. Available online at: https://www.thepharmaletter.com/in-brief/brief-dutch-group-to-address-unreasonably-high-pricing. Issued 03/09/2018. Last accessed 12/18/2018.

[8] Strimvelis. The European Medicines Agency. Available online at: https://www.ema.europa.eu/en/medicines/human/EPAR/strimvelis. Last revised 05/09/2018. Last accessed 12/18/2018.

[9] Orchard Therapeutics. Orchard Therapeutics Announces That OTL-101 Has Received a Rare Paediatric Disease Designation. *B3C Newswire*. Available online at: https://www.b3cnewswire.com/201707241613/orchard-therapeutics-announces-that-otl-101-has-received-a-rare-paediatric-disease-designation.html. Issued 07/24/2017. Last accessed 12/18/2018.

[10] Revcovi™ Prescribing Information. Leadiant Biosciences, Inc. Available online at: https://revcovi.com/wp-content/uploads/2018/10/revcovi-final-labeling-text-10-05-2018.pdf. Last revised 10/2018. Last accessed 12/13/2018.

Appendix F

Fiscal Year 2018 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

Oklahoma Health Care Authority
January 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 (HF), 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, HF, diabetes mellitus (DM), 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.

Current Prior Authorization Criteria

Veltassa® (Patiromer) Approval Criteria:

1. An FDA approved diagnosis of hyperkalemia; and
2. A trial of a potassium-eliminating diuretic or documentation why a diuretic is not appropriate for the member; and
3. Documentation of a low potassium diet; and
4. A patient-specific, clinically significant reason why the member cannot use sodium polystyrene sulfonate (SPS) powder which is available without a prior authorization; and
5. A quantity limit of 30 packets per month will apply.

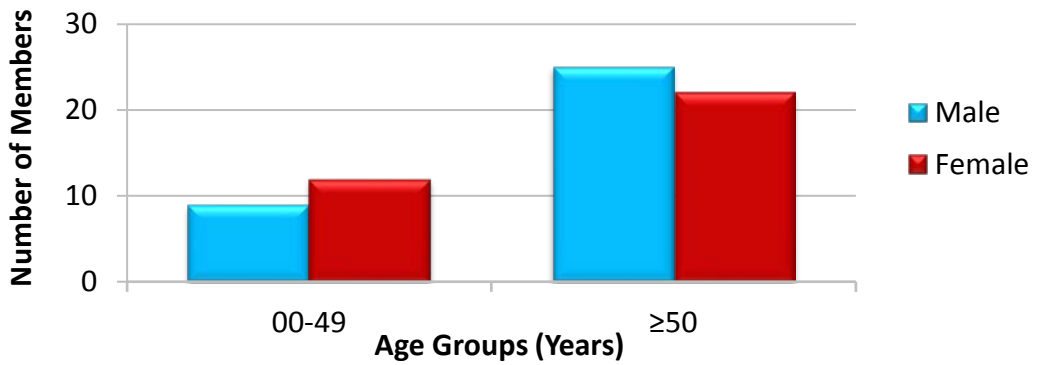
Utilization of Hyperkalemia Medications: Fiscal Year 2018

Comparison of Fiscal Years

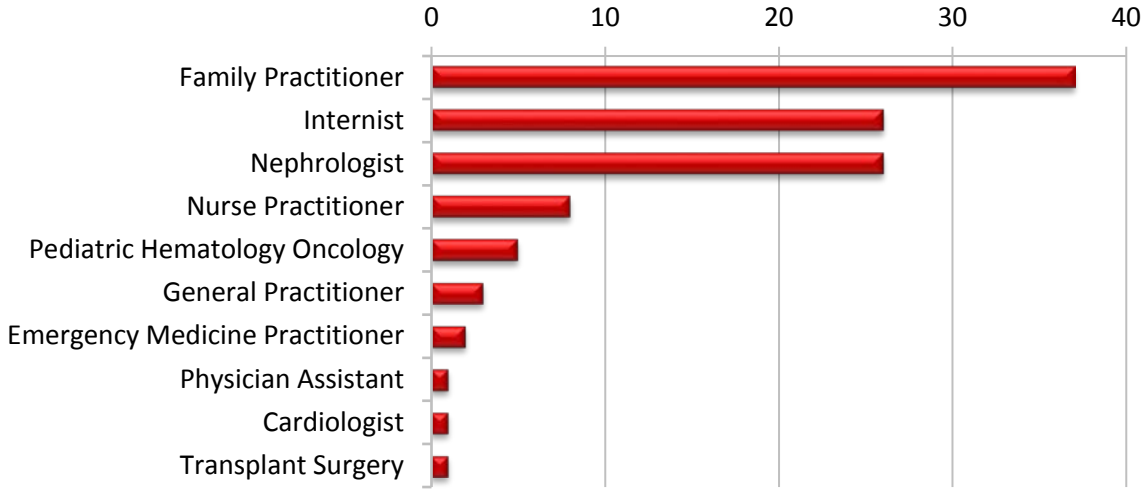
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	64	128	$16,142.37	$126.11	$8.82	43,911	1,831
2018	68	115	$13,266.15	$115.36	$8.87	46,797	1,496
% Change	**6.30%**	**-10.20%**	**-17.80%**	**-8.50%**	**0.60%**	**6.60%**	**-18.30%**
Change	**4**	**-13**	**-$2,876.22**	**-$10.75**	**$0.05**	**2,886**	**-335**

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

Demographics of Members Utilizing Hyperkalemia Medications



Top Prescriber Specialties of Hyperkalemia Medications by Number of Claims



Prior Authorization of Hyperkalemia Medications

There were 33 prior authorization requests submitted for hyperkalemia 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[4,5,6]

Anticipated Patent Expiration(s):

- Veltassa® (patiromer): October 2033

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

- **May 2018:** Lokelma™ (sodium zirconium cyclosilicate)
- **May 2018:** The FDA approved a supplemental New Drug Application (sNDA) to update the prescribing information for Veltassa® (patiromer) to include data showing patiromer can be taken with or without food. The updated label allows for increased dosing flexibility. The approval was based on data from the Phase 4 TOURMALINE trial, which showed no statistically-significant difference between groups taking patiromer with or without food in achieving serum potassium levels within target range (3.8 to 5.0mEq/L).

Lokelma™ (Sodium Zirconium Cyclosilicate) Product Summary[7]

Indication(s): Lokelma™ (sodium zirconium cyclosilicate) is a potassium binder indicated for the treatment of hyperkalemia in adults.

Dosing:

- Lokelma™ is supplied as powder packets for oral suspension in 2 strength packets: 5g packet and 10g packet, each strength in a box of 30 packets.
- The recommended starting dose is 10g administered 3 times daily for up to 48 hours.
- The recommended regimen for maintenance treatment is 10g once daily.
- The dose should be adjusted by 5g daily at 1-week intervals as needed to obtain the desired serum potassium target range.
- In an open-label 12-month study, the initial dose of sodium zirconium cyclosilicate was 5g once daily and was adjusted to a minimum of 5g every other day up to a maximum of 15g once daily based on serum potassium level for the maintenance phase.

Mechanism of Action: Sodium zirconium cyclosilicate is a non-absorbed zirconium silicate that preferentially captures potassium in exchange for hydrogen and sodium. *In vitro*, sodium zirconium cyclosilicate has a high affinity for potassium ions, even in the presence of other cations such as calcium and magnesium. Sodium zirconium cyclosilicate increases fecal potassium excretion through binding of potassium in the lumen of the GI tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, thereby lowering the serum potassium level.

Safety:

- GI Adverse Events in Patients with Motility Disorders: Sodium zirconium cyclosilicate should be avoided in patients with severe constipation, bowel obstruction, or impaction, including abnormal post-operative bowel motility disorders, because sodium zirconium cyclosilicate has not been studied in patients with these conditions and may be ineffective and worsen GI conditions.
- Edema: Each 5g dose of sodium zirconium cyclosilicate contains approximately 400mg of sodium. In clinical trials of sodium zirconium cyclosilicate, edema was generally mild-to-moderate in severity and was more commonly seen in patients treated with 15g once daily. Patients should be monitored for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., HF or renal disease). Patients should be advised to adjust dietary sodium if appropriate, and diuretic doses should be increased as needed.

Adverse Reactions: The most common adverse reaction with sodium zirconium cyclosilicate experienced during clinical studies was mild-to-moderate edema.

Efficacy: The safety and efficacy of sodium zirconium cyclosilicate was demonstrated in 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia (5 to 6.5mEq/L).

Study 1:

- A total of 753 patients with hyperkalemia (mean potassium 5.3mEq/L) were included in Study 1. The primary endpoint in the acute phase was the difference in the exponential rate of change in serum potassium levels during the initial 48 hours of study drug treatment, comparing placebo-treated patients and sodium zirconium cyclosilicate-treated patients. The study met its primary endpoint demonstrating a greater reduction in serum potassium levels for the 2.5g, 5g, and 10g (3 times daily) dose groups compared to the placebo group ($P<0.001$). In patients administered the 10g dose, the mean serum potassium reduction was -0.7mEq/L at 48 hours. Sodium zirconium cyclosilicate showed dose-dependent reductions in serum potassium and patients with higher starting potassium levels had a greater response to sodium zirconium cyclosilicate. Sodium zirconium cyclosilicate was effective in lowering potassium levels in patients with CKD, HF, DM, and those taking RAAS inhibitor therapy.
- Patients who achieved a potassium level between 3.5 to 5mEq/L after receiving sodium zirconium cyclosilicate during the acute phase of the study were re-randomized to receive once daily placebo or 1.25g, 2.5g, 5g, or 10g once-daily sodium zirconium cyclosilicate for 12 days. The primary endpoint in the maintenance phase was the difference in exponential rate of change in serum potassium levels over the 12-day treatment interval. The study met the primary efficacy endpoint at the 5g and 10g doses when compared to their retrospective placebo groups ($P<0.01$ and $P<0.001$, respectively).

Study 2:

- In Study 2, a 2-part trial with an open-label acute phase and a month-long randomized, double-blind, placebo-controlled withdrawal phase, 258 patients with hyperkalemia (baseline mean 5.6mEq/L) were given 10g of sodium zirconium cyclosilicate 3 times daily with meals for 48 hours. The average serum potassium levels decreased from 5.6mEq/L to 4.5mEq/L during the acute phase.
- Following the acute phase, there was a double-blind randomized withdrawal phase where patients who achieved potassium levels between 3.5 to 5mEq/L (92%) were randomized to 1 of 3 doses of sodium zirconium cyclosilicate or placebo administered once-daily for 28 days just before breakfast. The primary endpoint in the randomized withdrawal phase was mean serum potassium value over the period from day 8 to day 29, comparing sodium zirconium cyclosilicate-treated and placebo-treated patients. All 3 doses (5g, 10g, and 15g) of once-daily sodium zirconium cyclosilicate maintained mean potassium at lower levels than placebo [mean serum potassium was 4.8mEq/L, 4.5mEq/L, and 4.4mEq/L in the 5g, 10g, and 15g dose groups, respectively, vs. 5.1mEq/L in the placebo group ($P\leq0.001$ for all doses)].
- Patients who completed the 28-day randomized withdrawal phase had the option to continue treatment with sodium zirconium cyclosilicate, taken just before breakfast, in an open-label extension phase for up to 11 months. The treatment effect on serum potassium was maintained during therapy.

Study 3:

- Sodium zirconium cyclosilicate was evaluated in an open-label 12-month study in 751 hyperkalemic patients with a mean baseline potassium level of 5.6mEq/L. Following the

acute phase treatment of sodium zirconium cyclosilicate 10g administered 3 times daily, patients who achieved normal potassium levels (3.5 to 5mEq/L) within 72 hours (N=746; 99%) entered the maintenance phase. For the maintenance treatment, the initial dosage of sodium zirconium cyclosilicate was 5g once daily and was adjusted to a minimum of 5g every other day up to a maximum of 15g once daily, based on serum potassium level. The treatment effect on serum potassium was maintained during continued therapy.

Cost Comparison:

Medication	Cost Per Packet	Cost Per 30 Days	Cost Per Year
Lokelma™ (sodium zirconium cyclosilicate) 5g packet	**$21.83**	**$654.90**	**$7,858.80***
Lokelma™ (sodium zirconium cyclosilicate) 10g packet	**$21.83**	**$654.90**	**$7,858.80***
Veltassa® (patiromer) 25.2g packet	$27.36	$820.80	$9,849.60+

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
*Lokelma™ costs based on the FDA recommended maintenance dosing regimen of 1 packet once daily.
+Veltassa® costs based on FDA recommended maximum maintenance dose of 25.2g per day.

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 shown 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.

Utilization Details of Hyperkalemia Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
SODIUM POLYSTYRENE SULFONATE PRODUCTS						
SPS SUS 15GM/60ML	45	26	$2,012.70	$4.76	$44.73	15.17%
KIONEX SUS 15GM/60ML	27	20	$2,006.44	$5.95	$74.31	15.12%
SOD POLY SUL SUS 15GM/60ML	16	13	$416.44	$3.79	$26.03	3.14%
SOD POLY SUL POW	15	9	$657.02	$2.47	$43.80	4.95%
SUBTOTAL	**103**	**68**	**$5,092.60**	**$4.48**	**$49.44**	**38.38%**
PATIROMER PRODUCTS						
VELTASSA POW 8.4GM	7	6	$4,471.15	$21.29	$638.74	33.70%
VELTASSA POW 16.8GM	5	2	$3,702.40	$24.68	$740.48	27.91%
SUBTOTAL	**12**	**8**	**$8,173.55**	**$22.70**	**$681.13**	**61.61%**
TOTAL	**115**	**68***	**$13,266.15**	**$8.87**	**$115.36**	**100%**

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

[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 12/19/2018.

[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 12/19/2018.

[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 12/19/2018.

[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 12/19/2018.

[5] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 11/2018. Last accessed 12/19/2018.

[6] Vifor Pharma. Brief-US FDA Approves New Label for Veltassa. *The Pharma Letter*. Available online at: https://www.thepharmaletter.com/in-brief/brief-us-fda-approves-new-label-for-veltassa?print=1. Issued 08/05/2018. Last accessed 12/19/2018.

[7] Lokelma™ (sodium zirconium cyclosilicate) Prescribing Information. AstraZeneca. Available online at: https://www.azpicentral.com/pi.html?product=lokelma&country=us&popup=no. Last revised 07/2018. Last accessed 12/19/2018.

Appendix G

Fiscal Year 2018 Annual Review of Mepsevii™ (Vestronidase Alfa-vjbk)

Oklahoma Health Care Authority
January 2019

Introduction[1,2,3,4]

Sly syndrome, also known as mucopolysaccharidosis VII or MPS VII, is a rare disorder caused by mutations in the gene encoding beta-glucuronidase (GUSB). The enzyme deficiency causes accumulation of heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, and chondroitin-6-sulfate. Sly syndrome is inherited in an autosomal recessive pattern. The exact incidence of Sly syndrome is unknown; however, it is estimated to occur in 1 in 250,000 newborns. Sly syndrome is one of the rarest forms of MPS.

Clinical presentation of Sly syndrome is variable. Clinical features and complications of Sly syndrome may be similar to MPS I, with significant soft tissue and skeletal abnormalities. The most severe cases are characterized by hydrops fetalis and may account for a large proportion of patients that are unrecognized because they do not survive to be diagnosed. Other patients with more mild cases of MPS VII may begin to show symptoms in early childhood. The features of MPS VII include macrocephaly, hydrocephalus, macroglossia, and distinctive-looking facial features that are described as “coarse”. Individuals affected with MPS VII frequently develop hepatosplenomegaly, heart valve abnormalities, and umbilical or inguinal hernias. Patients may have developmental delay, but in some patients with this condition, intelligence is unaffected. The life expectancy of MPS VII depends on the severity of symptoms with some affected individuals not surviving infancy while others may live into adolescence or adulthood. Life expectancy is reduced as a result of frequent upper respiratory tract infections, neurodegenerative complications, and abnormalities of the gastrointestinal tract.

The U.S. Food and Drug Administration (FDA) approved Mepsevii™ (vestronidase alfa-vjbk), an enzyme replacement therapy (ERT), in November 2017 for the treatment of Sly syndrome. Mepsevii™ is the first FDA-approved ERT for Sly syndrome. Other treatment options for Sly syndrome include supportive and symptomatic management. Hematopoietic cell transplantation (HCT) may potentially be used in some cases.

Current Prior Authorization Criteria

Mepsevii™ (Vestronidase Alfa-vjbk) Approval Criteria:

1. An FDA approved diagnosis of Sly syndrome (mucopolysaccharidosis VII; MPS VII) confirmed by:
    a. Enzyme analysis demonstrating a deficiency of beta-glucuronidase activity; or
    b. Genetic testing to confirm diagnosis of MPS VII; and
2. Mepsevii™ must be administered by a health care professional prepared to manage anaphylaxis; and

3. Initial approvals will be for the duration of 12 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment; 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.

Utilization of Mepsevii™ (Vestronidase Alfa-vjbk): Fiscal Year 2018

There was no SoonerCare utilization of Mepsevii™ (vestronidase alfa-vjbk) during fiscal year 2018.

Prior Authorization of Mepsevii™ (Vestronidase Alfa-vjbk)

There were no prior authorization requests submitted for Mepsevii™ (vestronidase alfa-vjbk) during fiscal year 2018.

Market News and Updates[5]

News:

- **August 2018:** Ultragenyx Pharmaceutical, Inc. announced that the European Commission (EC) has approved the Marketing Authorization Application for Mepsevii™ (vestronidase alfa-vjbk) for the treatment of non-neurological manifestations of MPS VII (Sly syndrome).

Recommendations

The College of Pharmacy does not recommend any changes to the current Mepsevii™ (vestronidase alfa-vjbk) prior authorization criteria at this time.

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[1] Jones S, Wynn R. Mucopolysaccharidoses: Clinical features and diagnosis. *UpToDate*. Available online at: http://www.uptodate.com/contents/mucopolysaccharidoses-clinical-features-and-diagnosis?search=sly+syndrome&sectionRank=1&anchor=H12&source=machineLearning&selectedTitle=1%7E8#H12. Last revised 09/12/2017. Last accessed 12/11/2018.

[2] NIH U.S. National Library of Medicine. Mucopolysaccharidosis Type VII. *Genetics Home Reference*. Available online at: https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-vii. Last reviewed 08/2010. Last accessed 12/11/2018.

[3] Mucopolysaccharidosis Type VII. *National Organization of Rare Disorders*. Available online at: https://rarediseases.org/rare-diseases/sly-syndrome/. Last accessed 12/11/2018.

[4] Jones S, Wynn R. Mucopolysaccharidoses: Treatment. *UpToDate*. Available online at: https://www.uptodate.com/contents/mucopolysaccharidoses-treatment?search=mepsevii&source=search_result&selectedTitle=2~2&usage_type=default&display_rank=1#H1119956597. Last revised 06/27/2017. Last accessed 12/19/2018.

[5] Ultragenyx Pharmaceutical, Inc. Ultragenyx Announces Approval of Mepsevii™ (vestronidase alfa) in Europe for the Treatment of Mucopolysaccharidosis VII. *Globe Newswire*. Available online at: https://globenewswire.com/news-release/2018/08/27/1557182/0/en/Ultragenyx-Announces-Approval-of-Mepsevii-vestronidase-alfa-in-Europe-for-the-Treatment-of-Mucopolysaccharidosis-VII.html. Issued 08/27/2018. Last accessed 12/11/2018.

Appendix H

Calendar Year 2018 Annual Review of Nuedexta® (Dextromethorphan/Quinidine)

Oklahoma Health Care Authority
January 2019

Current Prior Authorization Criteria

Nuedexta® (Dextromethorphan/Quinidine) Approval Criteria:

1. An FDA approved diagnosis of pseudobulbar affect (PBA) secondary to a neurological condition (e.g., amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, stroke, traumatic brain injury); and
2. Documentation of the neurological condition must be submitted; and
3. Member must be 18 years of age or older; and
4. Nuedexta® must be prescribed by, or in consultation with, a neurologist or psychiatrist (or be an advanced care practitioner with a supervising physician who is a neurologist or psychiatrist); and
5. Member must not have a contraindication to therapy [e.g., concomitant use with quinidine, quinine, or mefloquine; history of quinidine, quinine, or mefloquine-induced thrombocytopenia, hepatitis, or other hypersensitivity reactions; known hypersensitivity to dextromethorphan; use with a monoamine oxidase inhibitor (MAOI) or within 14 days of stopping an MAOI; prolonged QT interval, congenital long QT syndrome, history suggestive of torsades de pointes, or heart failure; complete atrioventricular (AV) block without implanted pacemaker, or at high risk of complete AV block; currently taking other drugs that both prolong QT interval and are metabolized by CYP2D6 (e.g., thioridazine, pimozide)]; and
6. Prescriber must document baseline number of PBA laughing or crying episodes per day; and
7. A quantity limit of 60 capsules per 30 days will apply; and
8. Initial approvals will be for the duration of 12 weeks. Reauthorizations may be granted if the prescriber documents the member is responding well to treatment as indicated by a reduction in the number of PBA episodes of laughing or crying per day compared to baseline. Current users must meet the revised approval criteria when reapplying for prior authorization continuation.

Utilization of Nuedexta® (Dextromethorphan/Quinidine): Calendar Year 2018

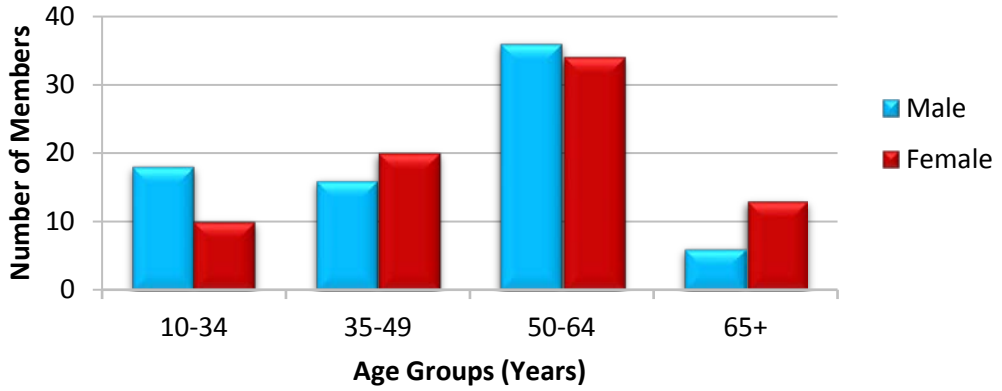
Please note: The following utilization data for calendar year 2018 includes pharmacy claim information from January 1, 2018 to December 5, 2018. The Drug Utilization Review (DUR) Board voted to implement revised prior authorization criteria for Nuedexta® in November 2017.

Comparison of Calendar Years

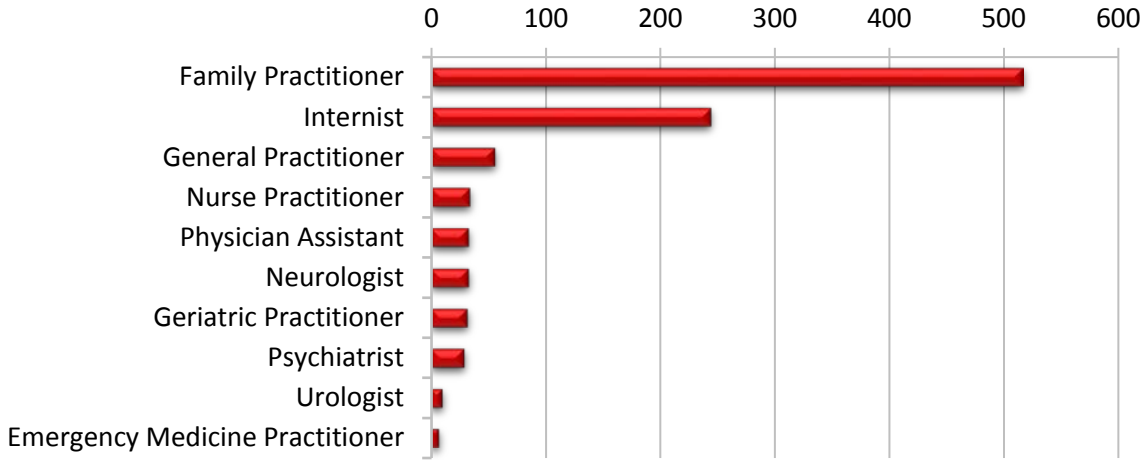
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	214	1,609	$1,041,215.79	$647.12	$23.88	85,082	43,606
2018	153	1,000	$832,884.15	$832.88	$30.97	52,102	26,891
% Change	**-28.50%**	**-37.80%**	**-20.00%**	**28.70%**	**29.70%**	**-38.80%**	**-38.30%**
Change	**-61**	**-609**	**-$208,331.64**	**$185.76**	**$7.09**	**-32,980**	**-16,715**

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

Demographics of Members Utilizing Nuedexta® (Dextromethorphan/Quinidine)

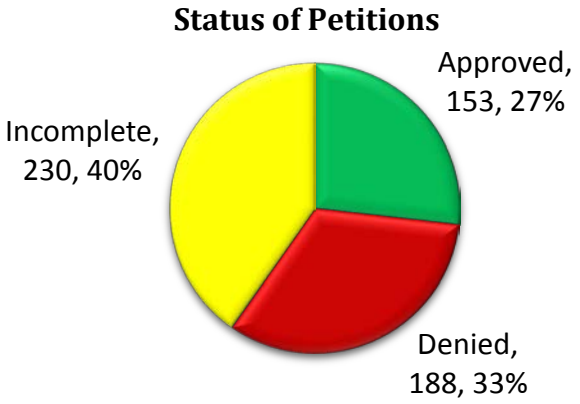


Top Prescriber Specialties of Nuedexta® (Dextromethorphan/Quinidine) by Number of Claims



Prior Authorization of Nuedexta® (Dextromethorphan/Quinidine)

There were 571 prior authorization requests submitted for Nuedexta® during calendar year 2018. The following chart shows the status of the submitted petitions for calendar year 2018. The DUR Board voted to implement revised prior authorization criteria for Nuedexta® in November 2017.



Market News and Updates[1,2]

Anticipated Patent Expiration(s):

- Nuedexta® (dextromethorphan/quinidine): August 2026

News:

- **June 2018:** The United States government issued a warning to insurance companies to watch for suspicious prescriptions for Nuedexta®. The medication is only approved by the U.S. Food and Drug Administration (FDA) to treat pseudobulbar affect (PBA), a rare condition marked by uncontrollable laughing and crying. The drug manufacturer, Avanir Pharmaceuticals, has stated that many dementia patients suffer from PBA; however, regulators are concerned that Medicare may be paying for the drug for unapproved and potentially fraudulent uses. While prescribing a medication for unapproved uses is not illegal, it is considered fraud to diagnose a patient with a condition in order to secure Medicare coverage. A CNN investigation was published in October 2017, which found that Avanir was aggressively targeting nursing home residents for whom the medication may be unnecessary or potentially unsafe. The investigation found multiple examples in which doctors had inappropriately prescribed Nuedexta® to dementia patients, using a diagnosis of PBA when it was actually being prescribed to control unruly behaviors. In March 2018, the Centers for Medicare and Medicaid Services (CMS) issued a memo specifically asking Medicare insurance providers to monitor prescriptions of the medication to ensure that it is being appropriately given to patients. CMS stated the memo was meant to "inform plan sponsors about increases in utilization that may not be readily discerned or may relate to potential fraud."

Recommendations

The College of Pharmacy does not recommend any changes to the current Nuedexta® (dextromethorphan/quinidine) prior authorization criteria at this time.

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[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 10/2018. Last accessed 12/12/2018.
[2] Ellis B, Hicken M. Government issues warning about pill pushed on the elderly. *CNN*. Available online at: https://www.cnn.com/2018/06/04/health/nuedexta-government-warning-insurers-invs/index.html. Last revised 06/05/2018. Last accessed 12/12/2018.

Appendix I

Fiscal Year 2018 Annual Review of Zilretta® [Triamcinolone Acetonide Extended-Release (ER) Injection]

Oklahoma Health Care Authority
January 2019

Current Prior Authorization Criteria

Zilretta® [Triamcinolone Acetonide Extended-Release (ER) Injection] Approval Criteria:

1. An FDA approved diagnosis of osteoarthritis (OA) pain of the knee; and
2. Zilretta® will only be approvable for use in the knee(s) for OA pain; and
3. A patient-specific, clinically significant reason why the member cannot use Kenalog-40® (triamcinolone acetonide 40mg injection) and Depo-Medrol® (methylprednisolone injection) must be provided; and
4. A quantity limit of 1 injection per knee per 12 weeks will apply.

Utilization of Zilretta® (Triamcinolone Acetonide ER Injection): Fiscal Year 2018

There was no SoonerCare utilization of Zilretta® during fiscal year 2018.

Prior Authorization of Zilretta® (Triamcinolone Acetonide ER Injection)

There were no prior authorization requests submitted for Zilretta® during fiscal year 2018.

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

Anticipated Patent Expiration(s):

- Zilretta® [triamcinolone acetonide ER (TA-ER) injection]: August 2031

News:

- **July 2018:** An open-label, Phase 3 study to assess the safety of repeat dosing with Zilretta® (TA-ER) in patients with osteoarthritis (OA) of the knee was completed according to the U.S. National Library of Medicine's database, *ClinicalTrials.gov*. A total of 208 OA patients were initially enrolled. All eligible patients received an initial treatment dose of TA-ER and were then evaluated at 12 weeks to determine eligibility to receive a second treatment dose. Patients that received 2 dose injections were followed and evaluated for a total of 52 weeks. Study results are not yet available.
- **September 2018:** Results from a randomized, Phase 2 study of 33 patients with knee OA and type 2 diabetes mellitus (T2DM) treated with intra-articular Zilretta® (TA-ER) injection (N=18) or triamcinolone acetonide immediate-release in crystalline suspension (TAcs) injection (N=15) were published in *Rheumatology (Oxford)*. The change in average daily continuous glucose monitoring-measured glucose (CGMG) from baseline to days 1 to 3 post injection was significantly lower for TA-ER than TAcs (14.7 vs. 33.9; P=0.0452).
- **October 2018:** A randomized, open-label study comparing the systemic exposure to triamcinolone acetonide following a single intra-articular dose of Zilretta® (TA-ER) or TAcs in patients with OA of the shoulder or hip was completed according to

ClinicalTrials.gov. A total of 55 patients were randomized 1:1 to treatment groups with either a single injection of TA-ER or TAcs. Approximately 12 patients per joint were randomized to each treatment group. Study results are not yet available.

- **October 2018:** Phase 2 clinical trial data evaluating the safety and pharmacokinetics of the administration of Zilretta® in both knees for patients with bilateral OA was presented at the American College of Rheumatology Annual Meeting. The Phase 2 open-label study included 24 patients who were randomized 1:1 to either Zilretta® or TAcs. Exposure to triamcinolone acetonide was lower in patients treated with Zilretta® compared to TAcs, with maximum plasma concentrations nearly 10-fold lower (2,577.8pg/mL vs. 24,289.4pg/mL). Lower maximum plasma concentrations suggest that treatment with Zilretta® would result in lower systemic concentrations of triamcinolone acetonide and would potentially lower the concern for systemic corticosteroid side effects. Both treatment groups had similar safety results.
- **November 2018:** Flexion Therapeutics, Inc. announced that the Centers for Medicare and Medicaid Services (CMS) has issued a product-specific J-code for Zilretta®. J3304 will become the permanent code for Zilretta® effective January 1, 2019. Previously, Zilretta® was billed under a miscellaneous J-code for SoonerCare claims.

Cost Comparison:

Medication	Cost Per Vial
Zilretta® (triamcinolone acetonide ER 32mg/5mL injection)	**$570.00**
triamcinolone acetonide 40mg/mL injection	$8.96
methylprednisolone 40mg/mL injection	$5.87

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

Recommendations

The College of Pharmacy does not recommend any changes to the current Zilretta® (triamcinolone acetonide ER injection) prior authorization criteria at this time.

[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 11/2018. Last accessed 12/19/2018.

[2] Flexion Therapeutics, Inc. Study to Assess the Safety of Repeat Administration of FX006 Administered to Patients With Osteoarthritis of the Knee. U.S. National Library of Medicine: *ClinicalTrials.gov*. Available online at: https://www.clinicaltrials.gov/ct2/show/record/NCT03046446?term=NCT03046446&rank=1. Last revised 08/21/2018. Last accessed 12/19/2018.

[3] Russell SJ, Sala R, Conaghan PG, et al. Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: a randomized, phase 2 study. *Rheumatology (Oxford)* 2018; 57(12):2235-2241.

[4] Flexion Therapeutics, Inc. Study to Compare Exposure of TA Following Administration of FX006 or TAcs in Patients With OA of the Shoulder or Hip. Available online at: https://www.clinicaltrials.gov/ct2/show/NCT03382262?term=zilretta&cond=Osteoarthritis&rank=2. Last revised 12/18/2018. Last accessed 12/19/2018.

[5] Flexion Therapeutics, Inc. Flexion Therapeutics to Present Results from Phase 2 Trial Evaluating ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) in Bilateral Knee OA at 2018 ACR Annual Meeting. *GlobeNewswire*. Available online at: https://globenewswire.com/news-release/2018/10/22/1624602/0/en/Flexion-Therapeutics-to-Present-Results-from-Phase-2-Trial-Evaluating-ZILRETTA-triamcinolone-acetonide-extended-release-injectable-suspension-in-Bilateral-Knee-OA-at-2018-ACR-Annua.html. Issued 10/22/2018. Last accessed 12/18/2018.

[6] Flexion Therapeutics, Inc. Flexion Therapeutics Announces Product-Specific J Code (J3304) for ZILRETTA® (triamcinolone acetonide extended-release injectable suspension) Effective January 1, 2019. *Globe Newswire*. Available online at: https://globenewswire.com/news-release/2018/11/05/1644874/0/en/Flexion-Therapeutics-Announces-Product-Specific-J-Code-J3304-for-ZILRETTA-triamcinolone-acetonide-extended-release-injectable-suspension-Effective-January-1-2019.html. Issued 11/05/2018. Last accessed 12/18/2018.

Appendix J

Industry News and Updates

Oklahoma Health Care Authority
January 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:

- **Opioids:** The U.S. Food and Drug Administration (FDA) Commissioner, Scott Gottlieb, said the agency is looking at a different way of reviewing new opioid drugs prior to approval. Gottlieb stated that he asked the FDA to consider weighing an opioid product's risks and benefits against those of opioids that are already approved. Currently, the FDA typically evaluates the individual qualities of each new opioid drug submission and whether it meets effectiveness and safety standards. Under the new framework, the FDA would compare the potential risks and benefits of new medications and public health implications to those of opioids already on the market.
- **Acute Myocardial Infarction (AMI):** According to results from the Atherosclerosis Risk in Communities (ARIC) Surveillance study, young adults, especially young women, make up an increasing proportion of patients hospitalized with AMI. In the United States, mortality from coronary artery disease has decreased dramatically in the past 4 decades; however, hospitalizations for AMI among young adults have not declined. Utilizing ARIC data, researchers examined trends in the incidence of AMI admissions among young women and men (35 to 54 years of age) from 1995 to 2014. The proportion of AMI admissions attributable to this group increased from 27% to 32% during this interval. According to the report, the trend was significant among young women (from 21% to 31%) but not among young men (30% to 33%).
- **Orphan Drug Program:** The Government Accountability Office (GAO) spent more than a year investigating the FDA's orphan drug program. Federal officials stated in a report that the FDA has failed to ensure that drugs given rare disease status meet the intent of the law. The investigation began at the request of 3 senators after a Kaiser Health News investigation. The report found the program was being manipulated by drug makers in order to maximize profits and to protect niche markets for medications. The GAO uncovered inconsistent and sometimes incomplete reviews early in the process of designating medications as orphan drugs and recommended "executive action" to correct the issues within the system. The investigation found that, in some cases, FDA reviewers did not check how many patients could be treated by a drug prior to being considered for orphan drug status and instead seemed to trust what drug makers reported to them. The FDA issued a statement in response to the GAO's investigation

and said it agreed with the report recommendations regarding documentation and that the agency is "streamlining our processes."

[1] FDA Looking Into New Review Process for Opioids, Gottlieb Says. *FDA News*. Available online at: https://www.fdanews.com/articles/189328-fda-looking-into-new-review-process-for-opioids-gottlieb-says?utm_campaign=Drug%20Daily%20Bulletin&utm_source=hs_email&utm_medium=email&utm_content=67900854&_hsenc=p2ANqtz-8t25zp0ICl288iCYt6YlTVxFHTkJpTOI3wcDXeOwaMf6oGoLjPxTYsZLbSV8OX7Jhex8iwMDAL0CtgEKmA7OeroaZlRmHFw9jThX2rXImf5kcKopk&_hsmi=67900854. Issued 11/29/2018. Last accessed 12/07/2018.

[2] Boggs W. Heart Attack Patients Are Getting Younger. *Managed Health Care Connect*. Available online at: https://www.managedhealthcareconnect.com/content/heart-attack-patients-are-getting-younger?hmpid=YmV0aGFueS1ob2xkZXJyZWFkQG91aHNjLmVkdQ==. Issued 11/23/2018. Last accessed 12/07/2018.

[3] Tribble SJ, Lupkin S. FDA Faulted for Lapses in Orphan Drug Program. *Shots*. Available online at: https://www.npr.org/sections/health-shots/2018/11/30/672287029/fda-faulted-for-lapses-in-orphan-drug-program. Issued 11/30/2018. Last accessed 12/07/2018.

Appendix K

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)

Safety Announcements

FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients

[12/20/2018] A FDA review found that fluoroquinolone antibiotics can increase the occurrence of rare but serious events of ruptures or tears in the main artery of the body (aorta). These tears, called aortic dissections, or ruptures of an aortic aneurysm can lead to dangerous bleeding or even death. They can occur with fluoroquinolones for systemic use given by mouth or through an injection.

Fluoroquinolones should not be used in patients at increased risk unless there are no other treatment options available. People at increased risk include those with a history of blockages or aneurysms (abnormal bulges) of the aorta or other blood vessels, high blood pressure, certain genetic disorders that involve blood vessel changes, and the elderly. The FDA is requiring that a new warning about this risk be added to the prescribing information and patient Medication Guide for all fluoroquinolones.

Fluoroquinolone antibiotics are approved to treat certain bacterial infections and have been used for more than 30 years. They work by killing or stopping the growth of bacteria that can cause illness. Without treatment, some infections can spread and lead to serious health problems.

Health care professionals should avoid prescribing fluoroquinolone antibiotics to patients who have an aortic aneurysm or are at risk for an aortic aneurysm, such as patients with peripheral atherosclerotic vascular diseases, hypertension, certain genetic conditions such as Marfan syndrome and Ehlers-Danlos syndrome, and elderly patients. Prescribers should use fluoroquinolones in these patients only when no other treatment options are available. All patients should be advised to seek immediate medical treatment for any symptoms associated with aortic aneurysm. Fluoroquinolone treatment should be stopped immediately if a patient reports side effects suggestive of aortic aneurysm or dissection.

Patients should seek medical attention immediately by going to an emergency room or calling 911 if they experience sudden, severe, and constant pain in the stomach, chest or back. Patients should be aware that symptoms of an aortic aneurysm often do not show up until the aneurysm becomes large or bursts, so any unusual side effects from taking fluoroquinolones should be reported to their health care professional immediately. Before starting an antibiotic prescription, patients should inform their health care professional if they have a history of aneurysms, blockages, or hardening of the arteries, high blood pressure, or genetic conditions such as Marfan syndrome, or Ehlers-Danlos syndrome. If patients have been prescribed a fluoroquinolone to treat an infection, they should not stop the antibiotic without first talking to their health care professional.

The FDA reviewed cases reported to FDA and 4 published observational studies that showed an increased risk of aortic aneurysm or dissection associated with fluoroquinolone use. How some of the studies were designed or carried out, and the ways the data were analyzed could affect the study findings; however, taken together, the results of all 4 studies provide consistent evidence of an association between fluoroquinolone use and aortic aneurysm or dissection. The underlying mechanism for this risk cannot be determined from these studies, and the background risk of aortic aneurysm can vary depending on the population. The background risk has been estimated from 9 aortic aneurysm events per 100,000 people per year in the general population to 300 aortic aneurysm events per 100,000 people per year in individuals at highest risk. Because multiple studies showed higher rates of about twice the risk of aortic aneurysm rupture and dissection in those taking fluoroquinolones, the FDA determined the warnings were warranted to alert health care professionals and patients.

The FDA communicated safety information associated with fluoroquinolones in July 2018 (significant decreases in blood sugar and certain mental health side effects), July 2016 (disabling side effects of the tendons, muscles, joints, nerves, and central nervous system), May 2016 (restricting use for certain uncomplicated infections), August 2013 (peripheral neuropathy), and July 2008 (tendinitis and tendon rupture). To help the FDA track safety issues with medicines, they urge patients and health care professionals to report side effects involving fluoroquinolones or other medicines to the FDA MedWatch program.

Current Drug Shortages Index (as of Dec 31st, 2018):

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***
Atenolol Tablets	***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***
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***
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***
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***
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***
Liotrix (Thyrolar) Tablets	***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 Chew Tabs	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLIVANT XR) for Extended-Release Oral Susp	***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***
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***
Trifluoperazine Hydrochloride Tablets	***Currently in Shortage***
Valsartan Tablets	***Currently in Shortage***