Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday, May 8, 2019

No live May meeting. May 2019 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 – May 8, 2019

DATE: May 1, 2019

Enclosed are the following items related to the May packet.
Material is arranged in order of the agenda.
No live May meeting. May 2019 is a packet only meeting.

DUR Board Meeting Minutes – Appendix A

Update on Medication Coverage Authorization Unit/2019 Spring Pipeline Update – Appendix B

Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize Plenvu® [Polyethylene Glycol (PEG)-3350/Sodium Ascorbate/Sodium Sulfate/Ascorbic Acid/Sodium Chloride/Potassium Chloride] – Appendix C

Annual Review of Ophthalmic Anti-Inflammatories and 30-Day Notice to Prior Authorize Dextenza® (Dexamethasone Ophthalmic Insert), Inveltys™ (Loteprednol Etabonate Suspension), Lotemax® SM (Loteprednol Etabonate Gel), and Oxervate™ (Cenegermin-bkbj) – Appendix D

Annual Review of Testosterone Products and 30-Day Notice to Prior Authorize Xyosted™ [Testosterone Enanthate Subcutaneous (Sub-Q) Auto-Injector] and Jatenzo® (Testosterone Undecanoate Oral Capsule) – Appendix E

Annual Review of H.P. Acthar® Gel (Repository Corticotropin Injection) – Appendix F

Annual Review of Jynarque® (Tolvaptan) – Appendix G

Industry News and Updates – Appendix H

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

Future Business

Oklahoma Health Care Authority

Drug Utilization Review Board (DUR Board) Packet

May 8, 2019

No live May meeting. May 2019 is a packet only meeting.

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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. April 10, 2019 DUR Minutes
B. April 10, 2019 DUR Recommendations Memorandum

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

2. Update on Medication Coverage Authorization Unit/2019 Spring Pipeline Update – See Appendix B

A. Medication Coverage Activity for April 2019
B. Pharmacy Helpdesk Activity for April 2019
C. 2019 Spring Pipeline Update

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

3. Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize Plenvu® [Polyethylene Glycol (PEG)-3350/Sodium Ascorbate/Sodium Sulfate/Ascorbic Acid/Sodium Chloride/Potassium Chloride] – See Appendix C

A. Current Prior Authorization Criteria
B. Utilization of Bowel Preparation Medications
C. Prior Authorization of Bowel Preparation Medications
D. Market News and Updates
E. Plenvu® (PEG-3350/Sodium Ascorbate/Sodium Sulfate/Ascorbic Acid/Sodium Chloride/Potassium Chloride) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Bowel Preparation Medications

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

4. Annual Review of Ophthalmic Anti-Inflammatories and 30-Day Notice to Prior Authorize Dextenza® (Dexamethasone Ophthalmic Insert), Inveltys™ (Loteprednol Etabonate Suspension), Lotemax® SM (Loteprednol Etabonate Gel), and Oxervate™ (Cenegermin-bkbj) – See Appendix D

A. Current Prior Authorization Criteria
B. Utilization of Ophthalmic Anti-Inflammatories
C. Prior Authorization of Ophthalmic Anti-Inflammatories
D. Market News and Updates
E. Dextenza® (Dexamethasone Ophthalmic Insert) Product Summary
F. Inveltys™ (Loteprednol Etabonate Suspension) Product Summary
G. Lotemax® SM (Loteprednol Etabonate Gel) Product Summary
H. Oxervate™ (Cenegermin-bkbj) Product Summary
I. College of Pharmacy Recommendations
J. Utilization Details of Ophthalmic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
K. Utilization Details of Ophthalmic Corticosteroids

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

5. Annual Review of Testosterone Products and 30-Day Notice to Prior Authorize Xyosted™ [Testosterone Enanthate Subcutaneous (Sub-Q) Auto-Injector] and Jatenzo® (Testosterone Undecanoate Oral Capsule) – See Appendix E

A. Current Prior Authorization Criteria
B. Utilization of Testosterone Products
C. Prior Authorization of Testosterone Products
D. Market News and Updates
E. Xyosted™ (Testosterone Enanthate Sub-Q Auto-Injector) Product Summary
F. Jatenzo® (Testosterone Undecanoate Oral Capsule) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Testosterone Products

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

6. Annual Review of H.P. Acthar® Gel (Repository Corticotropin Injection) – See Appendix F

A. Current Prior Authorization Criteria
B. Utilization of H.P. Acthar® Gel (Repository Corticotropin Injection)
C. Prior Authorization of H.P. Acthar® Gel (Repository Corticotropin Injection)
D. Market News and Updates
E. College of Pharmacy Recommendations

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

7. Annual Review of Jynarque® (Tolvaptan) – See Appendix G

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Jynarque® (Tolvaptan)
D. Prior Authorization of Jynarque® (Tolvaptan)
E. Market News and Updates
F. College of Pharmacy Recommendations

Non-Presentation; Questions Only:

8. Industry News and Updates – See Appendix H

A. Introduction
B. News and Updates

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

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

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

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

A. Attention-Deficit/Hyperactivity Disorder (ADHD) and Narcolepsy Medications
B. Atypical Antipsychotic Medications
C. Various Special Formulations
D. Opioid Analgesics and Medication Assisted Treatment (MAT) Medications
E. Spinal Muscular Atrophy Medications

**Future business subject to change.*

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF APRIL 10, 2019

BOARD MEMBERS:	PRESENT	ABSENT
Stephen Anderson, Pharm.D.	x	
Markita Broyles, D.Ph.; MBA	x	
Darlla D. Duniphin, MHS; PA-C	x	
Theresa Garton, M.D.	x	
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	

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: 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
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:		
Bob Atkins, Biogen	Jason Russell, Genzyme	Mark Friederich, DZ
Edward Drea, Sanofi-Genzyme	Jomy Joseph, Sanofi-Genzyme	Ron Cain, Pfizer
Frances Bauman, Novo Nordisk	Jim Chapman, AbbVie	Brant Hildebrand, Gilead
Brian Maves, Pfizer	Jim Dunlap, PhRMA	

PRESENT FOR PUBLIC COMMENT:	
Jomy Joseph	Sanofi-Genzyme

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. 13 JOMY JOSEPH

ACTION: NONE REQUIRED

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

3A: MARCH 13, 2019 DUR MINUTES – VOTE

3B: MARCH 13, 2019 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Cothran

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/LONG-ACTING BETA$_2$-AGONIST UTILIZATION: PEDIATRIC MEMBERS

4A: MEDICATION COVERAGE ACTIVITY FOR MARCH 2019

4B: PHARMACY HELPDESK ACTIVITY FOR MARCH 2019

4C: LONG-ACTING BETA$_2$-AGONIST UTILIZATION: PEDIATRIC MEMBERS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE TAKHZYRO™ (LANADELUMAB-FLYO) AND TO UPDATE THE PRIOR AUTHORIZATION CRITERIA FOR CINRYZE® (C1 ESTERASE INHIBITOR), HAEGARDA® (C1 ESTERASE INHIBITOR), AND KALBITOR® (ECALLANTIDE)

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE ADCETRIS® (BRENTUXIMAB VEDOTIN), BELEODAQ® (BELINOSTAT), CALQUENCE® (ACALABRUTINIB), FOLOTYN® (PRALATREXATE), ISTODAX® (ROMIDEPSIN), POTELIGEO® (MOGAMULIZUMAB-KPKC), TRUXIMA® (RITUXIMAB-ABBS), ZEVALIN® (IBRITUMOMAB TIUXETAN), AND ZOLINZA® (VORINOSTAT)

6A: INTRODUCTION

6B: MARKET NEWS AND UPDATES

6C: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Schmidt

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE COPIKTRA™ (DUVELISIB)

7A: INTRODUCTION

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

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE LUTATHERA® (LUTETIUM LU 177 DOTATATE) AND VITRAKVI® (LAROTRECTINIB)
8A: INTRODUCTION
8B: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Schmidt
Dr. Munoz moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF LUNG CANCER MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE LORBRENA® (LORLATINIB), MVASI® (BEVACIZUMAB-AWWB), AND VIZIMPRO® (DACOMITINIB)
9A: INTRODUCTION
9B: CURRENT PRIOR AUTHORIZATION CRITERIA
9C: UTILIZATION OF LUNG CANCER MEDICATIONS
9D: PRIOR AUTHORIZATION OF LUNG CANCER MEDICATIONS
9E: MARKET NEWS AND UPDATES
9F: PRODUCT SUMMARIES
9G: RECOMMENDATIONS
9H: UTILIZATION DETAILS OF LUNG CANCER MEDICATIONS
Materials included in agenda packet; presented by Dr. Schmidt
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: ANNUAL REVIEW OF THE SOONERCARE PHARMACY BENEFIT
10A: SUMMARY
10B: MEDICAID DRUG REBATE PROGRAM
10C: ALTERNATIVE PAYMENT MODELS
10D: DRUG APPROVAL TRENDS
10E: TRADITIONAL VERSUS SPECIALTY PHARMACY PRODUCTS
10F: TOP 10 THERAPEUTIC CLASSES BY REIMBURSEMENT
10G: TOP 10 MEDICATIONS BY REIMBURSEMENT
10H: COST PER CLAIM
10I: CONCLUSION
10J: TOP 100 REIMBURSED DRUGS BY FISCAL YEAR
10K: TOP 50 MEDICATIONS BY TOTAL NUMBER OF CLAIMS
10L: TOP 10 TRADITIONAL AND SPECIALTY THERAPEUTIC CATEGORIES BY FISCAL YEAR
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 11: ANNUAL REVIEW OF GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSFS) AND 30-DAY NOTICE TO PRIOR AUTHORIZE FULPHILA® (PEGFILGRASTIM-JMDB), NIVESTYM™ (FILGRASTIM-AAFI), AND UDENYCA™ (PEGFILGRASTIM-CBQV)
11A: CURRENT PRIOR AUTHORIZATION CRITERIA
11B: UTILIZATION OF G-CSFS
11C: PRIOR AUTHORIZATION OF G-CSFS
11D: MARKET NEWS AND UPDATES
11E: COLLEGE OF PHARMACY RECOMMENDATIONS
11F: UTILIZATION DETAILS OF G-CSFS
Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: **ANNUAL REVIEW OF ANTI-DIABETIC MEDICATIONS**

12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF ANTI-DIABETIC MEDICATIONS
12C: PRIOR AUTHORIZATION OF ANTI-DIABETIC MEDICATIONS
12D: MARKET NEWS AND UPDATES
12E: COLLEGE OF PHARMACY RECOMMENDATIONS
12F: UTILIZATION DETAILS OF NON-INSULIN ANTI-DIABETIC MEDICATIONS
12G: UTILIZATION DETAILS OF INSULIN MEDICATIONS

Materials included in agenda packet; presented by Dr. Nawaz

ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **30-DAY NOTICE TO PRIOR AUTHORIZE CABLIVI® (CAPLACIZUMAB-YHDP)**

13A: INTRODUCTION
13B: CABLIVI® (CAPLACIZUMAB-YHDP) PRODUCT SUMMARY
13C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: **30-DAY NOTICE TO PRIOR AUTHORIZE ALDURAZYME® (LARONIDASE) AND NAGLAZYME® (GALSULFASE)**

14A: INTRODUCTION
14B: ALDURAZYME® (LARONIDASE) PRODUCT SUMMARY
14C: NAGLAZYME® (GALSULFASE) PRODUCT SUMMARY
14D: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Connell

ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: **ANNUAL REVIEW OF ANTIHYPERTENSIVE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE CONSENSI® (AMLODIPINE/CELECOXIB) AND KAPSPARGO™ SPRINKLE [METOPROLOL SUCCINATE EXTENDED-RELEASE (ER)]**

15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF ANTIHYPERTENSIVE MEDICATIONS
15C: PRIOR AUTHORIZATION OF ANTIHYPERTENSIVE MEDICATIONS
15D: MARKET NEWS AND UPDATES
15E: CONSENSI® (AMLODIPINE/CELECOXIB TABLETS) PRODUCT SUMMARY
15F: KAPSPARGO™ SPRINKLE (METOPROLOL SUCCINATE ER CAPSULES) PRODUCT SUMMARY
15G: COLLEGE OF PHARMACY RECOMMENDATIONS
15H: UTILIZATION DETAILS OF ANTIHYPERTENSIVE MEDICATIONS

Materials included in agenda packet; presented by Dr. Abbott

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 in May 2019. May 2019 will be a packet only meeting.

18A: BOWEL PREPARATION MEDICATIONS
18B: H.P. ACTHAR® GEL (REPOSITORY CORTICOTROPIN INJECTION)
18C: OPHTHALMIC ANTI-INFLAMMATORIES
18D: TESTOSTERONE PRODUCTS
**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 4:56pm.

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

Memorandum

Date: April 11, 2019

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

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

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of April 10, 2019

Recommendation 1: Long-Acting Beta$_2$-Agonist Utilization: Pediatric Members

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Takhzyro™ (Lanadelumab-flyo) and to Update the Prior Authorization Criteria for Cinryze® (C1 Esterase Inhibitor), Haegarda® (C1 Esterase Inhibitor), and Kalbitor® (Ecallantide)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Takhzyro™ (lanadelumab-flyo) with criteria similar to Cinryze® and Haegarda® (C1 esterase inhibitors) and to update the current Cinryze® and Haegarda® criteria to be consistent with current guideline recommendations (changes shown in red):

Cinryze® (C1 Esterase Inhibitor), ~~and~~ Haegarda® (C1 Esterase Inhibitor), and Takhzyro™ (Lanadelumab-flyo) Approval Criteria:

1. An FDA approved diagnosis of hereditary angioedema (HAE); and
2. Must be used for *prophylaxis* of HAE; and
3. Not currently taking an angiotensin converting enzyme (ACE) inhibitor or estrogen replacement therapy; and
4. History of at least 1 or more abdominal or respiratory HAE attacks per month, or history of laryngeal attacks, or 3 or more emergency medical treatments per year; or
5. ~~Member meets the following:~~ Approval consideration will be given if the member has a recent hospitalization for a severe episode of angioedema; and
   a. ~~Documented intolerance, insufficient response, or contraindication to attenuated androgens (e.g., danazol, stanozolol, oxandrolone, methyltestosterone); and~~
   b. ~~Documented intolerance, insufficient response, or contraindication to antifibrinolytic agents (e.g., ε – aminocaproic acid, tranexamic acid); or~~
   c. ~~Recent hospitalization for severe episode of angioedema; and~~
6. Authorization of Takhzyro™ (lanadelumab-flyo) will also require a patient-specific, clinically significant reason why the member cannot use Cinryze® or Haegarda® (C1 esterase inhibitor); and
7. Cinryze® Dosing:
   a. The recommended dose of Cinryze® is 1,000 units intravenously (IV) every 3 to 4 days, approximately 2 times per week, to be infused at a rate of 1mL/min; and
   b. Initial doses should be administered in an outpatient setting by a health care provider (members can be taught by their health care provider to self-administer Cinryze® IV); and
   c. A quantity limit of 8,000 units per month will apply (i.e., 2 treatments per week or 8 treatments per 28 days); or
8. Haegarda® Dosing:
   a. The recommended dose of Haegarda® is 60 IU/kg subcutaneously (sub-Q) twice weekly; and
   b. 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
   c. A quantity limit of 2 treatments per week or 8 treatments 28 days will apply; or
9. Takhzyro™ Dosing:
   a. The recommended dose of Takhzyro™ is 300mg sub-Q every 2 weeks (dosing every 4 weeks may be considered in some members); and
   b. Prescriber must verify member or caregiver has been trained by a health care professional on proper storage and sub-Q administration of Takhzyro™; and
   c. A quantity limit of (2) 300mg/2mL vials per 28 days will apply.

Additionally, the College of Pharmacy recommends updating the current Kalbitor® (ecallantide) criteria based on net cost (changes shown in red):

Ruconest® (C1 Esterase Inhibitor) and Kalbitor® (Ecallantide) Approval Criteria:

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

3. A patient-specific, clinically significant reason why the member cannot use Berinert® (C1 esterase inhibitor) and Firazyr® (icatibant) must be provided.

Recommendation 3: Vote to Prior Authorize Adcetris® (Brentuximab Vedotin), Beleodaq® (Belinostat), Calquence® (Acalabrutinib), Folotyn® (Pralatrexate), Istodax® (Romidepsin), Poteligeo® (Mogamulizumab-kpkc), Truxima® (Rituximab-abbs), Zevalin® (Ibritumomab Tiuxetan), and Zolinza® (Vorinostat)

MOTION CARRIED by unanimous approval.

- Update the prior authorization criteria to reflect new U.S. Food and Drug Administration (FDA) approved indications and guideline recommendations; changes can be seen in the following criteria listed in red (only criteria with updates listed)
- The prior authorization of Adcetris® (brentuximab vedotin), Beleodaq® (belinostat), Calquence® (acalabrutinib), Folotyn® (pralatrexate), Istodax® (romidepsin), Poteligeo® (mogamulizumab-kpkc), Truxima® (rituximab-abbs), Zevalin® (ibritumomab tiuxetan), and Zolinza® (vorinostat) with the following criteria listed in red

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

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

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

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

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

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

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

1. Relapsed or progressive disease; and
2. Member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
3. Member must have been previously treated with sorafenib.

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

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

Adcetris® (Brentuximab Vedotin) Approval Criteria [Anaplastic Large Cell Lymphoma (ALCL), Primary Cutaneous Diagnosis]:

1. As a single-agent in members with multifocal lesions or regional nodes either as primary treatment or in relapsed/refractory disease; or
2. In combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for primary treatment or in relapsed/refractory disease with regional nodes.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Anaplastic Large Cell Lymphoma (ALCL), Systemic Diagnosis]:

1. In previously untreated disease in combination with cyclophosphamide, doxorubicin, and prednisone (CHP); or
2. In members who have received ≥1 line of therapy as a single-agent.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Classical Hodgkin Lymphoma Diagnosis]:

1. In previously untreated Stage III or IV disease in combination with doxorubicin, vinblastine, and dacarbazine; or

2. In relapsed/refractory disease after failure of ≥2 multi-agent chemotherapy regimens in non-autologous stem cell transplant (SCT) candidates or after failure of autologous SCT as a single-agent; or
3. In relapsed/refractory disease if not previously used in combination with multi-agent chemotherapy; or
4. Consolidation following autologous SCT in members at high risk of relapse or progression.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Diffuse Large B-Cell Lymphoma (DLBCL) or High Grade Lymphoma Diagnosis]:

1. As a single-agent; and
2. CD30+ disease; and
3. For DLBCL relapsed/refractory disease in non-autologous stem cell transplant (SCT) candidates; or
4. For members who have transformed to DLBCL from follicular lymphoma or marginal zone lymphoma and received ≥2 lines of therapy for indolent or transformed disease.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. As a single-agent as primary treatment or in relapsed/refractory disease.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Peripheral T-Cell Lymphoma (PTCL) Diagnosis]:

1. Treatment of previously untreated CD30+ disease in combination with cyclophosphamide, doxorubicin, and prednisone (CHP); or
2. In members who have received ≥1 line of therapy as a single-agent.

Adcetris® (Brentuximab Vedotin) Approval Criteria [Adult T-Cell Leukemia/Lymphoma Diagnosis]:

1. CD30+ disease; and
2. Member meets 1 of the following:
    a. In combination with cyclophosphamide, doxorubicin, and prednisone (CHP) in nonresponders to first-line therapy for chronic/smoldering subtype; or
    b. In combination with CHP for first-line therapy for acute or lymphoma subtype; or
    c. In combination with CHP for continued treatment in responders to first-line therapy for acute or lymphoma subtype; or
    d. In members who have received ≥1 line of therapy as a single-agent.

Adcetris® (Brentuximab Vedotin) Approval Criteria [T-Cell Lymphoma, Extranodal NK/T-Cell Lymphoma, Nasal Type Diagnosis]:

1. CD30+ disease; and
2. As a single-agent; and
3. Relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen not previously used.

Beleodaq® (Belinostat) Approval Criteria [Anaplastic Large Cell Lymphoma (ALCL), Primary Cutaneous Diagnosis]:

1. As a single-agent for primary treatment or relapsed refractory with multifocal lesions, or cutaneous ALCL with regional nodes.

Beleodaq® (Belinostat) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. Primary treatment in Stage IV non Sézary or visceral disease (solid organ) with or without radiation therapy for local control; or
2. Primary treatment for large cell transformation with generalized cutaneous or extracutaneous lesions with or without skin-directed therapy; or
3. As a single-agent (with or without skin-directed therapy) in relapsed/refractory disease.

Beleodaq® (Belinostat) Approval Criteria [Peripheral T-Cell Lymphoma (PTCL) Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Beleodaq® (Belinostat) Approval Criteria [Adult T-Cell Leukemia/Lymphoma Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Beleodaq® (Belinostat) Approval Criteria [T-Cell Lymphoma, Extranodal NK/T-Cell Lymphoma, Nasal Type Diagnosis]:

1. As a single-agent; and
2. Relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen not previously used.

Calquence® (Acalabrutinib) Approval Criteria [Mantle Cell Lymphoma (MCL) Diagnosis]:

1. As a single-agent in members who have received ≥1 prior therapy.

Calquence® (Acalabrutinib) Approval Criteria [Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Folotyn® (Pralatrexate) Approval Criteria [Adult T-Cell Leukemia/Lymphoma Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Folotyn® (Pralatrexate) Approval Criteria [Anaplastic Large Cell Lymphoma (ALCL), Primary Cutaneous Diagnosis]:

1. As a single-agent in members with multifocal lesions or regional nodes either as primary treatment or in relapsed/refractory disease.

Folotyn® (Pralatrexate) Approval Criteria [Peripheral T-Cell Lymphoma (PTCL) Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Folotyn® (Pralatrexate) Approval Criteria [T-Cell Lymphoma, Extranodal NK/T-Cell Lymphoma, Nasal Type Diagnosis]:

1. As a single-agent; and
2. Relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen not previously used.

Folotyn® (Pralatrexate) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. As a single-agent as primary treatment or in relapsed/refractory disease.

Istodax® (Romidepsin) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. As a single-agent as primary treatment or in relapsed/refractory disease.

Istodax® (Romidepsin) Approval Criteria [Anaplastic Large Cell Lymphoma (ALCL), Primary Cutaneous Diagnosis]:

1. As a single-agent in members with multifocal lesions or regional nodes either as primary treatment or in relapsed/refractory disease.

Istodax® (Romidepsin) Approval Criteria [Peripheral T-Cell Lymphoma (PTCL) Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Istodax® (Romidepsin) Approval Criteria [T-Cell Lymphoma, Extranodal NK/T-Cell Lymphoma, Nasal Type Diagnosis]:

1. As a single-agent; and
2. Relapsed/refractory disease following additional therapy with an alternate combination chemotherapy regimen not previously used.

Poteligeo® (Mogamulizumab-kpkc) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. As a single-agent as primary treatment or in relapsed/refractory disease.

Poteligeo® (Mogamulizumab-kpkc) Approval Criteria [Adult T-Cell Leukemia/Lymphoma Diagnosis]:

1. As a single-agent in relapsed/refractory disease.

Truxima® (Rituximab-abbs) Approval Criteria:

1. An FDA approved diagnosis; and
2. A patient-specific, clinically significant reason why the member cannot use Rituxan® (rituximab) must be provided.

Zevalin® (Ibritumomab Tiuxetan) Approval Criteria [Follicular Lymphoma (FL) (Grade 1-2) Diagnosis]:

1. As a single-agent in relapsed or refractory disease.

Zevalin® (Ibritumomab Tiuxetan) Approval Criteria [Follicular Lymphoma (FL) or Marginal Zone Lymphoma (MZL) Transformed to Diffuse Large B-Cell Lymphoma (DLBCL) Diagnosis]:

1. As a single-agent; and
2. Member meets 1 of the following:
    a. Minimal or no chemotherapy prior to histologic transformation to DLBCL (FISH for MYC and BCL2 and/or BCL6 must show no translocation) and have partial response, no response, or progressive disease after chemoimmunotherapy; or
    b. ≥2 prior therapies of chemoimmunotherapy for indolent or transformed disease.

Zolinza® (Vorinostat) Approval Criteria [Primary Cutaneous Lymphomas – Mycosis Fungoides (MF)/Sézary Syndrome (SS) Diagnosis]:

1. As a single-agent as primary treatment or in relapsed/refractory disease.

Recommendation 4: Vote to Prior Authorize Copiktra™ (Duvelisib)

MOTION CARRIED by unanimous approval.

- Update the prior authorization criteria to reflect new FDA approved indications and guideline recommendations; changes can be seen in the following criteria listed in red (only criteria with updates listed)
- The prior authorization of Copiktra™ (duvelisib) with the following criteria listed in red

Gazyva® (Obinutuzumab) Approval Criteria [Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Diagnosis]:

1. In combination with chlorambucil, bendamustine, or ibrutinib for first-line therapy; or
2. As a single-agent for relapsed or refractory disease.

Imbruvica® (Ibrutinib) Approval Criteria [Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Diagnosis]:

1. As first-line or subsequent therapy for CLL/SLL; and
2. As a single-agent or in combination with bendamustine, rituximab, or obinutuzumab.

Imbruvica® (Ibrutinib) Approval Criteria [Waldenström's Macroglobulinemia (WM)/ Lymphoplasmacytic Lymphoma Diagnosis]:

1. As first-line or subsequent therapy; and
2. As a single-agent or in combination with rituximab.

Venclexta® (Venetoclax) Approval Criteria [Acute Myeloid Leukemia (AML) Diagnosis]:

1. Member meets 1 of the following:
   a. Member must be 75 years of age or older; or
   b. If the member is younger than 75 years of age, they must be unable to tolerate intensive induction chemotherapy; and
2. Must be used as first-line therapy; and
3. Must be used in combination with azacitidine, or decitabine, or low-dose cytarabine (LDAC).

Copiktra™ (Duvelisib) Approval Criteria [Follicular Lymphoma (FL) Diagnosis]:

1. A diagnosis of relapsed or refractory FL; and
2. Progression of disease following 2 or more lines of systemic therapy; and
3. Must be used as a single-agent.

Copiktra™ (Duvelisib) Approval Criteria [Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) Diagnosis]:

1. A diagnosis of relapsed or refractory CLL or SLL; and
2. Progression of disease following 2 or more lines of systemic therapy; and
3. Must be used as a single-agent.

Recommendation 5: Vote to Prior Authorize Lutathera® (Lutetium Lu 177 Dotatate) and Vitrakvi® (Larotrectinib)

MOTION CARRIED by unanimous approval.

Lutathera® (Lutetium Lu 177 Dotatate) Approval Criteria [Gastroenteropancreatic Neuroendocrine Tumor (GEP-NET) Diagnosis]:

1. Diagnosis of progressive locoregional advanced disease or metastatic disease; and
2. Positive imaging of somatostatin receptor; and
3. Must be used as second-line or subsequent therapy following progression on octreotide or lanreotide; or
4. May be used first-line for treatment of pheochromocytoma/paraganglioma.

Vitrakvi® (Larotrectinib) Approval Criteria [Solid Tumors With Neurotrophic Receptor Tyrosine Kinase (*NTRK*) Gene Fusion Diagnosis]:

1. Diagnosis of a solid tumor with a *NTRK* gene fusion without a known acquired resistance mutation; and
2. Disease is metastatic or surgical resection (or radioactive iodine refractory if thyroid carcinoma) is contraindicated; and
3. Documentation of no satisfactory alternative treatments or progression following acceptable alternative treatments.

Recommendation 6: Annual Review of Lung Cancer Medications and 30-Day Notice to Prior Authorize Lorbrena® (Lorlatinib), Mvasi® (Bevacizumab-awwb), and Vizimpro® (Dacomitinib)

NO ACTION REQUIRED.

Recommendation 7: Annual Review of the SoonerCare Pharmacy Benefit

NO ACTION REQUIRED.

Recommendation 8: Annual Review of Granulocyte Colony-Stimulating Factors (G-CSFs) and 30-Day Notice to Prior Authorize Fulphila® (Pegfilgrastim-jmdb), Nivestym™ (Filgrastim-aafi), and Udenyca™ (Pegfilgrastim-cbqv)

NO ACTION REQUIRED.

Recommendation 9: Annual Review of Anti-Diabetic Medications

NO ACTION REQUIRED.

Recommendation 10: 30-Day Notice to Prior Authorize Cablivi® (Caplacizumab-yhdp)

NO ACTION REQUIRED.

Recommendation 11: 30-Day Notice to Prior Authorize Aldurazyme® (Laronidase) and Naglazyme® (Galsulfase)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Antihypertensive Medications and 30-Day Notice to Prior Authorize Consensi® (Amlodipine/Celecoxib) and Kapspargo™ Sprinkle [Metoprolol Succinate Extended-Release (ER)]

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

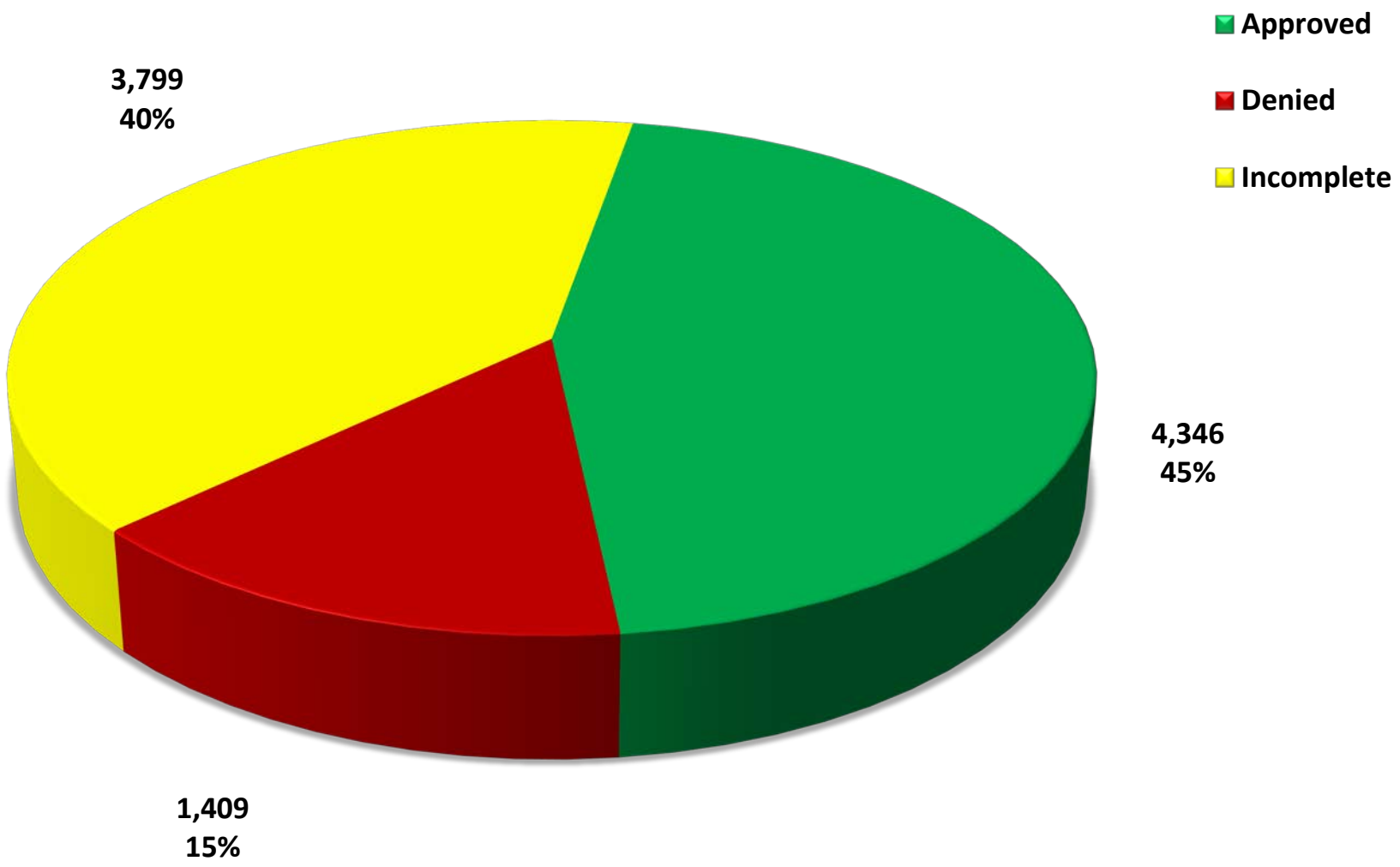
NO ACTION REQUIRED.

Recommendation 15: Future Business

NO ACTION REQUIRED.

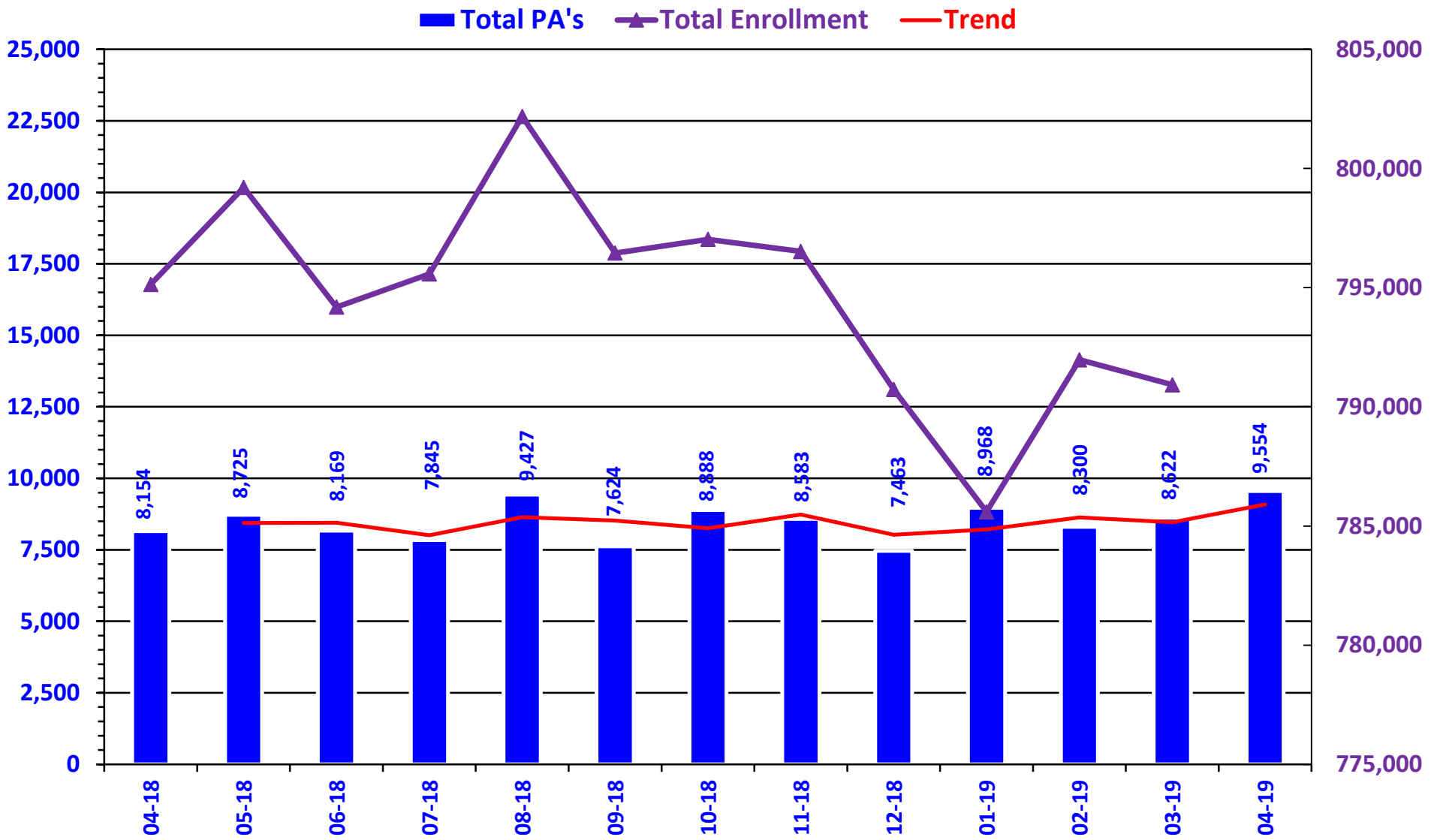
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: APRIL 2019



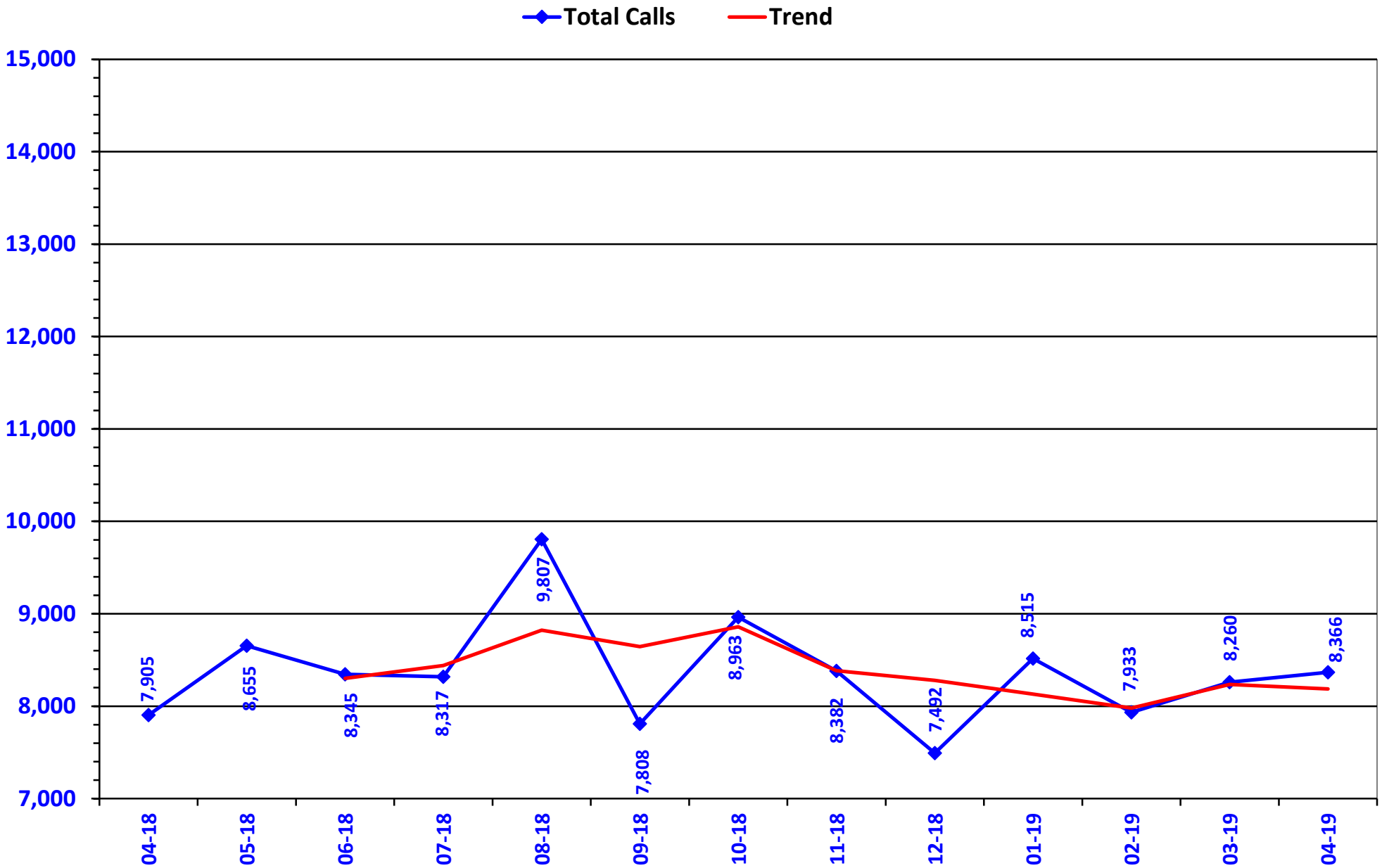
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: APRIL 2018 – APRIL 2019



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
APRIL 2018 – APRIL 2019



Prior Authorization Activity

4/1/2019 Through 4/30/2019

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	107	13	41	53	353
Analgesic - NonNarcotic	25	0	9	16	0
Analgesic, Narcotic	410	180	45	185	156
Angiotensin Receptor Antagonist	20	5	4	11	170
Antiasthma	121	22	34	65	288
Antibiotic	47	26	4	17	266
Anticonvulsant	243	89	34	120	277
Antidepressant	238	62	43	133	329
Antidiabetic	302	129	54	119	348
Antigout	12	4	2	6	290
Antihistamine	41	10	15	16	330
Antimigraine	137	16	40	81	92
Antineoplastic	92	63	10	19	169
Antiparasitic	46	12	6	28	3
Antiulcers	188	53	61	74	146
Anxiolytic	14	3	1	10	267
Atypical Antipsychotics	281	133	24	124	333
Biologics	155	73	28	54	287
Bladder Control	60	16	12	32	358
Blood Thinners	328	176	17	135	326
Botox	37	24	6	7	315
Buprenorphine Medications	596	341	24	231	77
Calcium Channel Blockers	11	4	0	7	114
Cardiovascular	63	30	10	23	323
Chronic Obstructive Pulmonary Disease	185	31	43	111	341
Constipation/Diarrhea Medications	173	33	62	78	215
Contraceptive	16	9	3	4	322
Dermatological	375	104	95	176	90
Diabetic Supplies	497	277	16	204	208
Endocrine & Metabolic Drugs	139	86	8	45	153
Erythropoietin Stimulating Agents	31	16	6	9	108
Fibric Acid Derivatives	10	3	0	7	358
Fibromyalgia	15	1	2	12	20
Gastrointestinal Agents	118	29	29	60	216
Genitourinary Agents	13	1	8	4	361
Growth Hormones	108	76	7	25	150
Hematopoietic Agents	21	3	8	10	253
Hepatitis C	162	87	25	50	8
HFA Rescue Inhalers	68	1	3	64	18
Insomnia	45	6	16	23	204
Insulin	152	59	23	70	325
Miscellaneous Antibiotics	23	5	5	13	10
Multiple Sclerosis	65	30	13	22	209
Muscle Relaxant	66	7	24	35	44
Nasal Allergy	99	13	34	52	128
Neurological Agents	134	44	25	65	198
Neuromuscular Agents	12	6	4	2	297
NSAIDs	26	2	9	15	46
Ocular Allergy	65	8	20	37	83

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

Ophthalmic Anti-infectives	12	1	3	8	54

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Osteoporosis	19	6	7	6	358
Other*	356	57	112	187	251
Otic Antibiotic	27	1	10	16	7
Pediculicide	16	0	5	11	0
Respiratory Agents	35	24	3	8	218
Statins	24	4	9	11	268
Stimulant	760	352	80	328	350
Testosterone	48	14	9	25	315
Topical Antifungal	36	2	10	24	16
Topical Corticosteroids	64	0	33	31	0
Vitamin	88	21	35	32	230
Pharmacotherapy	64	59	0	5	240
Emergency PAs	0	0	0	0	
Total	**7,741**	**2,962**	**1,328**	**3,451**	
Overrides					
Brand	57	34	8	15	268
Compound	9	9	0	0	70
Cumulative Early Refill	1	0	0	1	0
Diabetic Supplies	3	2	0	1	62
Dosage Change	480	448	4	28	12
High Dose	9	7	0	2	126
IHS-Brand	2	1	0	1	65
Ingredient Duplication	10	7	1	2	20
Lost/Broken Rx	99	88	2	9	14
NDC vs Age	286	181	23	82	276
Nursing Home Issue	49	43	1	5	11
Opioid MME Limit	31	17	3	11	49
Opioid Quantity	33	28	1	4	153
Other*	69	54	5	10	16
Quantity vs. Days Supply	603	411	33	159	250
STBS/STBSM	26	20	0	6	69
Stolen	20	15	0	5	12
Third Brand Request	26	19	0	7	67
Overrides Total	**1,813**	**1,384**	**81**	**348**	
Total Regular PAs + Overrides	**9,554**	**4,346**	**1,409**	**3,799**	

Denial Reasons	
Unable to verify required trials.	3,061
Does not meet established criteria.	1,428
Lack required information to process request.	707
Other PA Activity	
Duplicate Requests	673
Letters	12,908
No Process	16
Changes to existing PAs	682
Helpdesk Initiated Prior Authorizations	680
PAs Missing Information	32

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

2019 Spring Pipeline Update

Oklahoma Health Care Authority
May 2019

Introduction

The following report is a pipeline review compiled by the University of Oklahoma College of Pharmacy. Information in this report is focused on medications not yet approved by the U.S. Food and Drug Administration (FDA). The pipeline report is not an all-inclusive list, and medications expected to be highly utilized or have a particular impact in the SoonerCare population have been included for review. Pipeline data is collected from a variety of sources and is subject to change; dates listed are projections and all data presented are for informational purposes only. Costs listed in the following report do not reflect rebated prices or net costs.

NKTR-181[1,2,3,4]

Anticipated Indication(s): Orally administered full mu-opioid agonist indicated for the treatment of moderate-to-severe chronic low back pain in opioid-naïve adults

Clinical Trial(s): NKTR-181 was evaluated in a Phase 3 randomized, withdrawal design trial comparing twice-daily dosing of NKTR-181 to placebo in the treatment of over 600 patients with moderate-to-severe chronic low back pain who were opioid-naïve. The primary outcome was the change in weekly pain score at 12 weeks from randomization baseline. Secondary outcomes included responder rates defined by ≥30% and ≥50% improvement in pain score from screening to 12 weeks. The mean pain score decreased from 6.73 to 2.32 during open-label titration. At 12 weeks, the responder rates of ≥30% and ≥50% improvement in pain score occurred in 71.2% and 51.1% of NKTR-181-treated patients, respectively; placebo responder rates of ≥30% and ≥50% were 57.1% and 37.9%, respectively. NKTR-181 was well tolerated with a low incidence (<3%) of central nervous system (CNS)-related adverse events (AEs) during the randomized treatment phase.

Place in Therapy: Pain is the most common reason patients seek medical treatment, and back pain is the second most common reason for disability for adults in the United States. Opioids are commonly used to treat chronic pain, but as the opioid crisis continues, the FDA has encouraged the development of abuse-deterrent and tamper-resistant formulations. NKTR-181 is a first-in-class opioid analgesic that is a full mu-opioid agonist designed to provide potent pain relief without the CNS side effects that can lead to addiction. Studies have shown that the chemical structure of NKTR-181 leads to a lower rate of absorption across the blood-brain barrier.

Projected FDA Decision: May 28, 2019

SoonerCare Impact: During calendar year 2018, a total of 34,257 SoonerCare members had at least 1 submitted diagnosis for low back pain. A total of 89,543 members had a paid pharmacy claim for narcotic analgesics in calendar 2018, accounting for 316,930 claims totaling $17,789,766.81 in drug spending and an average cost per claim of $56.31.

Bronchitol® (Mannitol)[1,5,6,7,8,9,10]

Anticipated Indication(s): Spray-dried formulation of mannitol for inhalation for the treatment of cystic fibrosis (CF) in adults

Clinical Trial(s): Bronchitol® was evaluated in an international, 26-week, randomized, double-blind, parallel-group Phase 3 trial. The study assessed improvements in lung function and other parameters in 423 adults with CF who received mannitol 400mg or mannitol 50mg (subtherapeutic dose) twice daily. At week 26, there was a significant improvement in forced expiratory volume (FEV_1) for the mannitol treatment group compared to the subtherapeutic mannitol group [change from baseline 118.9mL (6.5%) vs. 26.0mL (2.4%), respectively; P<0.001].

Place in Therapy: More than 30,000 people are living with CF in the United States with approximately 1,000 new cases of CF diagnosed each year. Current CF treatments include targeting the defective protein, thinning of mucus, opening airways, and treatment of secondary lung infections. Mannitol works by rehydrating the airways and promoting a productive cough. Clinical trials have shown that mannitol helps to increase mucus clearance and improve the lung function of people living with CF. Bronchitol® is currently approved in Australia, the United Kingdom, and several other countries.

Projected FDA Decision: June 20, 2019

SoonerCare Impact: During calendar year 2018, a total of 58 adult members had at least 1 submitted diagnosis of CF.

Vyndaqel® (Tafamidis)[1,11,12,13,14,15,16]

Anticipated Indication(s): Orally administered amyloid fibril inhibitor for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM)

Clinical Trial(s): The efficacy, safety, and tolerability of oral tafamidis 20mg and 80mg were evaluated in a Phase 3 international, multicenter, double-blind, placebo-controlled, randomized, 3-arm clinical study in 441 patients with ATTR-CM. The study included both patients with the hereditary form of the disease and the wild-type form. The primary analysis assessed all-cause mortality. Key secondary end-points were the change from baseline to month 30 for the 6-minute walk test (6-MWT) and the score on the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS), with higher scores indicating better health status. Tafamidis was associated with lower all-cause mortality compared to placebo [29.5% vs. 42.9%; hazard ratio (HR), 0.70]. At month 30, tafamidis was also associated with a lower rate of decline in distance for the 6-MWT (P<0.001) and a lower rate of decline in

the KCCQ-OS score (P<0.001). The incidence and types of AEs were similar between the treatment and placebo groups.

Place in Therapy: ATTR-CM is a late-onset disease, with symptoms predominately manifesting in male patients 60 years of age or older. Transthyretin amyloidosis can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene *TTR* (ATTRm) or caused by the deposition of wild-type transthyretin protein (ATTRwt). The incidence of ATTRm in the United States is estimated to be 1:100,000 individuals. The prevalence of ATTRwt is uncertain, but studies have estimated a prevalence of 13% among patients with preserved ejection fraction heart failure (HFpEF). Treatment options for patients with ATTR-CM include treatment of heart failure symptoms and treatment of the underlying disease. If approved, tafamidis would be the first FDA approved treatment targeted at treating ATTR-CM. Vandaqel® was approved in the European Union for the treatment of transthyretin amyloid polyneuropathy in 2011.

Projected FDA Decision: July 1, 2019

SoonerCare Impact: During calendar year 2018, a total of 34 members had at least 1 submitted diagnosis of amyloidosis. A new diagnosis code was created in October 2018 for ATTRwt. SoonerCare does not currently have any members with a submitted diagnosis of ATTRwt.

Lefamulin[1,17,18,19,20,21,22,23]

Anticipated Indication(s): Intravenous (IV) and oral (PO) pleuromutilin antibiotic for the treatment of community-acquired bacterial pneumonia (CABP)

Clinical Trial(s): Lefamulin was evaluated in 2 Phase 3 studies (LEAP 1 and LEAP 2). In the LEAP 1 trial, 551 patients were randomized 1:1 to lefamulin 150mg IV every 12 hours or moxifloxacin 400mg IV every 24 hours. After 6 doses, patients could be switched to a PO study drug if they met pre-specified improvement criteria. The LEAP 2 trial included 738 patients with CABP, randomized 1:1 to receive lefamulin 600mg PO every 12 hours for 5 days or moxifloxacin 400mg PO every 24 hours for 7 days. The primary endpoint was early clinical response (ECR) after the first dose. Lefamulin was noninferior to moxifloxacin for ECR (87.3% vs. 90.2%, respectively) in LEAP 1; similar results were seen in LEAP 2.

Place in Therapy: Community acquired pneumonia (CAP) is a leading cause of morbidity and mortality worldwide. In the United States, CAP accounts for over 4.5 million outpatient and emergency department visits annually. Approximately 650 adults are hospitalized with CAP every year per 100,000 population. CAP is most commonly caused by a bacterial infection. Choice of treatment for CABP depends on antimicrobial resistance and risk factors. *Streptococcus pneumoniae (S. pneumoniae)*, the most common bacterial pathogen that causes CABP, may be resistant to 1 or more of the commonly used antibiotics. Lefamulin displays activity against gram-positive and atypical organisms associated with CABP including *S. pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydophila pneumoniae*. If approved, lefamulin would be the first PO or IV pleuromutilin antibiotic approved for the monotherapy treatment of CABP.

Projected FDA Decision: August 20, 2019

SoonerCare Impact: During calendar year 2018, a total of 408 members had at least 1 submitted diagnosis of pneumonia due to *S. pneumoniae* or a diagnosis of pneumonia due to *Haemophilus influenzae*, 2 of the most common pathogens in CABP. A total of 89,307 members had paid claims for doxycycline, azithromycin, or clarithromycin, which are commonly used to treat CABP, during calendar year 2018, accounting for 119,924 claims totaling $2,255,583.58 in drug spending and an average cost per claim of $25.26.

Lumateperone[1,24,25,26,27,28,29]

Anticipated Indication(s): Orally administered antipsychotic that provides selective and simultaneous modulation of serotonin, dopamine, and glutamate for the treatment of schizophrenia

Clinical Trial(s): Lumateperone was evaluated in 3 large, randomized, double-blind, placebo-controlled trials of 1,481 patients. The primary outcome of all 3 studies was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score compared to placebo. In 2 of the randomized studies, lumateperone met the primary endpoint of a statistically significant improvement in the PANSS score compared to placebo (P=0.017 and P=0.022). In the third study, there was a high placebo effect and the study failed to reach statistical significance. Across all 3 efficacy trials, lumateperone improved symptoms of schizophrenia with the same trajectory and same magnitude of improvement from baseline to endpoint in the PANSS total score. Lumateperone was well-tolerated with a favorable safety profile in all studies.

Place in Therapy: Schizophrenia is among the most disabling and economically catastrophic medical disorders, ranked by the World Health Organization as 1 of the top 10 illnesses contributing to the global burden of disease. The prevalence of schizophrenia is nearly 1% worldwide with an incidence of 1.5 per 10,000 people. Lumateperone modulates the activity of 3 neurotransmitter pathways implicated in severe mental illness. Comorbid depression can occur in 23 to 57% of patients with schizophrenia, and long-term study data has shown that lumateperone treatment was associated with a decrease in depression symptoms in schizophrenic patients.

Projected FDA Decision: September 27, 2019

SoonerCare Impact: During calendar year 2018, a total of 7,195 members had at least 1 submitted diagnosis of schizophrenia. A total of 17,309 members had paid claims for atypical antipsychotics during calendar year 2018, accounting for 112,685 claims totaling $17,157,139.76 in drug spending and an average cost per claim of $152.26.

Pipeline Table[1,2,30]

Medication Name*	Manufacturer	Therapeutic Use	Route of Admin	Approval Status	Anticipated FDA Response
amisulpride	Acacia	Nausea/vomiting	IV	Filed NDA	05/05/2019

Medication Name*	Manufacturer	Therapeutic Use	Route of Admin	Approval Status	Anticipated FDA Response
Slinda® (drospirenone)	Exeltis	Pregnancy prevention	PO	Filed NDA	05/27/2019
NKTR-181	Nektar	Chronic low back pain	PO	Filed NDA	05/28/2019
Bronchitol® (mannitol)	Pharmaxis	Asthma/cystic fibrosis	INH	Filed NDA	06/20/2019
Edsivo™ (celiprolol HCl)	Acer Therapeutics	vEDS	PO	Filed NDA	06/25/2019
fosfomycin	Nabriva	Complicated UTI	IV	Filed NDA	06/30/2019
Thiola® (tiopronin)	Retrophin	Cystinuria	PO	Filed NDA	06/30/2019
Ryplazim™ (human plasminogen)	ProMetic/ Hematech	Plasminogen deficiency	IV	Filed BLA	Mid-2019
kleptose	Sucampo/INDPA	Niemann-Pick disease	Intracerebral/ intrathecal	FastTrk/ Breakthru	2H2019
Vyndaqel® (tafamidis)	Pfizer	Amyloid cardiomyopathy/ familial amyloid polyneuropathy/ cardiomyopathy	PO	Filed NDA	07/01/2019
Doptelet® (avatrombopag)	Dova	ITP	PO	Filed sNDA	07/04/2019
Scenesse® (afamelanotide)	Clinuvel	Erythropoietic protoporphyria/ polymorphous light eruption/vitiligo	SC	Filed NDA	07/08/2019
riluzole	Portage/Biohaven/ Catalent	ALS/migraines/ social anxiety disorder	SL/ transmucosal	Filed NDA	07/15/2019
relebactam/imipenem/ cilastatin	Merck	Bacterial infections	IV	Filed NDA	07/16/2019
Feraccru® (ferric trimaltol)	Shield Therapeutics	Anemia/IBD	PO	Filed NDA	07/23/2019
Fintepla® (fenfluramine)	Zogenix	Dravet syndrome/LGS	PO	Filed NDA	08/06/2019
loteprednol etabonate	Kala	Dry eyes	OP	Filed NDA	08/15/2019
Hetlioz® (tasimelteon)	Vanda	Jet lag disorder	PO	Filed sNDA	08/16/2019
lefamulin	Nabriva Therapeutics	Bacterial infections	IV/PO	Filed NDA	08/20/2019
golodirsen	Sarepta	DMD	IV	Filed NDA	08/20/2019
AR-101	Aimmune/ Regeneron/Sanofi	Peanut allergy	PO	Filed BLA	08/21/2019
tenapanor	Ardelyx	IBS/ hyperphosphatemia	PO	Filed NDA	09/13/2019
lumateperone	Intra-Cellular Therapies/Bristol-Myers Squibb	Schizophrenia/ bipolar disorder/AD	PO	Filed NDA	09/27/2019
teriparatide	Pfenex/Alvogen	Osteoporosis	SC	Filed NDA	10/01/2019
Xarelto® (rivaroxaban)	Janssen	VTE prevention in medically ill patients	PO	Filed sNDA	10/14/2019

Medication Name*	Manufacturer	Therapeutic Use	Route of Admin	Approval Status	Anticipated FDA Response
Zilretta® (triamcinolone ER)	Flexion	OA of the knee (repeat dosing)	Intra-articular	Filed sNDA	10/17/2019
monomethyl fumarate (diroximel fumarate)	Biogen/Alkermes	MS	PO	Filed NDA	10/17/2019
cosyntropin	Assertio	Adrenocortical insufficiency	INJ	Filed NDA	10/18/2019
triamcinolone acetonide	Clearside	Macular edema	IO/subretinal	Filed NDA	10/19/2019
minocycline	Foamix	Acne vulgaris/ rosacea	TOP	Filed NDA	10/21/2019
naloxone	Adamis	Opioid dependence	IM	Filed NDA	10/31/2019
Emflaza® (deflazacort)	PTC Therapeutics	DMD (ages 2-5 years)	PO	Filed sNDA	Oct-Nov 2019
methotrexate	Cumberland	Psoriasis/arthritis	SC	Filed NDA	11/01/2019
lasmiditan	CoLucid/Ill dong/Eli Lilly	Acute migraines	PO	Filed NDA	11/14/2019
cenobamate	SK Biopharmaceuticals	Seizure	PO	Filed NDA	11/21/2019
upadacitinib	AbbVie	RA/PsA/CD/atopic dermatitis	PO	Filed NDA	12/20/2019
eflapegrastim	Spectrum/Hanmi	Neutropenia	SC	Filed BLA	12/27/2019
lemborexant	Eisai/Purdue	Insomnia/sleep-wake rhythm disorder	PO	Filed NDA	12/27/2019
CM-AT	Curemark	Autism	PO	FastTrk/ Breakthru	Late 2019

NDA = New Drug Application; BLA = Biologics License Application; FastTrk/Breakthru = Fast Track/Breakthrough Therapy designation; sBLA = supplemental Biologics License Application; sNDA = supplemental New Drug Application; Admin = administration; IV = intravenous; INJ = injection; PO = oral; OP = ophthalmic; SL = sublingual; SC = subcutaneous; IM = intramuscular; IO = intraocular; INH = inhaled; TOP = topical; HCl = hydrochloride; vEDS = vascular Ehlers-Danlos Syndrome; UTI = urinary tract infection; ITP = idiopathic thrombocytopenic purpura; ALS = amyotrophic lateral sclerosis; IBD = inflammatory bowel disease; IBS = irritable bowel syndrome; LGS = Lennox-Gastaut syndrome; DMD = Duchenne muscular dystrophy; AD = Alzheimer's disease; VTE = venous thromboembolism; ER = extended-release; OA = osteoarthritis; MS = multiple sclerosis; RA = rheumatoid arthritis; PsA = psoriatic arthritis; CD = Crohn's disease; 2H2019 = second half of 2019
*Most biosimilars and oncology medications excluded from table. Medications known to have received a Complete Response Letter (CRL) from the FDA that have not resubmitted were also excluded.

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Appendix C

Calendar Year 2018 Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize Plenvu® [Polyethylene Glycol (PEG)-3350/Sodium Ascorbate/Sodium Sulfate/ Ascorbic Acid/Sodium Chloride/Potassium Chloride]

Oklahoma Health Care Authority
May 2019

Current Prior Authorization Criteria

Clenpiq™, ColPrep™ Kit, OsmoPrep®, Prepopik®, and SUPREP® Approval Criteria:

1. An FDA approved indication for use in cleansing of the colon as a preparation for colonoscopy; and
2. A patient-specific, clinically significant reason other than convenience why the member cannot use other bowel preparation medications available without prior authorization must be provided.
3. If the member requires a low volume polyethylene glycol electrolyte lavage solution, Moviprep® is available without prior authorization. Other medications currently available without a prior authorization include: Colyte®, Gavilyte®, Golytely®, and Trilyte®.

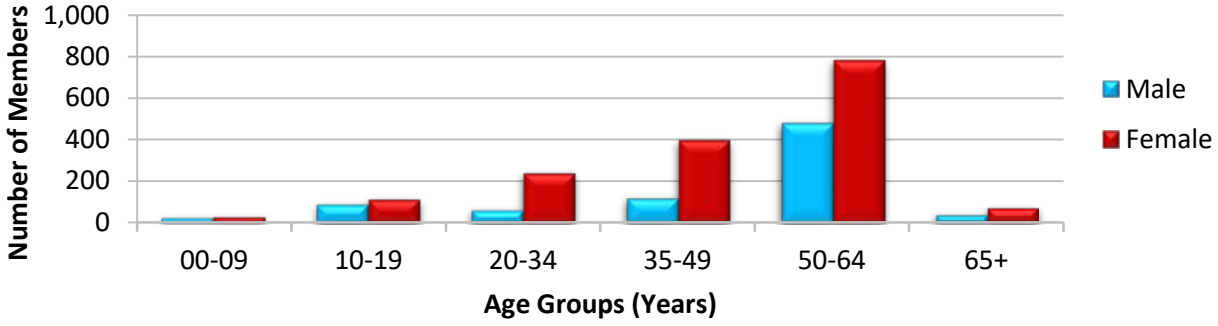
Utilization of Bowel Preparation Medications: Calendar Year 2018

Comparison of Calendar Years

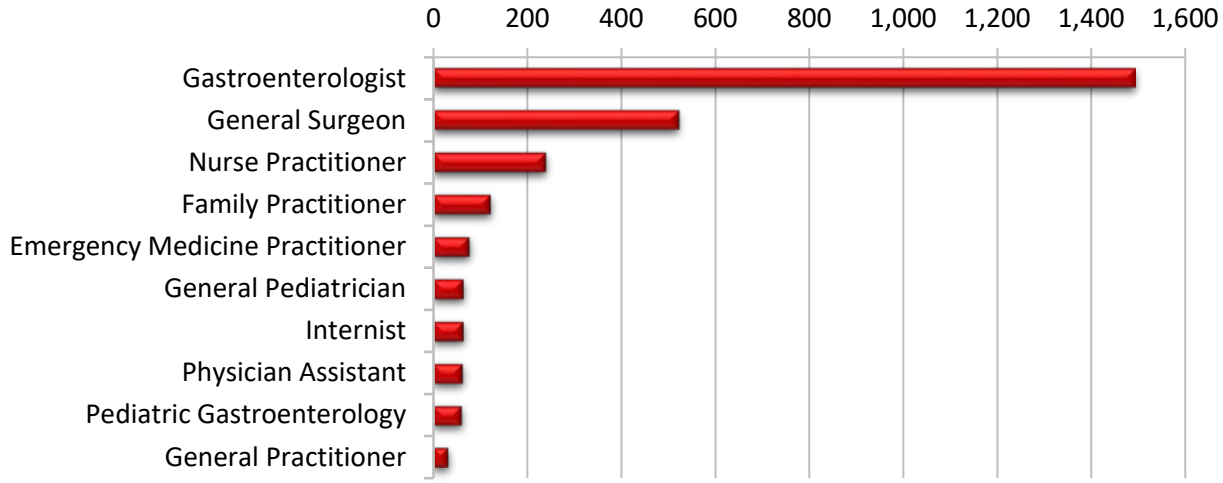
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	2,630	2,915	$87,435.58	$30.00	$9.57	10,096,079	9,139
2018	2,449	2,795	$87,887.99	$31.44	$11.49	9,416,687	7,646
% Change	**-6.90%**	**-4.10%**	**0.50%**	**4.80%**	**20.10%**	**-6.70%**	**-16.30%**
Change	**-181**	**-120**	**$452.41**	**$1.44**	**$1.92**	**-679,392**	**-1,493**

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

Demographics of Members Utilizing Bowel Preparation Medications



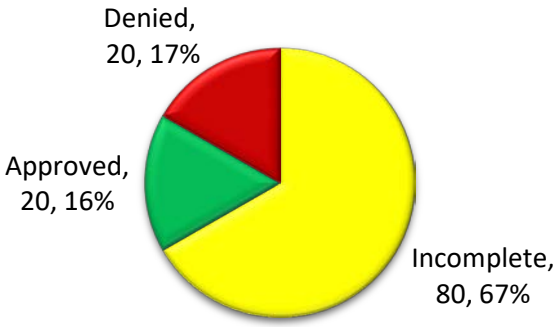
Top Prescriber Specialties of Bowel Preparation Medications by Number of Claims



Prior Authorization of Bowel Preparation Medications

There were 120 prior authorization requests submitted for bowel preparation medications during calendar year 2018. The following chart shows the status of the submitted petitions for calendar year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Moviprep® [polyethylene glycol (PEG)-3350/sodium sulfate/sodium chloride/potassium chloride/sodium ascorbate/ascorbic acid]: September 2024
- Osmoprep® (sodium phosphate monobasic/sodium phosphate dibasic): June 2028
- Prepopik® (sodium picosulfate/magnesium oxide/anhydrous citric acid): October 2028
- Plenvu® (PEG-3350/sodium ascorbate/sodium sulfate/ascorbic acid/sodium chloride/ potassium chloride): September 2033
- Clenpiq™ (sodium picosulfate/magnesium oxide/anhydrous citric acid): June 2034

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

- **May 2018:** The FDA approved Plenvu® (PEG-3350/sodium ascorbate/sodium sulfate/ ascorbic acid/sodium chloride/potassium chloride) for cleansing of the colon as a preparation for colonoscopy in adults. This is the lowest, total-volume preparation

bowel cleanser available in the United States and is also the only FDA-approved bowel cleanser with same-day morning-of-colonoscopy dosing.

Guideline Update(s):

- **August 2018:** The American Cancer Society (ACS) released an updated guideline for colorectal cancer screening. The new guideline recommends the age for colorectal screenings for average risk people be lowered from 50 to 45 years. The new recommendation is the result of an analysis led by ACS researchers that found that new cases of colorectal cancer are occurring at an increasing rate among younger adults. The new guidelines also included recommendations on how long to continue colorectal screenings and options for screening types. The guideline did not make any recommendations on a preferred screening option, but instead chose to make a general recommendation for screening, allowing the patient the opportunity to select a screening method.

Plenvu® (PEG-3350/Sodium Ascorbate/Sodium Sulfate/Ascorbic Acid/Sodium Chloride/Potassium Chloride) Product Summary[5]

Indication(s): Plenvu® (PEG-3350/sodium ascorbate/sodium sulfate/ascorbic acid/sodium chloride/potassium chloride) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.

Dosing:

- Plenvu® is supplied as a white to yellow powder for reconstitution. Dose 1 contains 100 grams of PEG-3350, 9 grams of sodium sulfate, 2 grams of sodium chloride, and 1 gram of potassium chloride. Dose 2 Pouch A contains 40 grams of PEG-3350, 3.2 grams of sodium chloride, and 1.2 grams of potassium chloride. Dose 2 Pouch B contains 48.11 grams of sodium ascorbate and 7.54 grams of ascorbic acid.
- Plenvu® single-use cartons include a disposable mixing container with lid, patient information, and 3 pouches labeled Dose 1, Dose 2 Pouch A, and Dose 2 Pouch B.
- Two doses of Plenvu® are required for a complete preparation for colonoscopy, using a "2-Day" or "1-Day" dosing regimen.
    - 2-Day Method: The first dose should be administered during the evening before the colonoscopy. The dose should be fully administered over 30 minutes. Following the first dose, the patient should drink an additional 16 ounces over the next 30 minutes. If severe bloating, distention, or abdominal pain occurs following the first dose, the second dose should be delayed until the symptoms resolve. The second dose should be administered the next morning on the day of colonoscopy (approximately 12 hours after the start of the first dose). Following the second dose, the patient should drink at least an additional 16 ounces of clear liquids up to 2 hours before the colonoscopy.
    - 1-Day Method: On the day before the colonoscopy, the patient should consume a light breakfast and lunch and clear broth or plain yogurt for dinner, with nothing consumed after approximately 8:00PM. The first dose should be taken the morning of the day of the colonoscopy (e.g., 3:00 to 7:00AM) over 30 minutes. The patient

should then drink an additional 16 ounces of clear liquids over the next 30 minutes. If severe bloating, distention, or abdominal pain occurs following the first dose, the second dose should be delayed until the symptoms resolve. The second dose should be taken a minimum of 2 hours after the start of dose 1. Following the second dose, the patient should drink an additional 16 ounces of clear liquids over the next 30 minutes. Patients should be instructed to ensure completion of dose 2, including all additional liquids, at least 2 hours before the colonoscopy. The patient can consume additional water or clear liquids up to 2 hours before the colonoscopy.

Contraindication(s):

- Gastrointestinal (GI) obstruction
- Bowel perforation
- Gastric retention
- Ileus
- Toxic megacolon
- Hypersensitivity to any of the ingredients in Plenvu®

Warnings and Precautions:

- Serious Fluid and Electrolyte Abnormalities: Patients should be advised to hydrate adequately before, during, and after the use of Plenvu®. Post-colonoscopy laboratory tests [electrolytes, creatinine, and blood urea nitrogen (BUN)] should be considered if a patient develops significant vomiting or signs of dehydration after taking Plenvu®. Bowel preparations can cause fluid and electrolyte disturbances, which can lead to serious adverse reactions including cardiac arrhythmias, seizures, and renal impairment. Fluid and electrolyte abnormalities should be corrected before treatment with Plenvu®. Plenvu® should be used with caution in patients using concomitant medications that increase the risk of electrolyte abnormalities [e.g., diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)]. Pre-dose and post-colonoscopy laboratory tests (sodium, potassium, calcium, creatinine, and BUN) should be considered in patients receiving these medications concomitantly.
- Cardiac Arrhythmias: There have been rare reports of serious arrhythmias associated with the use of ionic osmotic laxative products for bowel preparation. Caution should be exercised when prescribing Plenvu® for patients at increased risk of arrhythmias [e.g., patients with a history of prolonged QT, uncontrolled arrhythmias, recent myocardial infarction (MI), unstable angina, congestive heart failure (CHF), cardiomyopathy]. Pre-dose and post-colonoscopy electrocardiograms (ECGs) in patients at increased risk of serious cardiac arrhythmias should be considered.
- Seizures: There have been reports of generalized tonic-clonic seizures (GTCS) with the use of bowel preparation products in patients with no prior history of seizures. The seizure cases were associated with electrolyte abnormalities and low serum osmolality.
- Use in Patients with Renal Impairment: Plenvu® should be used with caution in patients with renal impairment or in patients taking concomitant medications that affect renal function [e.g., diuretics, ACE inhibitors, ARBs, or non-steroidal anti-inflammatory drugs

(NSAIDs)]. These patients may be at risk for renal injury. Patients should be advised of the importance of adequate hydration before, during, and after the use of Plenvu®, and consideration should be given to performing pre-dose and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) in these patients.

- Colonic Mucosal Ulceration, Ischemic Colitis, and Ulcerative Colitis: Osmotic laxatives may produce colonic mucosal aphthous ulcerations, and there have been reports of more serious cases of ischemic colitis requiring hospitalization. Concurrent use of additional stimulant laxatives with Plenvu® may increase this risk.
- Use in Patients with Significant GI Disease: If GI obstruction or perforation is suspected, appropriate diagnostic studies should be performed before administering Plenvu® to rule out these conditions.
- Aspiration: Patients with impaired gag reflex are at risk for regurgitation or aspiration during the administration of Plenvu®.
- Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency: Caution should be used in patients with G6PD deficiency, especially G6PD deficiency patients with an active infection, with a history of hemolysis, or who are taking concomitant medications known to precipitate hemolytic reactions due to the presence of sodium ascorbate and ascorbic acid in Plenvu®.
- Risks in Patients with Phenylketonuria (PKU): Each treatment of Plenvu® contains 491mg of phenylalanine, a component of aspartame. Phenylalanine can be harmful to patients with PKU. The combined daily amount of phenylalanine from all sources, including Plenvu®, should be considered before prescribing Plenvu® to a patient with PKU.
- Hypersensitivity Reactions: Plenvu® contains PEG and may cause serious hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and pruritus. Patients should be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should signs and symptoms occur.

Adverse Reactions: The safety of Plenvu® was evaluated in 2 randomized, parallel group, multicenter, investigator-blinded clinical trials. The most common adverse reactions (>2%) in the Plenvu® treatment groups in both trials were nausea, vomiting, dehydration, and abdominal pain/discomfort.

Drug Interactions:

- Drugs That May Increase Risks of Fluid and Electrolyte Abnormalities: Caution should be exercised when prescribing Plenvu® to patients with conditions or who are taking other drugs that increase the risk for fluid and electrolyte disturbances or may increase the risk of renal impairment, seizures, arrhythmias, or QT prolongation in the setting of fluid and electrolyte abnormalities.
- Potential for Reduced Drug Absorption: Plenvu® can reduce the absorption of other co-administered drugs. Oral medications should be administered at least 1 hour before the start of administration of each dose of Plenvu®.
- Stimulant Laxatives: Concurrent use of stimulant laxatives and Plenvu® may increase the risk of mucosal ulceration or ischemic colitis. It is recommended to avoid use of stimulant laxatives while taking Plenvu®.

Use in Specific Populations:

- Pregnancy: There is no data with Plenvu® use in pregnant women to determine a drug-associated risk. Animal studies have not been conducted with Plenvu®.
- Lactation: There are no data on the presence of Plenvu® in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation does not allow for a clear determination of risk to a child during lactation. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Plenvu®.
- Pediatric Use: The safety and effectiveness of Plenvu® in pediatric patients have not been established.
- Geriatric Use: Of the approximately 1,000 patients in clinical trials who utilized Plenvu®, 217 (21%) patients were 65 years of age or older. No overall differences in safety or effectiveness were observed between geriatric patients and younger patients.
- Renal Impairment: Caution should be used in patients with renal impairment or in patients taking concomitant medications that may affect renal function when using Plenvu®. These patients may be at risk for renal injury. Patients should be advised of the importance of adequate hydration before, during, and after the use of Plenvu®, and baseline and post-colonoscopy laboratory tests (electrolytes, creatinine, and BUN) should be considered in these patients.

Efficacy: The colon cleansing efficacy, safety, and tolerability of Plenvu® were evaluated in 2 randomized, parallel-group, multicenter, investigator-blinded trials in adult patients scheduled to undergo a screening, surveillance, or diagnostic colonoscopy. The primary efficacy endpoint in both trials was the proportion of patients achieving "overall bowel cleansing success," which was defined by a result of Grade A or B [Grades A or B correspond to full visualization of the bowel mucosa on the Harefield Cleansing Scale (HCS)], as assessed on withdrawal of the colonoscope. Trial 1 compared the 2-day split-dosing regimen of Plenvu® with a trisulfate bowel cleansing solution. The 2-day split-dosing regimen of Plenvu® was shown to be non-inferior (NI) to the trisulfate solution comparator. Trial 2 compared the 2-day split-dosing and the 1-day morning dosing to a 2L PEG + electrolyte preparation. Both the Plenvu® 2-day split-dosing regimen and the Plenvu® 1-day morning dosing regimen were shown to be NI to the 2L PEG + electrolyte treatment comparator.

Cost Comparison:

Medication	Cost per Course of Therapy
Plenvu® (PEG-3350/sodium ascorbate/sodium sulfate/ascorbic acid/ sodium chloride/potassium chloride)	**$105.51**
Clenpiq™ (sodium picosulfate/magnesium oxide/anhydrous citric acid)	$131.08
Moviprep® (PEG-3350/sodium sulfate/sodium chloride/potassium chloride/ sodium ascorbate/ascorbic acid)	$101.24
PEG-3350/sodium sulfate/sodium bicarbonate/sodium chloride/potassium chloride (generic Gavilyte®-G)	$11.32

PEG-3350 = polyethylene glycol 3350

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

Recommendations

The College of Pharmacy recommends the prior authorization of Plenvu® (PEG-3350/sodium ascorbate/sodium sulfate/ascorbic acid/sodium chloride/potassium chloride) with criteria similar to the other prior authorized bowel preparation medications:

Clenpiq™, ColPrep™ Kit, OsmoPrep®, Plenvu®, Prepopik®, and SUPREP® Approval Criteria:

1. An FDA approved indication for use in cleansing of the colon as a preparation for colonoscopy; and
2. A patient-specific, clinically significant reason other than convenience why the member cannot use other bowel preparation medications available without prior authorization must be provided.
3. If the member requires a low volume polyethylene glycol electrolyte lavage solution, Moviprep® is available without prior authorization. Other medications currently available without a prior authorization include: Colyte®, Gavilyte®, Golytely®, and Trilyte®.

Utilization Details of Bowel Preparation Medications: Calendar Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
POLYETHYLENE GLYCOL ELECTROLYTE SOLUTION PRODUCTS					
GAVILYTE-G SOL	1,205	1,024	$22,663.76	1.18	$18.81
MOVIPREP SOL	413	401	$42,485.75	1.03	$102.87
PEG-3350/KCL SOL/SODIUM	385	362	$7,069.78	1.06	$18.36
PEG-3350 SOL ELECTROL	314	294	$4,716.62	1.07	$15.02
GAVILYTE-N SOL FLAV PK	162	150	$3,464.95	1.08	$21.39
PEG-3350 SOL ELECTROL	147	129	$2,807.12	1.14	$19.10
GAVILYTE-C SOL	114	105	$1,953.82	1.09	$17.14
GOLYTELY SOL	28	28	$558.54	1	$19.95
TRILYTE SOL	13	13	$297.67	1	$22.90
SUBTOTAL	**2,781**	**2,506**	**$86,018.01**	**1.11**	**$30.93**
SODIUM SULFATE SOLUTION PRODUCTS					
SUPREP BOWEL SOL PREP KIT	8	8	$761.66	1	$95.21
SUBTOTAL	**8**	**8**	**$761.66**	**1**	**$95.21**
SODIUM PHOSPHATE TABLET PRODUCTS					
OSMOPREP TAB 1.5GM	4	4	$847.02	1	$211.76
SUBTOTAL	**4**	**4**	**$847.02**	**1**	**$211.76**
SODIUM PICOSULFATE SOLUTION PRODUCTS					
PREPOPIK PAK	2	2	$261.30	1	$130.65
SUBTOTAL	**2**	**2**	**$261.30**	**1**	**$130.65**
TOTAL	**2,795**	**2,449***	**$87,887.99**	**1.14**	**$31.44**

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

[1] U.S. Food and Drug Administration (FDA): Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 03/2019. Last accessed 04/08/2019.

[2] Salix Pharmaceuticals, Ltd. Salix Receives FDA Approval For PLENVU®, Next Generation 1-Liter Bowel Cleansing Preparation For Colonoscopies. *PR Newswire*. Available online at: https://ir.bauschhealth.com/news-releases/2018/05-07-2018-115934867. Issued 05/07/2018. Last accessed 04/08/2019.

[3] Salix Pharmaceuticals, Ltd. Salix Announces U.S. Launch of PLENVU®, the First and Only 1-Liter PEG Bowel Cleansing Preparation for Colonoscopies. *PR Newswire*. Available online at: https://www.prnewswire.com/news-releases/salix-announces-us-launch-of-plenvu-the-first-and-only-1-liter-peg-bowel-cleansing-preparation-for-colonoscopies-300709082.html. Issued 09/11/2018. Last accessed 04/08/2019.

[4] Wolf AM, Fontham ET, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA: A Cancer Journal for Clinicians* 2018; 68(4):250-281.

[5] Plenvu® (polyethylene glycol 3350/sodium ascorbate/sodium sulfate/ascorbic acid/sodium chloride/potassium chloride) Prescribing Information. Salix Pharmaceuticals, Ltd. Available online at: https://shared.salix.com/shared/pi/plenvu-pi.pdf. Last revised 05/2018. Last accessed 04/08/2019.

Appendix D

Calendar Year 2018 Annual Review of Ophthalmic Anti-Inflammatories and 30-Day Notice to Prior Authorize Dextenza® (Dexamethasone Ophthalmic Insert), Inveltys™ (Loteprednol Etabonate Suspension), Lotemax® SM (Loteprednol Etabonate Gel), and Oxervate™ (Cenegermin-bkbj)

Oklahoma Health Care Authority
May 2019

Current Prior Authorization Criteria

Ophthalmic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	
Tier-1	**Tier-2**
diclofenac (Voltaren®) 0.1% soln	bromfenac (Bromday®) 0.09% soln
flurbiprofen (Ocufen®) 0.03% soln$^{\Delta}$	bromfenac (BromSite™) 0.075% soln
ketorolac (Acular®) 0.5% soln	bromfenac (Prolensa®) 0.07% soln
nepafenac (Ilevro®) 0.3% susp	ketorolac (Acular LS®) 0.4% soln
	ketorolac (Acuvail®) 0.45% soln
	nepafenac (Nevanac®) 0.1% susp

soln = solution; susp = suspension
$^{\Delta}$ Not a required Tier-1 trial; does not have to be attempted for approval of a Tier-2 medication.
Tier structure based on supplemental rebate participation, and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Ophthalmic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) Tier-2 Approval Criteria:

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

Ophthalmic Corticosteroids	
Tier-1	**Tier-2**
dexamethasone (Maxidex®) 0.1% susp	fluorometholone (FML Forte®) 0.25% susp
dexamethasone sodium phosphate 0.1% soln	fluorometholone (FML S.O.P®) 0.1% oint
difluprednate (Durezol®) 0.05% emul	loteprednol (Lotemax®) 0.5% gel
fluorometholone (Flarex®) 0.1% susp	loteprednol (Lotemax®) 0.5% oint
fluorometholone (FML Liquifilm®) 0.1% susp	prednisolone acetate (Pred Forte®) 1% susp
loteprednol (Lotemax®) 0.5% susp	
prednisolone acetate (Omnipred®) 1% susp	
prednisolone acetate (Pred Mild®) 0.12% susp	
prednisolone sodium phosphate 1% soln	

soln = solution; susp = suspension; emul = emulsion; oint = ointment
Tier structure based on supplemental rebate participation, and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Ophthalmic Corticosteroids Tier-2 Approval Criteria:

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

Utilization of Ophthalmic Anti-Inflammatories: Calendar Year 2018

Comparison of Calendar Years: Ophthalmic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	580	740	$12,458.37	$16.84	$0.78	4,016	15,940
2018	541	733	$41,555.04	$56.69	$2.30	3,712	18,031
% Change	**-6.70%**	**-0.90%**	**233.60%**	**236.60%**	**194.90%**	**-7.60%**	**13.10%**
Change	**-39**	**-7**	**$29,096.67**	**$39.85**	**$1.52**	**-304**	**2,091**

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

- Some Tier-1 products participate in supplemental rebates; therefore, costs shown do not reflect net costs.

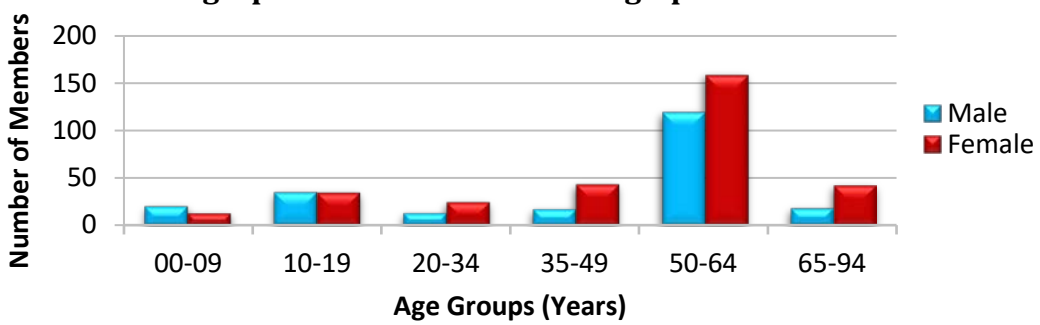
Comparison of Calendar Years: Ophthalmic Corticosteroids

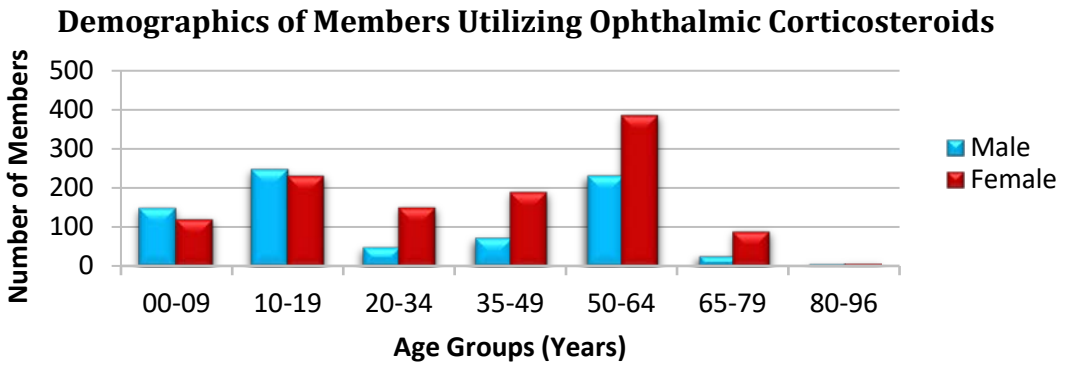
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	2,089	3,019	$272,898.92	$90.39	$3.54	20,813	77,061
2018	1,966	2,919	$246,791.99	$84.55	$3.26	19,557	75,614
% Change	**-5.90%**	**-3.30%**	**-9.60%**	**-6.50%**	**-7.90%**	**-6.00%**	**-1.90%**
Change	**-123**	**-100**	**-$26,106.93**	**-$5.84**	**-$0.28**	**-1,256**	**-1,447**

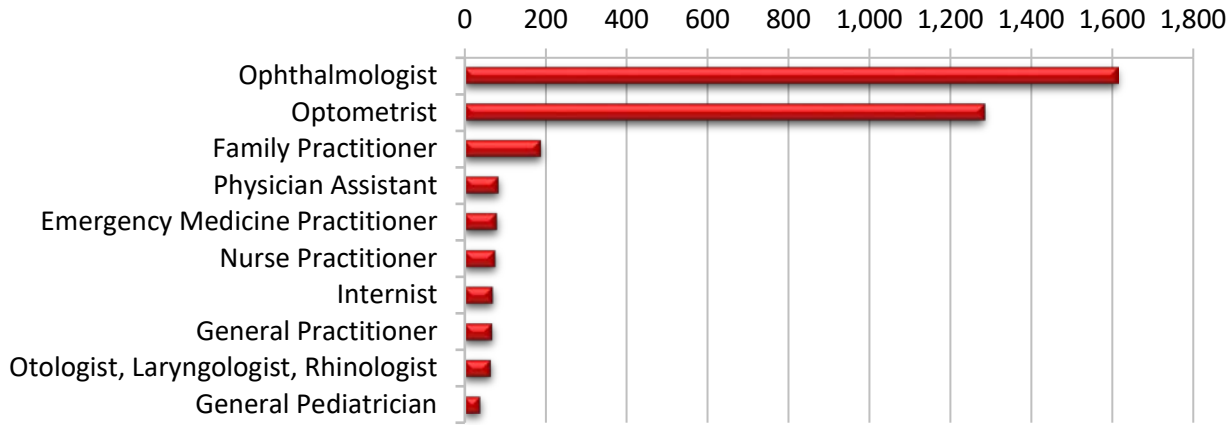
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- Some Tier-1 products participate in supplemental rebates; therefore, costs shown do not reflect net costs.

Demographics of Members Utilizing Ophthalmic NSAIDs

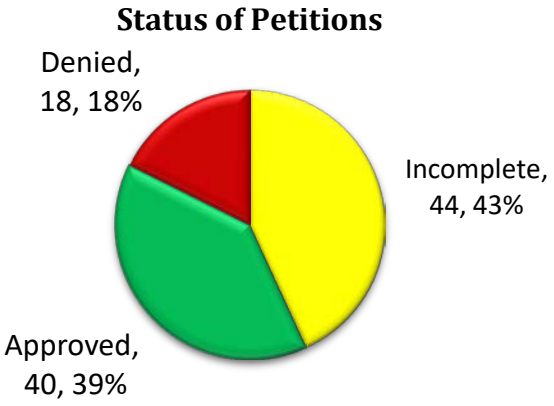






Prior Authorization of Ophthalmic Anti-Inflammatories

There were 102 prior authorization requests submitted for ophthalmic anti-inflammatories during calendar year 2018. The following chart shows the status of the submitted petitions for calendar year 2018.



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

Anticipated Patent Expiration(s):

- Durezol® (difluprednate 0.05%): November 2019
- Nevanac® (nepafenac 0.1%): January 2027

- Acular LS® (ketorolac 0.4%): November 2027
- Acuvail® (ketorolac 0.45%): August 2029
- BromSite™ (bromfenac 0.075%): August 2029
- Ilevro® (nepafenac 0.3%): March 2032
- Prolensa® (bromfenac 0.07%): November 2033

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

- **August 2018:** Kala Pharmaceuticals announced that the FDA approved Inveltys™ (loteprednol etabonate 1% ophthalmic suspension) for the treatment of postoperative inflammation and pain following ocular surgery. Inveltys™ is the first twice-daily (BID) ocular corticosteroid approved for this indication. All other ocular corticosteroids are approved for four-times-a-day (QID) dosing.
- **August 2018:** Dompé announced that the FDA approved Oxervate™ (cenegermin-bkbj ophthalmic solution), a breakthrough therapy for neurotrophic keratitis (NK), a rare and progressive eye disease that can lead to corneal scarring and vision loss. Oxervate™ is the first-ever application of a human nerve growth factor as drug or treatment and is the first-ever topical biologic medication approved in ophthalmology.
- **November 2018:** Ocular Therapeutix, Inc. announced that the FDA approved Dextenza® (dexamethasone 0.4mg ophthalmic insert) for intracanalicular use for the treatment of ocular pain following ophthalmic surgery. Dextenza® is the first FDA-approved intracanalicular insert delivering dexamethasone to treat postoperative ocular pain for up to 30 days with a single administration.
- **February 2019:** Bausch + Lomb announced that the FDA approved Lotemax® SM (loteprednol etabonate 0.38% gel), a new gel formulation for the treatment of postoperative inflammation and pain following ocular surgery. Lotemax® SM delivers a submicron particle size for faster drug dissolution in tears and provides 2 times greater penetration to the aqueous humor compared to Lotemax® Gel (loteprednol etabonate 0.5% gel).

Pipeline:

- **December 2018:** Kala Pharmaceuticals, Inc. announced that the New Drug Application (NDA) for KPI-121 (loteprednol etabonate 0.25%) was accepted for review by the FDA. The FDA set a Prescription Drug User Fee Act (PDUFA) target action date of August 15, 2019. If KPI-121 0.25% is approved, it is expected to be the first product indicated for the temporary relief of the signs and symptoms of dry eye disease, which would include treatment of dry eye flares. KPI-121 0.25% utilizes Kala's proprietary AMPPLIFY drug delivery technology to enhance penetration of loteprednol etabonate into target tissues of the eye. The NDA submission was supported by data from 1 Phase 2 and 2 Phase 3 efficacy and safety trials, studying over 2,000 patients with dry eye disease.
- **April 2019:** Ocular Therapeutix announced that the FDA accepted the filing of a supplemental New Drug Application (sNDA) for Dextenza® (dexamethasone ophthalmic insert) to include the treatment of ocular inflammation following ophthalmic surgery in its label. The notice of acceptance confirms the FDA has completed its initial review of the filing and has determined that the sNDA is sufficiently complete to permit formal

review. The FDA has set a PDUFA target action date of November 10, 2019 for review of the sNDA. Dextenza® previously received FDA approval in November 2018 for the treatment of ocular pain following ophthalmic surgery.

Dextenza® (Dexamethasone Ophthalmic Insert) Product Summary[8,9,10]

Indication(s): Dextenza® (dexamethasone ophthalmic insert) is a corticosteroid indicated for the treatment of ocular pain following ophthalmic surgery.

Dosing:

- Dextenza® is supplied as a single-use, sterile, ophthalmic insert contained in a foil laminate pouch in a foam carrier.
- The 3 millimeter, cylindrical-shaped insert releases a 0.4mg dose of dexamethasone for up to 30 days following insertion.
- Dextenza® should be refrigerated at 36 to 46°F (2 to 8°C) in the original container to protect from light.
- Dextenza® is placed in the lower lacrimal punctum and then into the canaliculus by a physician.
- Dextenza® is resorbable and does not require removal. Saline irrigation or manual expression can be performed to remove the insert if necessary.

Contraindication(s): Dextenza® is contraindicated in patients with active corneal, conjunctival or canalicular infections, including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; dacryocystitis; mycobacterial infections; and fungal diseases of the eye.

Efficacy: Dextenza® was studied in 488 adult patients in 2 randomized, multicenter, double-masked, parallel-group, vehicle-controlled Phase 3 clinical trials. Patients were randomized (1:1) to receive Dextenza® or vehicle immediately upon completion of cataract surgery. The coprimary efficacy endpoints were complete absence of anterior chamber cells (a measure of inflammation) at day 14 and complete absence of pain at day 8. Pain was assessed using a numerical rating scale from 0 to 10, where 0 is no pain and 10 is severe pain. Inflammation was measured using slitlamp biomicroscopy; cells and flare were graded from 0 to 4+ indicating 0 to >50 cells in the visualized field. Both primary endpoints were met.

- In Study 1, 80.4% of Dextenza®-treated patients were pain-free at day 8 compared to 43.4% of vehicle-treated patients (P<0.0001). Similarly, a greater proportion of Dextenza®-treated patients had an absence of anterior chamber cells at day 14, 33.1% versus 14.5% (P=0.0018).
- In Study 2, 77.5% of Dextenza®-treated patients were pain-free at day 8 compared to 58.8% of vehicle-treated patients (P=0.025). In this study, 39.4% of Dextenza®-treated patients had an absence of anterior chamber cells at day 14 compared to 31.3% of vehicle-treated patients, which was not statistically significant (P=0.2182).

Cost Comparison:

Medication	Cost Per Unit[+]	Cost Per Treatment, 1 Eye[Δ]	Cost Per Treatment, Both Eyes[Δ]
Dextenza® (dexamethasone 0.4mg ophthalmic insert)	**$538.83**	**$538.83**	**$1,077.66**
dexamethasone sodium phosphate 0.1% solution	$9.16	$137.40	$274.80
prednisolone acetate 1% suspension	$6.27*	$94.05	$188.10

[+]Unit = single Dextenza® insert or milliliter (mL)
*Cost per mL for prednisolone acetate 1% suspension based on average cost per mL of the 3 different available volumes.
[Δ]Cost per treatment based on FDA recommended dosing for disorders of the eye and 1 Dextenza® insert or a 30 day-supply of dexamethasone sodium phosphate 0.1% solution or prednisolone acetate 1% suspension.
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.

Inveltys™ (Loteprednol Etabonate Suspension) Product Summary[11,12]

Indication(s): Inveltys™ (loteprednol etabonate suspension) is a corticosteroid indicated for the treatment of postoperative inflammation and pain following ocular surgery.

Dosing:

- Inveltys™ is a 1% (10mg/mL of loteprednol etabonate) sterile, ophthalmic suspension supplied in a 5mL plastic dropper bottle containing 2.8mL of suspension. Each bottle has a controlled-drop tip and tamper-evident cap.
- Inveltys™ should be stored upright at 59 to 77°F (15 to 25°C).
- After shaking the bottle for 1 to 2 seconds, the recommended dosing is 1 to 2 drops into the affected eye(s) BID beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period.

Contraindication(s): Inveltys™ is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infections; and fungal diseases of the eye.

Efficacy: Inveltys™ was studied in 2 multicenter, randomized, double-masked, parallel-group, vehicle-controlled clinical trials. The studies included 386 adult patients with anterior chamber cells grade 2 or higher (≥6 cells) on the day following routine cataract surgery who were treated with Inveltys™ and 325 adult patients who were treated with placebo (vehicle). Each group was dosed BID for 2 weeks. Primary efficacy endpoints were complete resolution of ocular inflammation and complete resolution of subject-rated ocular pain at days 8 and 15 with no rescue medication before day 15. Both primary endpoints were met in both trials.

- In Study 1, patients were randomized to 1 of 4 treatment arms in a 2:2:1:1 ratio: 1) KPI-121 0.25% QID, 2) Inveltys™ 1% BID, 3) vehicle A QID, and 4) vehicle B BID. Regimens were administered to 1 eye for 2 weeks. The 2 vehicle groups in Study 1 were pooled for all analyses of Study 1 findings because preliminary analyses illustrated no statistically significant differences between the 2 vehicle groups for the primary efficacy endpoints. Data from the KPI-121 0.25% QID group was not provided as the purpose of the studies was to evaluate Inveltys™ 1% BID compared with vehicle. Complete resolution of

anterior chamber cells was demonstrated in 31.2% of patients in the Inveltys™ 1% BID group, compared with 15.1% of patients in the pooled vehicle group (P<0.0024) at day 8 and maintained through day 15 with no rescue medication prior to day 15. Complete resolution of ocular pain was demonstrated in 53.6% of patients in the Inveltys™ 1% BID group, compared with 34.1% of patients in the pooled vehicle group (P=0.0019) at day 8 and maintained through day 15 with no rescue medication prior to day 15.

- In Study 2, the safety and efficacy of Inveltys™ 1% BID compared with vehicle BID administered to 1 eye for 2 weeks were evaluated. In Study 2, complete resolution of anterior chamber cells was demonstrated in 20.7% of patients in the Inveltys™ 1% BID group, compared with 12.4% of patients in the vehicle BID group (P=0.0105) at day 8 and maintained through day 15 with no rescue medication prior to day 15. Complete resolution of ocular pain was demonstrated in 57.1% of patients in the Inveltys™ 1% BID group, compared with 37.1% of patients in the vehicle BID group (P<0.0001) at day 8 and maintained through day 15 with no rescue medication prior to day 15.

Cost Comparison:

Medication	Cost Per mL	Cost Per Treatment, 1 Eye[Δ]	Cost Per Treatment, Both Eyes[Δ]
Inveltys™ (loteprednol etabonate 1% suspension)	**$80.36**	**$401.80**	**$803.60**
Lotemax® (loteprednol etabonate 0.5% suspension)	$45.55	$455.50	$911.00
prednisolone acetate 1% suspension	$6.27*	$62.70	$125.40

*Cost per mL for prednisolone acetate 1% suspension based on average cost per mL of the 3 different available volumes.
[Δ]Cost per treatment based on FDA recommended dosing for postoperative inflammatory disorder of the eye for 2 weeks following the procedure.
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.

Lotemax® SM (Loteprednol Etabonate Gel) Product Summary[13,14]

Indication(s): Lotemax® SM (loteprednol etabonate gel) is a corticosteroid indicated for the treatment of postoperative inflammation and pain following ocular surgery.

Dosing:

- Lotemax® SM is a 0.38% (3.8mg/mL of loteprednol etabonate) sterile, ophthalmic submicron gel supplied in a 10mL plastic bottle with a controlled-drop tip containing 5 grams of gel.
- Lotemax® SM should be stored upright at 59 to 77°F (15 to 25°C).
- After inverting the closed bottle and shaking once to fill the dropper tip, the recommended dosing is 1 drop into the affected eye(s) 3 times daily (TID) beginning the day after surgery and continuing throughout the first 2 weeks of the postoperative period.

Contraindication(s): Lotemax® SM is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infections; and fungal diseases of the eye.

Efficacy: The efficacy and safety of Lotemax® SM were studied in a randomized, multicenter, double-masked, parallel-group, vehicle-controlled trial. The study included patients 18 years of age or older who underwent cataract extraction with intraocular lens implantation and who had anterior chamber cells grade 2 or higher on day 1 after uncomplicated cataract surgery. The patients were randomized to 14 days of treatment with Lotemax® SM BID, Lotemax® SM TID, or vehicle. The primary endpoints were the proportion of patients with resolution of anterior chamber cells and grade 0 (no) pain at postoperative day 8. There were 352 patients that completed the study. Compared with vehicle, complete resolution of anterior chamber cells on day 8 was significantly greater in patients in the Lotemax® SM BID (P<0.0001) and Lotemax® SM TID (P<0.0001) groups. Similarly, the patients reporting complete resolution of ocular pain (grade 0) in the study eye at day 8 were significantly greater in the Lotemax® SM BID group (P<0.0001) and the Lotemax® SM TID group (P<0.0001) than in the vehicle group. In this study, Lotemax® SM, instilled either 2 or 3 times daily, appeared safe and effective for the treatment of postoperative inflammation and pain after cataract surgery. There were no severe or serious adverse events considered related to treatment, and no patients discontinued Lotemax® SM BID or TID because of a treatment-related adverse event.

Cost Comparison:

Medication	Cost Per Unit[+]	Cost Per Treatment, 1 Eye[Δ]	Cost Per Treatment, Both Eyes[Δ]
Lotemax® SM (loteprednol etabonate 0.38% gel)	**$38.15**	**$190.75**	**$381.50**
Lotemax® (loteprednol etabonate 0.5% gel)	$36.63	$183.15	$366.30
prednisolone acetate 1% suspension	$6.27*	$62.70	$125.40

[+]Unit = gram or mL

*Cost per mL for prednisolone acetate 1% suspension based on average cost per mL of the 3 different available volumes.

[Δ]Cost per treatment based on FDA recommended dosing for postoperative inflammatory disorder of the eye for 2 weeks following the procedure.

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.

Oxervate™ (Cenegermin-bkbj) Product Summary[15,16,17]

Background: Neurotrophic keratitis (NK) is a rare disease that affects <65,000 people in the United States. NK is caused by trigeminal nerve damage resulting in partial or total loss of corneal sensation, leading to visual impairment and potentially permanent blindness. Underlying causes of NK most commonly include herpetic infections and ocular or neurologic surgeries that impair corneal innervation. Disease severity is classified broadly into 3 stages: stage 1 (mild) NK exhibits ocular surface irregularity and reduced vision; stage 2 (moderate) NK exhibits a nonhealing persistent epithelial defect (PED); and stage 3 (severe) NK exhibits corneal ulceration involving subepithelial tissue, which may progress to corneal perforation. All disease stages cause some vision loss; however, if untreated, moderate NK progresses to severe disease with associated risks of profound vision loss. Conventional treatments include artificial tears, antibiotics, and surgical procedures. In August 2018, the FDA approved Oxervate™ (cenegermin-bkbj), the first treatment specifically indicated for NK.

Indication(s): Oxervate™ (cenegermin-bkbj) is a recombinant human nerve growth factor indicated for the treatment of NK.

Dosing:

- Oxervate™ is a 0.002% (20mcg/mL cenegermin-bkbj) sterile, ophthalmic solution in a multiple-dose vial.
- It is supplied in a weekly, insulated carton containing 7 multiple-dose vials and a delivery system kit. The delivery system kit contains 8 vial adapters, 45 pipettes, 45 sterile disinfectant wipes, and a dose card.
- Within 5 hours of leaving the pharmacy, the weekly carton should be refrigerated between 36 to 46°F (2 to 8°C) for up to 14 days. Opened vials may be refrigerated in the original weekly carton between 36 to 46°F (2 to 8°C) or at room temperature up to 77°F (25°C), for up to 12 hours (any unused portion should be discarded after 12 hours).
- The recommended dosing is 1 drop into the affected eye(s), 6 times daily at 2-hour intervals for 8 weeks.

Contraindication(s): None

Efficacy: The efficacy and safety of cenegermin for the treatment of NK were evaluated in (2) 8-week, randomized, multi-center, double-masked, vehicle-controlled studies, NGF0212 and NGF0214. The patients included in each study were ≥18 years of age and diagnosed with stage 2 (PED) or stage 3 (corneal ulceration) disease. Inclusion criteria included evidence of decreased corneal sensitivity within the corneal lesion and 1 or more corneal quadrants outside the lesion and no objective clinical evidence of improvement of the PED or corneal ulcer within 2 weeks before study enrollment. The primary efficacy variable was corneal healing, defined as <0.5mm fluorescein staining (the lower limit of reliable slit-lamp assessment) in the lesion area, assessed in clinical pictures by masked central readers as a yes-or-no binary variable at week 4 (primary end-point) and week 8 (prespecified secondary end-point).

- Study NGF0212: In this study, performed in Europe and published in the journal *Ophthalmology*, patients were randomized to receive cenegermin 10mcg/mL (N=52), cenegermin 20mcg/mL (N=52), or vehicle (N=52) dosed 6 times daily in the affected eye for 8 weeks. In study NGF0212, only patients with unilateral disease were enrolled. Corneal healing was achieved at week 4 in 19.6% of vehicle-treated patients versus 54.9% receiving cenegermin 10mcg/mL (P<0.001) and 58.0% receiving cenegermin 20mcg/mL (P<0.001). Corneal healing at week 8 was achieved in 43.1% of vehicle-treated patients versus 74.5% receiving cenegermin 10mcg/mL (P=0.001) and 74.0% receiving cenegermin 20mcg/mL (P=0.002).
- Study NGF0214: In this study, performed in the United States and presented at the 2017 Congress of the European Society of Ophthalmology, patients were randomized to receive cenegermin 20mcg/mL (N=24) or vehicle (N=24) dosed 6 times daily in the affected eye(s) for 8 weeks. In study NGF0214, patients with bilateral disease were enrolled and treated bilaterally. Results of this study trial are in preparation for publication. Results published in the Oxervate™ prescribing information *Clinical Studies*

section indicate 65.2% of cenegermin-treated patients achieved complete corneal healing at week 8 compared to 16.7% of vehicle-treated patients (P<0.01). Treatment with cenegermin was well tolerated; adverse effects were mostly local, mild, and transient. In patients who were healed after 8 weeks of treatment with cenegermin 20mcg/mL, recurrences occurred in approximately 20% of patients in study NGF0212 and 14% of patients in study NGF0214.

Cost: The Wholesale Acquisition Cost (WAC) of Oxervate™ is $1,685.71 per 1mL vial. This results in a cost per 8-week treatment of $94,399.76 for 1 eye. If both eyes are treated simultaneously, the cost per 8-week treatment is $188,799.52.

Recommendations

The College of Pharmacy recommends the prior authorization of Dextenza® (dexamethasone ophthalmic insert) with the following criteria:

Dextenza® (Dexamethasone Ophthalmic Insert) Approval Criteria:

1. An FDA approved indication of the treatment of ocular pain following ophthalmic surgery; and
2. Prescriber must verify that Dextenza® will be placed by a physician immediately following ophthalmic surgery; and
3. Date of ophthalmic surgery must be provided; and
4. A patient-specific, clinically significant reason why corticosteroid ophthalmic preparations, such as solution or suspension, typically used following ophthalmic surgery are not appropriate for the member must be provided; and
5. A quantity limit of 2 inserts per 30 days will apply.

Additionally, the College of Pharmacy recommends the placement of Inveltys™ (loteprednol etabonate 1% suspension) and Lotemax® SM (loteprednol etabonate 0.38% gel) into Tier-2 of the Ophthalmic Corticosteroids Product Based Prior Authorization (PBPA) category. Current Tier-2 criteria will apply. Recommended changes are shown in red in the following tier chart.

Ophthalmic Corticosteroids	
Tier-1	**Tier-2**
dexamethasone (Maxidex®) 0.1% susp	fluorometholone (FML Forte®) 0.25% susp
dexamethasone sodium phosphate 0.1% soln	fluorometholone (FML S.O.P®) 0.1% oint
difluprednate (Durezol®) 0.05% emul	**loteprednol (Inveltys™) 1% susp**
fluorometholone (Flarex®) 0.1% susp	loteprednol (Lotemax®) 0.5% gel
fluorometholone (FML Liquifilm®) 0.1% susp	loteprednol (Lotemax®) 0.5% oint
loteprednol (Lotemax®) 0.5% susp	**loteprednol (Lotemax® SM) 0.38% gel**
prednisolone acetate (Omnipred®) 1% susp	prednisolone acetate (Pred Forte®) 1% susp
prednisolone acetate (Pred Mild®) 0.12% susp	
prednisolone sodium phosphate 1% soln	

soln = solution; susp = suspension; emul = emulsion; oint = ointment
Tier structure based on supplemental rebate participation, and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Ophthalmic Corticosteroids Tier-2 Approval Criteria:

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

Finally, the College of Pharmacy recommends the prior authorization of Oxervate™ (cenegermin-bkbj) with the following criteria:

Oxervate™ (Cenegermin-bkbj) Approval Criteria:

1. An FDA approved diagnosis of neurotrophic keratitis; and
2. Oxervate® must be prescribed by or in consultation with an ophthalmologist; and
3. Prescriber must verify that the member has persistent epithelial defect (PED) (stage 2 disease) or corneal ulceration (stage 3 disease) of at least 2 weeks duration that is refractory to 1 or more conventional non-surgical treatments for neurotrophic keratitis; and
    a. Specific non-surgical treatments and dates of trials must be listed on the prior authorization request; and
4. Prescriber must verify that the member has evidence of decreased corneal sensitivity within the area of the PED or corneal ulcer and outside of the area of the defect in at least 1 corneal quadrant; and
5. Prescriber must verify the member has been counseled on the proper administration and storage of Oxervate™; and
6. Approvals will be for a maximum duration of 8 weeks of therapy; and
7. A quantity limit of 1 weekly kit per 7 days will apply. A quantity limit override will be approved for 2 weekly kits per 7 days with prescriber documentation of treatment in both eyes.

Utilization Details of Ophthalmic NSAIDs: Calendar Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
KETOROLAC PRODUCTS						
KETOROLAC SOL 0.5%	536	413	$9,256.21	$0.71	$17.27	22.27%
SUBTOTAL	**536**	**413**	**$9,256.21**	**$0.71**	**$17.27**	**22.27%**
NEPAFENAC PRODUCTS						
ILEVRO DROP 0.3%	124	88	$31,114.23	$8.79	$250.92	74.88%
SUBTOTAL	**124**	**88**	**$31,114.23**	**$8.79**	**$250.92**	**74.88%**
DICLOFENAC PRODUCTS						
DICLOFENAC SOL 0.1%	73	54	$1,184.60	$0.80	$16.23	2.85%
SUBTOTAL	**73**	**54**	**$1,184.60**	**$0.80**	**$16.23**	**2.85%**
TOTAL	**733**	**541***	**$41,555.04**	**$2.30**	**$56.69**	**100%**

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

- Some Tier-1 products participate in supplemental rebates; therefore, costs shown do not reflect net costs.

Utilization Details of Ophthalmic Corticosteroids: Calendar Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
TIER-1 MEDICATIONS						
PREDNISOLONE PRODUCTS						
PREDNISOLONE SUS 1%	1,950	1,365	$103,635.69	$2.00	$53.15	41.99%
PRED MILD SUS 0.12%	14	11	$2,048.03	$6.76	$146.29	0.83%
PRED SOD PHO SOL 1%	9	9	$567.96	$1.51	$63.11	0.23%
SUBTOTAL	**1,973**	**1,385**	**$106,251.68**	**$2.02**	**$53.85**	**43.05%**
DIFLUPREDNATE PRODUCTS						
DUREZOL EMU 0.05%	347	210	$61,183.46	$7.29	$176.32	24.79%
SUBTOTAL	**347**	**210**	**$61,183.46**	**$7.29**	**$176.32**	**24.79%**
FLUOROMETHOLONE PRODUCTS						
FLUOROMETH SUS 0.1%	204	152	$17,544.42	$2.93	$86.00	7.11%
FML LIQUIFLM SUS 0.1%	21	19	$3,846.12	$9.99	$183.15	1.56%
FLAREX SUS 0.1%	2	2	$150.96	$6.56	$75.48	0.06%
SUBTOTAL	**227**	**173**	**$21,541.50**	**$3.37**	**$94.90**	**8.73%**
DEXAMETHASONE PRODUCTS						
DEXAMETH PHOS SOL 0.1%	178	148	$10,879.87	$3.78	$61.12	4.41%
MAXIDEX SUS 0.1%	12	9	$1,284.96	$8.86	$107.08	0.52%
SUBTOTAL	**190**	**157**	**$12,164.83**	**$4.02**	**$64.03**	**4.93%**
LOTEPREDNOL PRODUCTS						
LOTEMAX SUS 0.5%	178	123	$44,886.93	$8.61	$252.17	18.19%
SUBTOTAL	**178**	**123**	**$44,886.93**	**$8.61**	**$252.17**	**18.19%**
TIER-1 SUBTOTAL	**2,915**	**2,048**	**$246,028.40**	**$3.26**	**$84.40**	**99.69%**
TIER-2 MEDICATIONS						
LOTEPREDNOL PRODUCTS						
LOTEMAX GEL 0.5%	2	2	$363.20	$5.77	$181.60	0.15%
LOTEMAX OIN 0.5%	1	1	$252.91	$8.43	$252.91	0.10%
SUBTOTAL	**3**	**3**	**$616.11**	**$6.62**	**$205.37**	**0.25%**
FLUOROMETHOLONE PRODUCTS						
FML OIN 0.1%	1	1	$147.48	$4.92	$147.48	0.06%
SUBTOTAL	**1**	**1**	**$147.48**	**$4.92**	**$147.48**	**0.06%**
TIER-2 SUBTOTAL	**4**	**4**	**$763.59**	**$6.21**	**$190.90**	**0.31%**
TOTAL	**2,919**	**1,966***	**$246,791.99**	**$3.26**	**$84.55**	**100%**

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

- Some Tier-1 products participate in supplemental rebates; therefore, costs shown do not reflect net costs.

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Appendix E

Calendar Year 2018 Annual Review of Testosterone Products and 30-Day Notice to Prior Authorize Xyosted™ [Testosterone Enanthate Subcutaneous (Sub-Q) Auto-Injector] and Jatenzo® (Testosterone Undecanoate Oral Capsule)

Oklahoma Health Care Authority
May 2019

Current Prior Authorization Criteria

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

*Tier-1 products include generic injectable products and supplementally rebated topical products.
+Brand name preferred
PA = prior authorization; IM = intramuscular; inj = injection; tab = tablet; cap = capsule

Initial Approval Criteria for All Testosterone Products:

1. An FDA approved diagnosis:
   a. Testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, or orchiectomy; or
   b. Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation; or
   c. Delayed puberty; or
   d. Advanced inoperable metastatic mammary cancer in females 1 to 5 years postmenopausal, or premenopausal females with breast cancer benefitting from oophorectomy and have been determined to have a hormone-responsive tumor; and
2. Must include 2 labs showing pre-medication, morning testosterone (total testosterone) levels <300ng/dL; and
3. Must include 1 lab showing abnormal gonadotropins and/or other information necessary to demonstrate diagnosis; or
4. Testosterone and gonadotropin labs are not required for authorization of testosterone therapy if documentation is provided for established hypothalamic pituitary or gonadal disease, if the pituitary gland or testes has/have been removed, or for postmenopausal

females with advanced inoperable metastatic mammary cancer or premenopausal females with breast cancer benefitting from oophorectomy and that have been determined to have a hormone-responsive tumor.

Testosterone Products Tier-2 Approval Criteria:

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

Testosterone Products Special Prior Authorization (PA) Approval Criteria:

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

Utilization of Testosterone Products: Calendar Year 2018

Comparison of Calendar Years for Testosterone Products: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	133	544	$107,974.05	$198.48	$4.44	19,389	24,314
2018	160	672	$154,097.53	$229.31	$5.22	24,845	29,522
% Change	**20.30%**	**23.50%**	**42.70%**	**15.50%**	**17.60%**	**28.10%**	**21.40%**
Change	**27**	**128**	**$46,123.48**	**$30.83**	**$0.78**	**5,456**	**5,208**

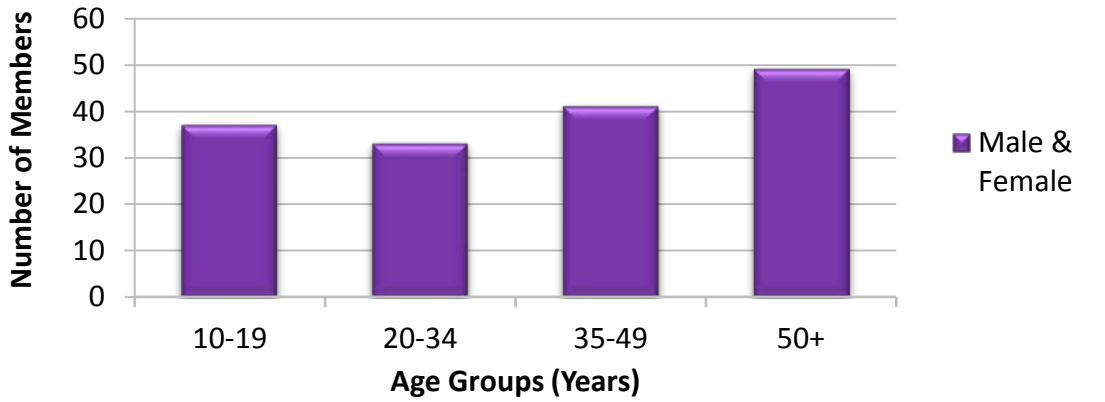
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Calendar Year 2018 Utilization of Testosterone Products: Medical Claims

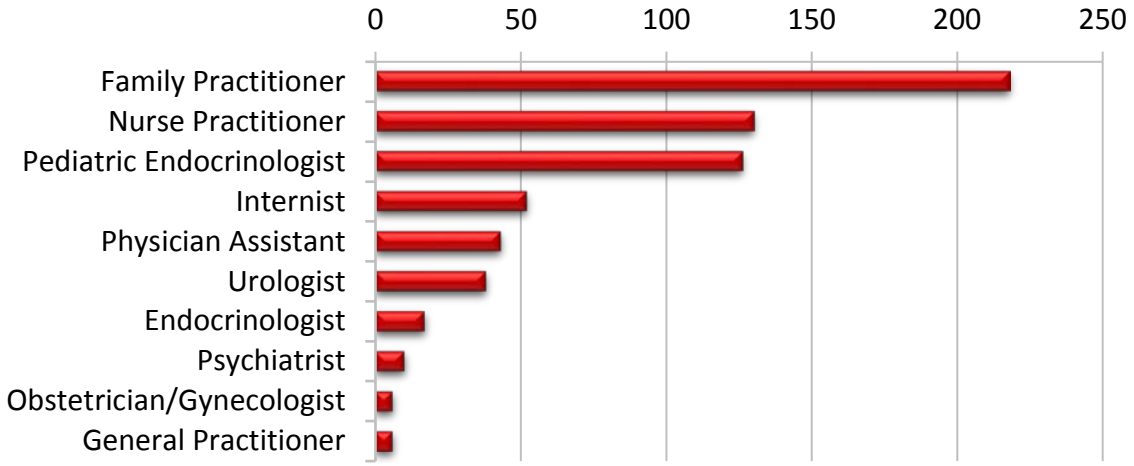
Calendar Year	*Total Members	†Total Claims	Total Cost	Cost/ Claim	Claims/ Member
2018	161	796	$2,890.49	$3.63	4.9

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

Demographics of Members Utilizing Testosterone Products: Pharmacy Claims



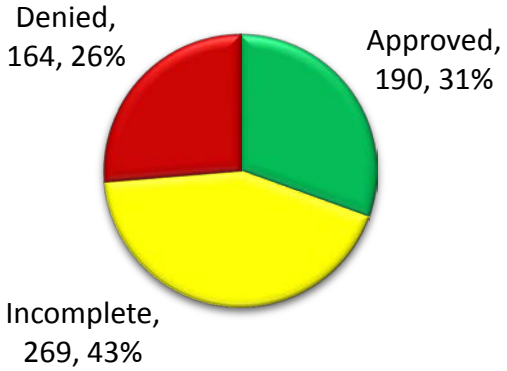
Top Prescriber Specialties of Testosterone Products by Number of Claims: Pharmacy Claims



Prior Authorization of Testosterone Products

There were 623 prior authorization requests submitted for 312 unique members for testosterone products during calendar year 2018. All testosterone products require prior authorization regardless of tier status in order to evaluate diagnosis and submitted labs. The following chart shows the status of the submitted petitions for calendar year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Striant® (testosterone buccal tablet): August 2019
- Natesto® (testosterone nasal gel): February 2024
- Testim® (testosterone topical gel): January 2025
- Aveed® [testosterone undecanoate intramuscular (IM) injection]: March 2027
- Jatenzo® (testosterone undecanoate oral capsule): December 2030
- Vogelxo® (testosterone topical gel): February 2034
- Xyosted™ [testosterone enanthate subcutaneous (sub-Q) auto-injector]: September 2036

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

- **September 2018:** The FDA approved Antares Pharma's Xyosted™ (testosterone enanthate sub-Q auto-injector) for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Xyosted™ is the first FDA-approved sub-Q auto-injector product for testosterone replacement therapy and is intended for once weekly, at-home, self-administration using a single-dose, disposable QuickShot® auto-injector.
- **March 2019:** The FDA approved Clarus Therapeutics' Jatenzo® (testosterone undecanoate oral capsule) for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, such as genetic disorders like Klinefelter syndrome or tumors that have damaged the pituitary gland. Jatenzo® should not be used to treat men with "age-related hypogonadism," in which testosterone levels decline due to aging, even if these men have symptoms that appear to be related to low testosterone, as the benefits of Jatenzo® do not outweigh the risks for that use. An FDA advisory panel previously voted against the approval of Jatenzo® and a similar oral product (Lipocine's Tlando™), citing concerns that ease of use and the potential for cardiovascular (CV) side effects could expose millions to unnecessary risk.

Pipeline:

- **Tlando™:** Lipocine is currently developing Tlando™, an oral testosterone undecanoate product candidate, and announced results from the Ambulatory Blood Pressure Monitoring (ABPM) clinical study in March 2019. The objective of the ABPM study was to characterize blood pressure (BP) effects of Tlando™ for appropriate FDA regulatory action, including Risk Evaluation and Mitigation Strategy (REMS) beyond labeling. Consistent with safety results from 12 previously completed clinical trials, Tlando™ was generally well tolerated in the ABPM study with no drug-related serious adverse events (SAEs), major adverse cardiac events (MACE), or deaths. The President and Chief Executive Officer of Lipocine stated, "We are pleased with the Tlando™ pressor results which we believe are in line with a recently approved testosterone replacement therapy." In April 2019, Lipocine filed a lawsuit against Clarus Therapeutics, alleging that Clarus' Jatenzo® product infringes on 6 of Lipocine's patents.

- **LPCN 1111:** Lipocine is also developing LPCN 1111, a novel, next-generation, oral testosterone therapy product candidate with potential for once daily dosing. LPCN 1111 is a novel ester prodrug of testosterone that uses Lip'ral technology to enhance solubility and improve systemic absorption. Lip'ral is a patented technology based on lipidic compositions which form an optimal dispersed phase in the gastrointestinal environment for improved absorption of an insoluble drug. LPCN 1111 has completed Phase 2 clinical trials and was overall well tolerated with no SAEs reported.

Xyosted™ (Testosterone Enanthate Sub-Q Auto-Injector) Product Summary[8]

Indication(s): Xyosted™ (testosterone enanthate sub-Q auto-injector) is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including:

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins [follicle-stimulating hormone (FSH), luteinizing hormone (LH)] above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins (FSH, LH) in the normal or low range.

Limitations of Use:

- The safety and efficacy of Xyosted™ in adult males with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
- The safety and efficacy of Xyosted™ in males younger than 18 years of age have not been established.

Dosing:

- Prior to initiating Xyosted™, the diagnosis of hypogonadism should be confirmed by ensuring that serum testosterone has been measured in the morning on at least 2 separate days and that these concentrations are below the normal range.
- Xyosted™ is supplied as 0.5mL of sterile solution in a single-dose auto-injector for sub-Q administration in 3 strengths: 50mg/0.5mL, 75mg/0.5mL, and 100mg/0.5mL. Xyosted™ should be stored at controlled room temperature (68 to 77°F).
- The recommended starting dose of Xyosted™ is 75mg administered sub-Q in the abdominal region once weekly. IM and intravascular administration should be avoided.
- Total testosterone trough concentrations should be obtained (measured 7 days after the most recent dose) following 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment with Xyosted™. A trough concentration between 350ng/dL and 650ng/dL generally provides testosterone exposures in the normal range during the entire dosing interval; the same Xyosted™ dose should be maintained if the total testosterone trough concentration is ≥350ng/dL and <650ng/dL. If the total testosterone trough concentration is ≥650ng/dL, the Xyosted™ dose should

be decreased by 25mg; if the total testosterone trough concentration is <350ng/dL, the Xyosted™ dose should be increased by 25mg.

Boxed Warning: BP Increases

- Xyosted™ can cause BP increases that can increase the risk for MACE, including non-fatal myocardial infarction (MI), non-fatal stroke, and CV death, with greater risk for MACE in patients with CV risk factors or established CV disease.
- Before initiating Xyosted™, the patient's baseline CV risk should be considered and the patient's BP should be adequately controlled.
- Starting approximately 6 weeks after initiating therapy, patients on Xyosted™ should be periodically monitored and treated for new-onset hypertension (HTN) or exacerbations of pre-existing HTN.
- Patients who develop CV risk factors or CV disease while on treatment with Xyosted™ should be reevaluated as to whether the benefits of Xyosted™ outweigh the risks.
- Due to this risk, Xyosted™ should only be used for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

Contraindication(s):

- Men with carcinoma of the breast or suspected carcinoma of the prostate
- Women who are pregnant (testosterone can cause virilization of the female fetus when administered to a pregnant woman)
- Men with known hypersensitivity to Xyosted™ or any of its ingredients (testosterone enanthate and sesame oil)
- Men with hypogonadal conditions, such as "age-related hypogonadism", that are not associated with structural or genetic etiologies (the efficacy of Xyosted™ has not been established for these conditions, and Xyosted™ can increase BP and subsequently increase the risk of MACE)

Wholesale Acquisition Cost (WAC): The WAC of Xyosted™ is $118.75 per single-dose auto-injector, regardless of strength, which results in a monthly cost of $475.00, based on once weekly dosing.

Jatenzo® (Testosterone Undecanoate Oral Capsule) Product Summary[9]

Indication(s): Jatenzo® (testosterone undecanoate oral capsule) is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone, including:

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (FSH, LH) above the normal range.
- Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or LHRH deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These

men have low testosterone serum concentrations but have gonadotropins (FSH, LH) in the normal or low range.

Limitations of Use:

- The safety and efficacy of Jatenzo® in males younger than 18 years of age have not been established.

Dosing:

- Prior to initiating Jatenzo®, the diagnosis of hypogonadism should be confirmed by ensuring that serum testosterone has been measured in the morning on at least 2 separate days and that these concentrations are below the normal range.
- Jatenzo® is supplied as gelatin capsules for oral use in 3 strengths: 158mg, 198mg, and 237mg.
- The recommended starting dose of Jatenzo® is 237mg taken orally twice daily, once in the morning and once in the evening. Jatenzo® should be taken with food.
- The dose should be individualized based on the patient's serum testosterone concentration response to the drug. The same dose should be administered in the morning and evening. The minimum recommended dose is 158mg twice daily; the maximum recommended dose is 396mg [administered as (2) 198mg capsules] twice daily.
- To ensure proper dose adjustment, serum testosterone concentrations should be obtained (measured 6 hours after the morning dose) 7 days after starting treatment or after adjusting the dose and periodically while on treatment with Jatenzo®. The following table (Table 1) summarizes the recommended dose adjustment based on the patient's serum testosterone concentration.

Table 1. Jatenzo® Dose Adjustment Scheme

Serum Testosterone Concentration*	Current Jatenzo® Dose (Taken Twice Daily)	New Jatenzo® Dose (Taken Twice Daily)
<425ng/dL	158mg	198mg
	198mg	237mg
	237mg	316mg$^{\Omega}$
	316mg$^{\Omega}$	396mg$^{¥}$
425-970ng/dL	no dose change	
>970ng/dL	396mg$^{¥}$	316mg$^{\Omega}$
	316mg$^{\Omega}$	237mg
	237mg	198mg
	198mg	158mg
	158mg	discontinue treatment

*Testosterone concentration in serum from plain tube drawn 6 hours after morning dose, clotted at room temperature for 30 minutes prior to centrifugation

$^{\Omega}$Dose administered as (2) 158mg capsules

$^{¥}$Dose administered as (2) 198mg capsules

Boxed Warning: BP Increases

- Jatenzo® can cause BP increases that can increase the risk of MACE, including non-fatal MI, non-fatal stroke, and CV death, with greater risk for MACE in patients with CV risk factors or established CV disease.
- Before initiating Jatenzo®, the patient's baseline CV risk should be considered and the patient's BP should be adequately controlled.
- Starting approximately 3 weeks after initiating therapy or changing the dose, patients on Jatenzo® should be periodically monitored and treated for new-onset HTN or exacerbations of pre-existing HTN.
- Patients who develop CV risk factors or CV disease while on treatment with Jatenzo® should be reevaluated as to whether the benefits of Jatenzo® outweigh the risks.
- Due to this risk, Jatenzo® should only be used for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies.

Contraindication(s):

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate
- Women who are pregnant (testosterone can cause virilization of the female fetus when administered to a pregnant woman)
- Men with known hypersensitivity to Jatenzo® or any of its ingredients
- Men with hypogonadal conditions, such as "age-related hypogonadism", that are not associated with structural or genetic etiologies (the efficacy of Jatenzo® has not been established for these conditions, and Jatenzo® can increase BP and subsequently increase the risk of MACE)

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

Recommendations

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

1. The placement of Xyosted™ (testosterone enanthate sub-Q auto-injector) into Tier-2. Current Tier-2 criteria will apply. Additionally, the member must be trained by a health care professional on sub-Q administration and storage of Xyosted™ sub-Q auto-injector.
2. The placement of Jatenzo® (testosterone undecanoate oral capsule) into the Special Prior Authorization (PA) Tier. Current Special PA criteria will apply.

Proposed changes are shown in red in the following Testosterone Products Tier Chart and Tier-2 Approval Criteria:

Testosterone Products		
Tier-1*	**Tier-2**	**Special PA**
methyltestosterone powder	**testosterone enanthate sub-Q auto-injector (Xyosted™)**	fluoxymesterone oral tab (Androxy®)
testosterone cypionate IM inj (Depo-Testosterone®)	testosterone nasal gel (Natesto®)	methyltestosterone oral tab/cap (Android®, Methitest®, Testred®)
testosterone enanthate IM inj (Delatestryl®)	testosterone patch (Androderm®)	testosterone buccal tab (Striant®)
testosterone topical gel (Androgel®)+	testosterone topical gel (Fortesta®, Testim®, Vogelxo®)	testosterone pellets (Testopel®)
	testosterone topical solution (Axiron®)	**testosterone undecanoate oral cap (Jatenzo®)**
	testosterone undecanoate IM inj (Aveed®)	

*Tier-1 products include generic injectable products and supplementally rebated topical products.
+Brand name preferred
PA = prior authorization; IM = intramuscular; inj = injection; sub-Q = subcutaneous; tab = tablet; cap = capsule

Testosterone Products Tier-2 Approval Criteria:

1. All diagnoses and laboratory requirements listed in the initial approval criteria for all testosterone products must be met; and
2. A trial of at least 2 Tier-1 products (must include at least 1 injectable and 1 topical formulation) at least 12 weeks in duration; or
3. A patient-specific, clinically significant reason why member cannot use all available Tier-1 products must be provided; or
4. Prior stabilization on a Tier-2 product (within the past 180 days); and
5. Approvals will be for the duration of 1 year; and
6. For Xyosted™ [testosterone enanthate subcutaneous (sub-Q) auto-injector]:
    a. Member must be trained by a health care professional on sub-Q administration and storage of Xyosted™ sub-Q auto-injector.

Utilization Details of Testosterone Products: Calendar Year 2018

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
TESTOSTERONE INJECTABLE PRODUCTS						
TESTOST CYP INJ 200MG/ML	429	114	$19,838.05	$46.24	3.8	12.87%
DEPO-TESTOST INJ 200MG/ML	30	9	$1,497.82	$49.93	3.3	0.97%
TESTOST CYP INJ 100MG/ML	12	5	$575.60	$47.97	2.4	0.37%
DEPO-TESTOST INJ 100MG/ML	4	3	$269.23	$67.31	1.3	0.17%
TESTOST ENAN INJ 200MG/ML	3	3	$213.95	$71.32	1.0	0.14%
SUBTOTAL	**478**	**134**	**$22,394.65**	**$46.85**	**3.6**	**14.53%**
TESTOSTERONE TOPICAL PRODUCTS						
ANDROGEL GEL 1.62%	132	25	$96,296.96	$729.52	5.3	62.49%
TESTOSTERONE GEL 1% (50MG)	28	4	$9,089.39	$324.62	7.0	5.90%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
ANDROGEL GEL 1% (50MG)	13	2	$15,726.11	$1,209.70	6.5	10.21%
ANDROGEL GEL 1.62%	8	3	$3,426.03	$428.25	2.7	2.22%
ANDROGEL GEL 1% (25MG)	5	2	$3,076.49	$615.30	2.5	2.00%
TESTOSTERONE SOL 30MG/ACT	3	1	$1,576.30	$525.43	3.0	1.02%
AXIRON SOL 30MG/ACT	3	1	$1,728.36	$576.12	3.0	1.12%
TESTOSTERONE GEL PUMP 1%	1	1	$151.63	$151.63	1.0	0.10%
ANDROGEL GEL 1.62%	1	1	$631.61	$631.61	1.0	0.41%
SUBTOTAL	**194**	**40**	**$131,702.88**	**$678.88**	**4.9**	**85.47%**
TOTAL	**672**	**160***	**$154,097.53**	**$229.31**	**4.2**	**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
TESTOSTERONE CYPIONATE INJ J1071	796	161	$2,890.49	$3.63	4.9
TOTAL	**796+**	**161***	**$2,890.49**	**$3.63**	**4.9**

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

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[7] Lipocine. Pipeline: LPCN 1111. Available online at: https://www.lipocine.com/pipeline/lpcn-1111/. Last accessed 04/10/2019.

[8] Xyosted™ (Testosterone Enanthate) Prescribing Information. Antares Pharma, Inc. Available online at: https://www.xyosted.com/PI.pdf. Last revised 09/2018. Last accessed 04/12/2019.

[9] Jatenzo® (Testosterone Undecanoate) Prescribing Information. Clarus Therapeutics, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/206089s000lbl.pdf. Last revised 03/2019. Last accessed 04/12/2019.

Appendix F

Calendar Year 2018 Annual Review of H.P. Acthar® Gel (Repository Corticotropin Injection)

Oklahoma Health Care Authority
May 2019

Current Prior Authorization Criteria

H.P. Acthar® Gel (Repository Corticotropin Injection) Approval Criteria:

1. An FDA approved diagnosis of infantile spasms; and
    a. Member must be 2 years of age or younger; and
    b. Must be prescribed by, or in consultation with, a neurologist or an advanced care practitioner with a supervising prescriber that is a neurologist; or
2. An FDA approved diagnosis of multiple sclerosis (MS); and
    a. Member is experiencing an acute exacerbation; and
    b. Must be prescribed by, or in consultation with, a neurologist or an advanced care practitioner with a supervising prescriber that is a neurologist or a prescriber that specializes in MS; and
    c. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy [e.g., intravenous (IV) methylprednisolone] must be provided; and
    d. Therapy will be limited to 5 weeks per approval (3 weeks of treatment, followed by taper). Additional approval, beyond the initial 5 weeks, will require prescriber documentation of response to initial treatment and need for continued treatment; or
3. An FDA approved diagnosis of nephrotic syndrome without uremia of the idiopathic type or that is due to lupus erythematosus to induce a diuresis or a remission of proteinuria; and
    a. Must be prescribed by, or in consultation with, a nephrologist or an advanced care practitioner with a supervising prescriber that is a nephrologist; and
    b. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy (e.g., prednisone) must be provided; or
4. An FDA approved diagnosis of the following disorders or diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; or edematous states; and
    a. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy must be provided.

Utilization of H.P. Acthar® Gel (Repository Corticotropin Injection): Calendar Year 2018

Comparison of Calendar Years: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	15	32	$1,881,126.06	$58,785.19	$3,104.17	265	606
2018	14	32	$2,263,524.92	$70,735.15	$3,692.54	295	613
% Change	**-6.70%**	**0.00%**	**20.30%**	**20.30%**	**19.00%**	**11.30%**	**1.20%**
Change	**-1**	**0**	**$382,398.86**	**$11,949.96**	**$588.37**	**30**	**7**

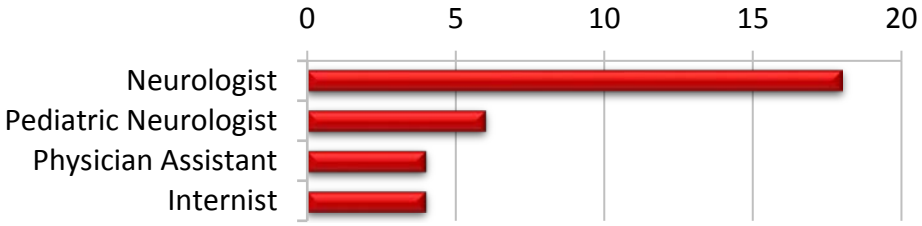
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- There were no paid medical claims for H.P. Acthar® Gel during calendar year 2018.

Demographics of Members Utilizing H.P. Acthar® Gel (Repository Corticotropin Injection)

- Due to the small number of members utilizing H.P. Acthar® Gel during calendar year 2018, detailed demographic information could not be provided. Of the 14 patients utilizing H.P. Acthar® Gel during calendar year 2018, 6 were pediatric members.

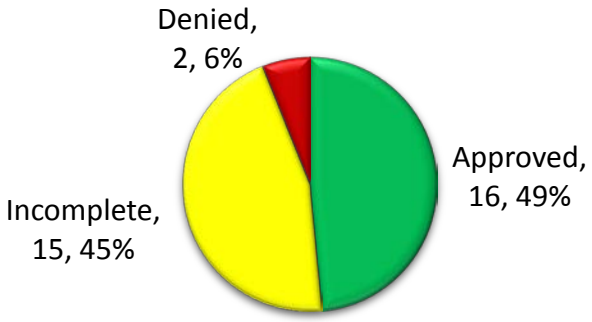
Top Prescriber Specialties of H.P. Acthar® Gel (Repository Corticotropin Injection) by Number of Claims



Prior Authorization of H.P. Acthar® Gel (Repository Corticotropin Injection)

There were 33 prior authorization requests submitted for H.P. Acthar® Gel during calendar year 2018. The following chart shows the status of the submitted petitions for calendar year 2018.

Status of Petitions



Market News and Updates[1,2]

News:

- **April 2018:** Data from an analysis presented at the 70th annual meeting of the American Academy of Neurology showed that H.P. Acthar® (repository corticotropin injection) may delay progression of amyotrophic lateral sclerosis (ALS). The therapy is under investigation for ALS and received U.S. Food and Drug Administration (FDA) Fast Track and Orphan Drug designation. Researchers used data from a pilot study of repository corticotropin injection and the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database to assess the impact of the therapy on ALS progression. In the pilot study, patients with ALS were randomized to receive repository corticotropin injection or a volume-matched placebo once daily for 36 weeks. The main study outcome was the change from baseline up to 36 weeks in the ALS Functioning Rating Scale (ALSFRS). At baseline, the mean ALSFRS scores were 27.8 in the repository corticotropin injection-treated group and 27.2 in the PRO-ACT control group. The case-match control analysis revealed that after 36 weeks of treatment, the ALSFRS scores of repository corticotropin injection-treated patients declined by a mean of 4.3 points and by 6.6 points in the control group - a statistically significant difference. In the post-hoc analysis, researchers generated a prediction algorithm that used the baseline characteristics to generate a 36-week estimate of patients' response. They compared it to the changes in ALSFRS score from the repository corticotropin injection pilot study. For the 21 patients who completed the study, the changes in progression in ALSFRS score were smaller, but still similar to that predicted by the algorithm. The researchers concluded that overall these results "suggest potential repository corticotropin injection efficacy in the treatment of ALS and support further study of repository corticotropin injection for ALS in controlled trials."
- **June 2018:** Results of a cross-sectional analysis of Centers for Medicare and Medicaid Services (CMS) 2015 Part D prescribing data of nephrologists, neurologists, and rheumatologists with more than 10 corticotropin prescriptions in 2015 were published in *JAMA Network Open*. The study found that of the 235 included physicians, 207 (88%) received a monetary payment from the drug's maker, with more than 20% of frequent prescribers receiving more than $10,000. There was a significant association between higher dollar amounts paid to these prescribers and higher spending by Medicare on their corticotropin prescriptions. The authors concluded that these findings suggest that financial conflicts of interest may be driving use of corticotropin in the Medicare program.

Recommendations

The College of Pharmacy recommends updating the H.P. Acthar® Gel (repository corticotropin injection) prior authorization criteria with the following changes noted in red:

H.P. Acthar® Gel (Repository Corticotropin Injection) Approval Criteria:

1. An FDA approved diagnosis of infantile spasms; and
    a. Member must be 2 years of age or younger; and

b. Must be prescribed by, or in consultation with, a neurologist or an advanced care practitioner with a supervising prescriber that is a neurologist; or

2. An FDA approved diagnosis of multiple sclerosis (MS); and
    a. Member is experiencing an acute exacerbation; and
    b. Must be prescribed by, or in consultation with, a neurologist or an advanced care practitioner with a supervising prescriber that is a neurologist or a prescriber that specializes in MS; and
    c. Prescriber must rule out pseudo-exacerbation from precipitating factors (e.g., pain, stress, infection, premenstrual syndrome); and
    d. Symptoms of acute exacerbation last at least 24 hours; and
    e. Member must be currently stable within the last 30 days on an immunomodulator agent, unless contraindicated; and
    f. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy [e.g., intravenous (IV) methylprednisolone, IV dexamethasone, oral prednisone) must be provided; and
    g. A quantity limit of daily doses of up to 120 units for up to 3 weeks for acute exacerbation will apply ~~Therapy will be limited to 5 weeks per approval (3 weeks of treatment, followed by taper). Additional approval, beyond the initial 5 weeks, will require prescriber documentation of response to initial treatment and need for continued treatment~~; or
3. An FDA approved diagnosis of nephrotic syndrome without uremia of the idiopathic type or that is due to lupus erythematosus to induce a diuresis or a remission of proteinuria; and
    a. Must be prescribed by, or in consultation with, a nephrologist or an advanced care practitioner with a supervising prescriber that is a nephrologist; and
    b. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy (e.g., prednisone) must be provided; or
4. An FDA approved diagnosis of the following disorders or diseases: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; or edematous states; and
    a. A patient-specific, clinically significant reason why the member cannot use alternative corticosteroid therapy must be provided.

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[1] Inacio P. #AAN2018 – H.P. Acthar Gel Shows Promise as Therapy to Delay Progression of ALS. *ALS News Today*. Available online at: https://alsnewstoday.com/2018/04/20/aan2018-hp-acthar-gel-shows-promise-delay-als-progression/. Issued 04/20/2018. Last accessed 04/03/2019.

[2] Hartung DM, Johnston K, Cohen DM, et al. Industry Payments to Physician Specialists Who Prescribe Repository Corticotropin. *JAMA Network Open* 2018; 1(2):e180482. doi:10.1001/jamanetworkopen.2018.0482

Appendix G

Calendar Year 2018 Annual Review of Jynarque® (Tolvaptan)

Oklahoma Health Care Authority
May 2019

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

Autosomal dominant polycystic kidney disease (ADPKD) is a progressively debilitating genetic disorder in which fluid-filled cysts develop in the kidneys over time. The cysts enlarge the kidneys and impair their ability to function normally, leading to kidney failure in most patients. ADPKD is the most common genetic cause of chronic kidney disease (CKD) occurring in all races, with an estimated prevalence of 140,000 people in the United States, and is the underlying cause of approximately 5% of patients who initiate hemodialysis in the United States. ADPKD is caused by 2 known genetic mutations: *PKD1* (encodes polycystin-1) on chromosome 16 and *PKD2* (encodes polycystin-2) on chromosome 4. *PKD1* mutations are the most common (estimated up to 85%), the most severe phenotype, and have an earlier onset than *PKD2* mutations [end-stage renal disease (ESRD) mean age 54 years in *PKD1* vs. 74 years in *PKD2*].

The diagnosis of ADPKD is based on imaging of the kidneys; typical findings include large kidneys and extensive cysts scattered throughout both kidneys. Screening in children younger than 18 years of age is not recommended since adverse effects from a pre-symptomatic diagnosis outweigh current benefits (e.g., career, education, emotional issues, insurability issues). Patients with ADPKD can present with hypertension (HTN), proteinuria, renal insufficiency, and flank pain due to renal hemorrhage, calculi, or urinary tract infection. Patients may also present with symptoms that are secondary to cysts in other organs such as the liver, pancreas, spleen, thyroid, or epididymis. The age at which individuals have clinical manifestations including renal failure or HTN is variable, and patients with *PKD1* present with symptoms at a younger age than *PKD2*. The diagnosis is most commonly made in the setting of routine screening in an asymptomatic patient with a positive family history of ADPKD, during initial work-up for new-onset HTN, as an accidental finding during an imaging study performed for an unrelated reason (e.g., trauma, pregnancy), or during evaluation of ADPKD-specific symptoms (e.g., hematuria, cyst rupture, kidney stones).

In most patients, renal function remains intact until the fourth decade of life. Once the estimated glomerular filtration rate (eGFR) starts to decline, the average eGFR reduction ranges from 4.4 to 5.9mL/min decline per year. Patients who present with symptoms at an early age are more likely to develop ESRD. Most patients with ADPKD die from cardiac causes.

The treatment of ADPKD patients include nonspecific measures such as strict blood pressure control, dietary protein restriction, a low-sodium diet, and statins, which may prevent progression of disease and reduce cardiovascular (CV) mortality. HTN occurs early, prior to the loss of kidney function, in about two-thirds of ADPKD patients and is associated with progressive renal disease. Rigorous control of blood pressure may prevent progression of renal disease and decrease the risk of CV morbidity that characterizes all patients with CKD.

Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may, in addition to lowering blood pressure, slow the rate of progression of ADPKD especially among patients with proteinuria. Based on the results of the Halt Progression of Polycystic Kidney Disease (HALT-PKD) trials, there is no advantage to combining an ACE inhibitor (lisinopril) with an ARB (telmisartan) compared with an ACE inhibitor alone in ADPKD patients. The HALT-PKD study showed that a blood pressure target of <110/75mmHg led to a lower total kidney volume (TKV), lower albumin excretion rate, and lower left ventricular mass index (LVMI) when compared with a blood pressure target of 120 to 130/70 to 80mmHg in relatively young, healthy ADPKD patients with preserved kidney function. Patients with ADPKD and renal failure are commonly treated with hemodialysis or undergo renal transplantation with equivalent or better overall outcomes compared with non-ADPKD patients.

In April 2018, Jynarque® (tolvaptan), the first treatment for ADPKD, was approved by the U.S. Food and Drug Administration (FDA). Jynarque® is a selective vasopressin V_2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing ADPKD. Jynarque® is available as oral tablets in 5 strengths: 15mg, 30mg, 45mg, 60mg, and 90mg. Due to the risk of serious liver injury, Jynarque® is only available through a restricted distribution program called Jynarque® Risk Evaluation Mitigation Strategy (REMS) program. Tolvaptan is also commercially available as Samsca® 15mg and 30mg oral tablets which was approved by the FDA in May 2009 for the treatment of patients with clinically significant hypervolemic or euvolemic hyponatremia (serum sodium <125mEq/L or less-marked hyponatremia that is symptomatic and has resisted correction with fluid restriction) including patients with heart failure, cirrhosis, and syndrome of inappropriate antidiuretic hormone (SIADH). Samsca® should only be initiated and re-initiated in a hospital where serum sodium can be monitored closely. Jynarque® may be initiated outpatient and abnormalities in sodium concentrations must be corrected prior to initiation of therapy. Due to the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS program for Jynarque®.

Current Prior Authorization Criteria

Jynarque® (Tolvaptan) Approval Criteria:

1. An FDA approved indication to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD); and
2. Member must be 18 years of age or older; and
3. Member must not have any contraindications to taking Jynarque® including the following:
    a. Taking any concomitant strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, conivaptan); and
    b. A history of signs or symptoms of significant liver impairment or injury (does not include uncomplicated polycystic liver disease); and
    c. Uncorrected abnormal blood sodium concentrations; and
    d. Unable to sense or respond to thirst; and
    e. Hypovolemia; and

f. Hypersensitivity to tolvaptan or any of its components; and
g. Uncorrected urinary outflow obstruction; and
h. Anuria; and

4. Member must not be taking any of the following medications concomitantly with Jynarque®:
   a. Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, lopinavir/ritonavir, indinavir/ritonavir, ritonavir, conivaptan); and
   b. Strong CYP3A inducers (e.g., rifampin); and
   c. OATP1B1/3 and OAT3 transporter substrates (e.g., statins, bosentan, glyburide, nateglinide, repaglinide, methotrexate, furosemide); and
   d. BCRP transporter substrates (e.g., rosuvastatin); and
   e. V_2-receptor agonists (e.g., desmopressin); and
5. Jynarque® must be prescribed by a nephrologist or specialist with expertise in the treatment of ADPKD (or be an advanced care practitioner with a supervising physician who is a nephrologist or specialist with expertise in the treatment of ADPKD); and
6. Prescriber must agree to assess ALT, AST, and bilirubin prior to initiation of Jynarque®, at 2 weeks and 4 weeks after initiation, then monthly for 18 months, and every 3 months thereafter; and
7. Female members must not be pregnant and must have a negative pregnancy test prior to therapy initiation; and
8. Prescriber, pharmacy, and member must be enrolled in the Jynarque® Risk Evaluation and Mitigation Strategy (REMS) program and maintain enrollment throughout therapy.

Utilization of Jynarque® (Tolvaptan): Calendar Year 2018

There were no paid claims for Jynarque® (tolvaptan) during calendar year 2018.

Prior Authorization of Jynarque® (Tolvaptan)

There were no prior authorization requests submitted for Jynarque® (tolvaptan) during calendar year 2018.

Market News and Updates[10,11,12,13,14,15]

Anticipated Patent Expiration(s):

- Jynarque® (tolvaptan): September 2026

Pipeline:

- **October 2018:** A study was published it the *Journal of the American Medical Association* (*JAMA*) regarding the effect of the somatostatin analog, lanreotide, on kidney function in patients with ADPKD. The randomized trial in the Netherlands included 305 adult patients with later-stage ADPKD. Treatment with lanreotide 120mg subcutaneously once every 4 weeks, compared with standard care resulted in a decline of eGFR rate of 3.53 versus 3.46mL/min/1.7m^2 per year over 2.5 years, a difference that was not statistically significant. Based on the study results, the researchers do not support the use of lanreotide to preserve kidney function in later-stage ADPKD.

- **December 2018:** Palladio Biosciences, Inc. announced the dosing of the first patients with lixivaptan in ELiSA, a Phase 2 clinical study in patients with ADPKD. Lixivaptan is a potent, selective vasopressin V2 receptor antagonist, a mechanism of action that has clinical proof of concept to slow kidney function decline in adults at risk of rapidly progressing ADPKD. The ELiSA study (Evaluation of Lixivaptan in Subjects with ADPKD), which is being conducted at several clinical sites in the United States, will look at how well 2 different doses of lixivaptan work in preserving kidney function. The study will also evaluate how well adult subjects with ADPKD tolerate the study drug, which will be given by mouth for 7 days. The study is enrolling male and female ADPKD patients between 18 and 60 years of age with an eGFR >30 mL/min/1.73m^2. Completion of the ELiSA study will pave the way for the initiation of a Phase 3 registration study in 2019. Lixivaptan was granted Investigational New Drug (IND) clearance by the FDA to proceed with a Phase 2 clinical trial of lixivaptan capsules in patients with ADPKD in April 2018; lixivaptan had previously received Orphan Drug designation by the FDA for the treatment of ADPKD. Lixivaptan was previously administered to more than 1,600 subjects across 36 clinical studies as part of a prior clinical development program for the treatment of hyponatremia. Palladio expects to leverage lixivaptan's large body of data generated in the hyponatremia clinical program to accelerate the development of lixivaptan for the treatment of ADPKD.
- **April 2019:** The Mario Negri Institute for Pharmacological Research completed and published the Phase 3 clinical evaluation of octreotide long-acting release (LAR) for slowing kidney and liver growth rate in patients with later-stage ADPKD. The study was an internally funded, parallel-group, double-blind, placebo-controlled Phase 3 trial to assess octreotide-LAR in adults with ADPKD with a GFR between 15 to 40mL/min/1.73m^2. Co-primary short- and long-term outcomes were 1-year TKV (computed tomography scan) growth and 3-year GFR (iohexol plasma clearance) decline. Participants were randomized to receive 2 intramuscular injections of 20mg octreotide-LAR (N=51) or 0.9% sodium chloride solution (placebo; N=49) every 28 days for 3 years. Compared to placebo, octreotide-LAR reduced median TKV growth from baseline by 96.8mL [95% confidence interval (CI), 10.8 to 182.7] at 1 year (P=0.027) and 422.6mL (95% CI, 150.3 to 695.0) at 3 years (P=0.002). Reduction in the median rate of GFR decline (0.56mL/min/1.73m^2 per year; 95% CI, −0.63 to 1.75) was not significant (P=0.295). TKV analyses were adjusted for age, sex, and baseline TKV. Over a median 36 months (24 to 37) of follow-up, 9 patients on octreotide-LAR and 21 patients on placebo progressed to a doubling of serum creatinine or ESRD (composite endpoint) [hazard ratio (HR): 0.307 (0.127 to 0.742), P=0.009]. One composite endpoint was prevented for every 4 treated patients. Among 63 patients with CKD stage 4, 3 on octreotide-LAR and 8 on placebo progressed to ESRD [adjusted HR: 0.121 (0.017 to 0.866), P=0.036]. The main study limitation was the small sample size. The study concluded that in later-stage ADPKD, octreotide-LAR slowed kidney growth and delayed progression to ESRD, in particular, in CKD stage 4.

Guideline Update(s):

- **October 2018:** A Practical Guide for Treatment of Rapidly Progressive ADPKD with Tolvaptan was published in the *Journal of the American Society of Nephrology* (*JASN*). The review intends to provide practical guidance and discuss steps that require consideration before and after prescribing tolvaptan to patients with ADPKD to ensure that this treatment is implemented safely and effectively. These steps include: confirmation of diagnosis; identification of rapidly progressive disease; implementation of basic renal protective measures; counseling of patients on potential benefits and harms; exclusions to use; education of patients on aquaresis and its expected consequences, initiation, titration, and optimization of tolvaptan treatment; prevention of aquaresis-related complications; evaluation and management of liver enzyme elevations; and monitoring of treatment efficacy. The recommendations are made on the basis of published evidence and collective experiences during the randomized, clinical trials and open-label extension studies of tolvaptan in ADPKD.
- **November 2018:** A new Renal Association clinical practice guideline has been published on monitoring children and young people with, or at risk of developing, ADPKD. One of the 6 guidelines include the recommendation in children and young people up to 18 years of age that the decision to test for ADPKD in asymptomatic children and young people at risk of developing ADPKD should be undertaken jointly between health professionals and parents or caregivers, and, wherever possible, the young person. The guidance also recommends that children and young people 5 years of age and older with, or at risk of developing, ADPKD should have an assessment of blood pressure at least once every 2 years.

Recommendations

The College of Pharmacy does not recommend any changes to the current Jynarque® (tolvaptan) prior authorization criteria at this time.

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Appendix H

Industry News and Updates

Oklahoma Health Care Authority
May 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:

- **Human Immunodeficiency Virus (HIV):** Using a model to estimate transmission rates in 2016 along the HIV continuum of care, the Centers for Disease Control and Prevention (CDC) researchers concluded that most new HIV transmissions arise from people with HIV infection who have not received a diagnosis or who have a diagnosed infection that is not controlled. In a press release, the director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Dr. Jonathan Mermin, noted that the research demonstrated a clear need to increase the proportion of people who are aware of their HIV infection, increase the number of people with diagnosed HIV infection to get into and stay in care, and encourage people with HIV to take their medication. Moving forward, increasing the percentage of people with HIV infections who have achieved viral suppression and do not transmit HIV will be critical to ending the HIV epidemic in the United States.
- **HIV Vaccine:** The International AIDS Vaccine Initiative (IAVI) announced the beginning of a Phase 1 clinical trial studying a novel HIV vaccine candidate (BG505 SOSIP.664 gp140). The trial's goals are to assess the vaccine safety and to determine if vaccination induces the human immune system to produce neutralizing antibodies. In animal testing, vaccination with BG505 SOSIP.664 gp140 caused B cells to produce antibodies that neutralized the virus type from which the engineered immunogen was derived. The trial will enroll approximately 60 healthy participants and participants will receive 3 administrations of the vaccine candidate or a placebo. According to the IAVI, it is not likely that vaccination with BG505 SOSIP.664 gp140 on its own will directly lead to the production of neutralizing antibodies, but investigators hope to better understand what is required to induce neutralizing antibody responses. Results of the trial are expected in 2020 and data will likely contribute to the development of the vaccine candidate for future trials.
- **Hepatitis C Virus (HCV):** The Louisiana Departments of Health and Corrections announced they selected Asegua Therapeutics, a generics subsidiary arm of Gilead Sciences, as their pharmaceutical partner for the state's "Netflix" subscription model for HCV treatment. The first of its kind alternative payment model allows the state to pay a subscription fee to the drug company whereby the state will receive unlimited access to

the drug. With this partnership, the Louisiana Departments of Health and Corrections will have 5 years of unrestricted access to Asegua's HCV treatment. The state's goal is to treat 10,000 patients with HCV by the end of 2020, which accounts for approximately a quarter of its infected population on Medicaid and in prison.

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Appendix I

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

FDA NEWS RELEASE

For Immediate Release: April 30th, 2019

FDA approves first treatment for all genotypes of hepatitis C in pediatric patients

The FDA approved Mavyret™ (glecaprevir and pibrentasvir) tablets to treat all six genotypes of hepatitis C virus (HCV) in children ages 12 to 17. Mavyret™ was previously approved to treat HCV in adults in 2017. HCV is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. According to the U.S. Centers for Disease Control and Prevention, an estimated 2.7 to 3.9 million people in the U.S. have chronic HCV, and children born to HCV-positive mothers are at risk for HCV infection. It is estimated that there are 23,000 to 46,000 children in the U.S. with HCV infection.

With today's approval, dosing information is provided for Mavyret™ for the treatment of adult or pediatric patients 12 years and older, or weighing at least 99 pounds, who are infected with any of six identified HCV genotypes either without cirrhosis or with compensated cirrhosis.

The safety and efficacy of Mavyret™ in pediatric patients was evaluated during clinical trials of 47 patients with genotype 1, 2, 3 or 4 HCV infection without cirrhosis or with mild cirrhosis. Results of the trials demonstrated that 100 percent of patients who received Mavyret™ for eight or 16 weeks had no virus detected in the blood 12 weeks after finishing treatment, suggesting that patients' infection had been cured. In pediatric patients with cirrhosis, history of a kidney and/or liver transplant, or genotype 5 or 6 HCV infection, the safety and efficacy of Mavyret™ are supported by previous studies observed in glecaprevir and pibrentasvir in adults. The adverse reactions observed were consistent with those observed in clinical studies of Mavyret™ in adults.

Treatment duration with Mavyret™ differs depending on treatment history, viral genotype and cirrhosis status. The most common adverse reactions in patients taking Mavyret™ were headache and fatigue. Mavyret™ is not recommended in patients with moderate cirrhosis and contraindicated in patients with severe cirrhosis. It is also contraindicated in patients taking the drugs atazanavir and rifampin.

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV coinfected adult patients who were undergoing or had completed treatment with HCV direct-acting antivirals, and who were not receiving HBV antiviral therapy. HBV reactivation in patients treated with direct-acting antiviral medicines can result in serious liver problems or death in some patients. Health care professionals should screen all patients for evidence of current or prior HBV infection before starting treatment with Mavyret™.

The FDA granted the approval of Mavyret™ to AbbVie Inc.

FDA NEWS RELEASE

For Immediate Release: April 26th, 2019

FDA approves first treatment for pediatric patients with lupus

The FDA approved Benlysta® (belimumab) intravenous (IV) infusion for treatment of children with systemic lupus erythematosus (SLE) – often referred to as simply "lupus" – a serious chronic disease that causes inflammation and damage to various body tissues and organs. This is the first time that the FDA has approved a treatment for pediatric patients with SLE. Benlysta® has been approved for use in adult patients since 2011. While childhood-onset SLE is rare, when diagnosed, it is generally more active in children and adolescents than adult patients, particularly in how it impacts organs such as the kidneys and central nervous system. As a result of the disease starting early in life, pediatric patients with SLE are at a higher risk for developing increased organ damage and complications from the disease as well as adverse events from the life-long treatments usually required.

The efficacy of Benlysta® IV for the treatment of SLE in pediatric patients was studied over 52 weeks in 93 pediatric patients with SLE. The proportion of pediatric patients achieving the composite primary endpoint, the SLE response index (SRI-4), was higher in pediatric patients receiving Benlysta® IV plus standard therapy compared to placebo plus standard therapy. Pediatric patients who received Benlysta® IV plus standard therapy also had a lower risk of experiencing a severe flare, as well as longer duration of time until a severe flare (160 days versus 82 days). The drug's safety and pharmacokinetic profiles in pediatric patients were consistent with those in adults with SLE.

Benlysta®'s doctor and patient information includes a warning for mortality, serious infections, hypersensitivity and depression, based on data from the clinical studies in adults with SLE. The drug should not be administered with live vaccines. The manufacturer is required to provide a Medication Guide to inform patients of the risks associated with Benlysta®.
The most common side effects in patients included nausea, diarrhea and fever. Patients also commonly experienced infusion reactions, so healthcare professionals are advised to pre-treat patients with an antihistamine.
The FDA granted this application a Priority Review designation. The FDA granted the approval of Benlysta® to GlaxoSmithKline.

FDA NEWS RELEASE

For Immediate Release: April 19th, 2019

FDA approves first generic naloxone nasal spray to treat opioid overdose

Agency is also taking new steps to support development of over-the-counter and additional generics of naloxone to help reduce opioid overdose deaths, increase access to emergency treatment

The FDA granted final approval of the first generic naloxone hydrochloride nasal spray, commonly known as Narcan®, a life-saving medication that can stop or reverse the effects of an opioid overdose. The agency is also planning new steps to prioritize the review of additional generic drug applications for products intended to treat opioid overdose, along with the previously announced action to help facilitate an over-the-counter naloxone product.
The approval is the first generic naloxone nasal spray for use in a community setting by individuals without medical training; however, generic injectable naloxone products have been available for years for use in a health care setting. The FDA also has previously approved a brand-name naloxone nasal spray and an auto-injector for use by those without medical training. While business and other considerations may impact how quickly this product becomes available, today's approval is an important step for the agency as it works toward expanding access to this live-saving drug. The FDA also held a two-day advisory committee meeting in December to solicit input and advice on strategies to increase the availability of naloxone products intended for use in the community.
According to the Centers for Disease Control and Prevention, almost 400,000 people died from an opioid overdose from 1999 to 2017, and on average, more than 130 Americans die every day from overdoses involving opioids, a class of drugs that include prescription medications such as fentanyl, oxycodone, hydrocodone and morphine, as well as illegal drugs such as heroin or drugs sold as heroin. Drugs like heroin often contain fentanyl or derivatives of fentanyl. When someone overdoses on an opioid, it can be difficult to revive the person to full consciousness, and breathing may become shallow or stop completely – leading to death without medical intervention. If naloxone nasal spray is administered quickly, it can counter the overdose effects, usually within minutes. However, it is important to note that it is not a substitute for immediate medical care, and the person administering naloxone nasal spray should seek further immediate medical attention on the patient's behalf.
As part of the U.S. Department of Health and Human Services' ongoing efforts to combat the opioid crisis and expand the use of naloxone, in April 2017, the Department announced its 5-Point Strategy to Combat the Opioids Crisis. Those efforts include: better addiction prevention, treatment, and recovery services; better data; better pain management; better targeting of overdose reversing drugs; and better research. In April 2018, Surgeon General VADM Jerome Adams issued an advisory encouraging more individuals, including family, friends and those who are personally at risk for an opioid overdose to carry naloxone. In December 2018, ADM Brett P. Giroir, M.D., Assistant Secretary for Health and the Secretary's Senior Advisor for Opioid Policy, released guidance for health care providers and patients detailing how naloxone can help save lives.
One of the ways the FDA is working to increase access to this life-saving treatment is through the approval of generic naloxone products. As part of HHS' public health emergency to address the ongoing opioid crisis, the FDA will grant priority review to all abbreviated new drug applications for products indicated for the emergency treatment of known or suspected opioid overdose. As part of the priority review, sponsors will receive shorter goal dates or standard goal dates with earlier reviewer deadlines; enhanced agency communication with sponsors; and expanded agency engagement similar to Generic Drug User Fee Act enhancements for complex products, such as pre-submission and midcycle meetings. The FDA has determined that further expanding availability of and access to overdose reversal drugs could help address the public health emergency.

More generally, in an effort to promote competition to help reduce drug prices and improve access to safe and effective generic medicines for Americans, the agency is taking a number of new steps as part of its Drug Competition Action Plan. These steps include important work to improve the efficiency of the generic drug approval process and address barriers to generic drug development.
The FDA also remains focused on several additional priorities to address the opioid crisis, including: decreasing exposure to opioids and preventing new addiction; fostering the development of novel pain treatment therapies; supporting treatment of those with opioid use disorder; and improving enforcement and assessing benefit-risk.
Naloxone nasal spray does not require assembly and delivers a consistent, measured dose when used as directed. This product can be used for adults or children and is easily administered by anyone, even those without medical training. The drug is sprayed into one nostril while the patient is lying on his or her back and can be repeated if necessary.
The use of naloxone nasal spray in patients who are opioid-dependent may result in severe opioid withdrawal characterized by body aches, diarrhea, increased heart rate (tachycardia), fever, runny nose, sneezing, goose bumps (piloerection), sweating, yawning, nausea or vomiting, nervousness, restlessness or irritability, shivering or trembling, abdominal cramps, weakness and increased blood pressure.
The FDA tentatively approved this generic drug product on June 8, 2018. Teva Pharmaceuticals USA Inc. has received final FDA approval to market generic naloxone nasal spray.

FDA NEWS RELEASE

For Immediate Release: April 12th, 2019

FDA approves first targeted therapy for metastatic bladder cancer

The FDA granted accelerated approval to Balversa™ (erdafitinib), a treatment for adult patients with locally advanced or metastatic bladder cancer that has a type of susceptible genetic alteration known as FGFR3 or FGFR2, and that has progressed during or following prior platinum-containing chemotherapy. Patients should be selected for therapy with Balversa™ using an FDA-approved companion diagnostic device.
The most common type of bladder cancer is transitional cell carcinoma, also called urothelial carcinoma. Bladder cancers are associated with genetic mutations that are present in the patient's bladder or entire urothelium (the lining of the lower urinary tract). Bladder cancer is the sixth most common cancer in the United States. Fibroblast growth factor (FGFR) alterations are present in approximately one in five patients with recurrent and refractory bladder cancer.
The efficacy of Balversa™ was studied in a clinical trial that included 87 patients with locally advanced or metastatic bladder cancer, with FGFR3 or FGFR2 genetic alterations, that had progressed following treatment with chemotherapy. The overall response rate in these patients was 32.2%, with 2.3% having a complete response and almost 30% having a partial response. The response lasted for an average of approximately five-and-a-half months. About a quarter of patients in the study were previously treated with anti PD-L1/PD-1 therapy, which is a standard treatment for patients with locally advanced or metastatic bladder cancer. Responses to Balversa™ were seen in patients who had previously not responded to anti PD-L1/PD-1 therapy.
Common side effects reported by patients taking Balversa™ were increased phosphate level, mouth sores, feeling tired, change in kidney function, diarrhea, dry mouth, nails separating from the bed or poor formation of the nail, change in liver function, low salt (sodium) levels, decreased appetite, change in sense of taste, low red blood cells (anemia), dry skin, dry eyes and hair loss. Other side effects include redness, swelling, peeling or tenderness on the hands or feet (hand foot syndrome), constipation, stomach pain, nausea and muscle pain.
Balversa™ may cause serious eye problems, including inflamed eyes, inflamed cornea and disorders of the retina. Patients are advised to have eye examinations intermittently and to tell their health care professional right away if they develop blurred vision, loss of vision or other visual changes. Health care professionals are advised to check patients' blood phosphate level between 14 and 21 days after starting treatment and monthly, and to increase the dose Balversa™ in patients whose serum phosphate is below the target level.
Health care professionals are advised to tell male patients with female partners of reproductive potential to use effective contraception during treatment with Balversa™ and for one month after the last dose. Pregnancy testing is recommended for females of reproductive potential prior to initiating treatment with Balversa™. Women who are pregnant or breastfeeding should not take Balversa™ because it may cause harm to a developing fetus or newborn baby. Balversa™ must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks.

Balversa™ received an Accelerated Approval, which enables the FDA to approve drugs for serious conditions to fill an unmet medical need using clinical trial data that is thought to predict a clinical benefit to patients. Further clinical trials are required to confirm Balversa™'s clinical benefit and the sponsor is conducting or plans to conduct these studies. Balversa™ was also granted Breakthrough Therapy designation.
The FDA granted the approval of Balversa™ to Janssen Pharmaceutical.

FDA NEWS RELEASE

For Immediate Release: April 9th, 2019

FDA approves new treatment for osteoporosis in postmenopausal women at high risk of fracture

The FDA approved Evenity™ (romosozumab-aqqg) to treat osteoporosis in postmenopausal women at high risk of breaking a bone (fracture). These are women with a history of osteoporotic fracture or multiple risk factors for fracture, or those who have failed or are intolerant to other osteoporosis therapies.
More than 10 million people in the U.S. have osteoporosis, which is most common in women who have gone through menopause. People with osteoporosis have weakened bones that are more likely to fracture.
Evenity™ is a monoclonal antibody that blocks the effects of the protein sclerostin and works mainly by increasing new bone formation. One dose of Evenity™ consists of two injections, one immediately following the other, given once a month by a health care professional. The bone forming effect of Evenity™ wanes after 12 doses so more than 12 doses should not be used. If osteoporosis therapy is needed after the 12 doses, patients should begin an osteoporosis treatment that reduces bone breakdown.
The safety and efficacy of Evenity™ were demonstrated in two clinical trials involving a total of more than 11,000 women with postmenopausal osteoporosis. In the first trial, one year of treatment with Evenity™ lowered the risk of a new fracture in the spine (vertebral fracture) by 73% compared to placebo. This benefit was maintained over the second year of the trial when Evenity™ was followed by one year of denosumab (another osteoporosis therapy) compared to placebo followed by denosumab. In the second trial, one year of treatment with Evenity™ followed by one year of alendronate (another osteoporosis therapy) reduced the risk of a new vertebral fracture by 50% compared to two years of alendronate alone. Evenity™ followed by alendronate also reduced the risk of fractures in other bones (nonvertebral fractures) compared to alendronate alone.
Evenity™ increased the risk of cardiovascular death, heart attack and stroke in the alendronate trial, but not in the placebo trial. Therefore, Evenity™ contains a boxed warning on its labeling stating that it may increase the risk of heart attack, stroke and cardiovascular death and should not be used in patients who have had a heart attack or stroke within the previous year. Health care professionals should also consider whether the benefits of Evenity™ outweigh its risks in those with other risk factors for heart disease and should discontinue Evenity™ in any patient who experiences a heart attack or stroke during treatment.
Common side effects of Evenity™ included joint pain and headache. Injection site reactions were also observed.
The FDA granted the approval of Evenity™ to Amgen.

FDA NEWS RELEASE

For Immediate Release: April 8th, 2019

FDA approves first two-drug complete regimen for HIV-infected patients who have never received antiretroviral treatment

The FDA approved Dovato (dolutegravir and lamivudine), as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults with no antiretroviral treatment history and with no known or suspected substitutions associated with resistance to the individual components of Dovato. This is the first FDA-approved two-drug, fixed-dose, complete regimen for HIV-infected adults who have never received treatment for HIV.
Approximately 1.1 million people in the U.S. are living with HIV. About 15 percent of them (1 in 7) are unaware they are infected. Effective treatment is important in reducing the amount of virus in the blood. A suppressed viral load in people living with HIV prevents disease progression, and helps them live longer, healthier lives. Also, people living with HIV who take HIV medication daily as prescribed and maintain an undetectable viral load have effectively no risk of sexually transmitting HIV to their HIV-negative partners.

The Dovato labeling includes a Boxed Warning, which cautions that patients infected with both HIV and hepatitis B should add additional treatment for their hepatitis B or consider a different drug regimen. Patients with both HIV and hepatitis B who take products containing lamivudine, an ingredient in Dovato, have developed hepatitis B variants associated with resistance to lamivudine and may have severe liver problems, including liver failure, when they stop taking drugs containing lamivudine. Patients who have both HIV and hepatitis B virus who stop using Dovato should be closely monitored by their health care provider.
The efficacy and safety of Dovato, one tablet taken daily, were demonstrated in two identical, randomized, double-blind, controlled clinical trials in 1,433 HIV-infected adults with no prior antiretroviral treatment history. The trials showed that a drug regimen containing dolutegravir and lamivudine had a similar effect of reducing the amount of HIV in the blood compared to another drug regimen, which included dolutegravir, emtricitabine, and tenofovir. The treatment was considered successful if the patient maintained low-levels (less than 50 copies/mL) of HIV RNA in their blood for at least 48 weeks.
The most common adverse reactions with Dovato were headache, diarrhea, nausea, insomnia and fatigue. As there is a known risk for neural tube defects with dolutegravir, patients are advised to avoid use of Dovato at the time of conception through the first trimester of pregnancy. In May 2018, the FDA released a Drug Safety Communication regarding reported neural tube birth defects in babies born to women treated with dolutegravir.
In Feb. 2019, the U.S. Department of Health and Humans Services announced a new initiative, Ending the HIV Epidemic: A Plan for America, a once-in-a-generation opportunity to eliminate new HIV infections in our nation. This initiative will provide the hardest hit communities with the additional expertise, technology and resources required to address the HIV epidemic in their communities, focusing on certain geographic hotspots. The aim is to reduce new infections by 75 percent in the next five years and by 90 percent in the next ten years, averting more than 250,000 HIV infections in that span.
The FDA granted approval of Dovato to ViiV Healthcare.

Safety Announcements

FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines

[4/30/19] The FDA is advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with eszopiclone (Lunesta®), zaleplon (Sonata®), and zolpidem (Ambien®, Ambien® CR, Edluar®, Intermezzo®, Zolpimist®) than other prescription medicines used for sleep.
As a result, the FDA requiring a ***Boxed Warning***, their most prominent warning, to be added to the prescribing information and the patient Medication Guides for these medicines. We are also requiring a *Contraindication*, their strongest warning, to avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem.
Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids, and anti-anxiety medicines.
Eszopiclone, zaleplon, and zolpidem are medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep. They are in a class of medicines called sedative-hypnotics and have been approved and on the market for many years. These insomnia medicines work by slowing activity in the brain to allow sleep. Quality sleep can have a positive impact on physical and mental health.
Health care professionals should not prescribe eszopiclone, zaleplon, or zolpidem to patients who have previously experienced complex sleep behaviors after taking any of these medicines. Advise all patients that although rare, the behaviors caused by these medicines have led to serious injuries or death. Tell the patient to discontinue taking these medicines if they experience an episode of complex sleep behavior.
Patients should stop taking your insomnia medicine and contact your health care professional right away if you experience a complex sleep behavior where you engage in activities while you are not fully awake or if you do not remember activities you have done while taking the medicine.
We identified 66 cases of complex sleep behaviors occurring with these medicines over the past 26 years that resulted in serious injuries, including death. This number includes only reports submitted to FDA or those found in the medical literature, so there may be additional cases about which we are unaware. These cases included accidental overdoses, falls, burns, near drowning, exposure to extreme cold temperatures leading to loss of

limb, carbon monoxide poisoning, drowning, hypothermia, motor vehicle collisions with the patient driving, and self-injuries such as gunshot wounds and apparent suicide attempts. Patients usually did not remember these events. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.
FDA is also reminding the public that all medicines taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia medicines, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia medicines can experience decreased mental alertness the morning after use even if they feel fully awake.
We communicated safety information associated with certain insomnia medicines in January 2013 (risk of next-morning impairment with zolpidem), May 2013 (approved lower recommended doses for zolpidem), and May 2014 (risk of next-morning impairment with eszopiclone; lowered recommended dose). We are continuing to monitor the safety of insomnia medicines and will update the public as new information becomes available.
To help FDA better track safety issues with medicines, we urge health care professionals and patients to report side effects involving eszopiclone, zaleplon, and zolpidem or other medicines to the FDA MedWatch program.

Safety Announcements

FDA orders important safety labeling changes for Addyi®

Studies affirm need for warnings related to alcohol use with Addyi®

[4/11/19] The FDA issued a safety labeling change order to Sprout Pharmaceuticals for their drug, Addyi® (flibanserin), that requires the company to revise important safety information that women and their health care professionals need to have when considering use of the drug. The changes are the result of the FDA's review of postmarketing studies, including one required of Sprout when Addyi® was approved in August 2015, to treat acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women, as well as other data.

At the time of approval, the FDA reviewed data that included several concerning cases of severe hypotension (low blood pressure) and syncope (passing out) when Addyi® and alcohol were taken together. As a result, Addyi®'s labeling currently includes a boxed warning, which states that alcohol must be avoided in women treated with Addyi®. The FDA also required a risk evaluation and mitigation strategy (REMS), which requires that health care professionals who prescribe Addyi® and pharmacies that dispense Addyi®, must be certified with the Addyi® REMS program and that patients must be counseled about the risk of hypotension and syncope. In addition, the FDA required Sprout to further study the interaction between Addyi® and alcohol after approval.
Based on the results of postmarketing studies, the FDA has determined that changes must be made to Addyi®'s labeling to clarify that there is still a concern about consuming alcohol close in time to taking Addyi® but that it does not have to be avoided completely. Specifically, the boxed warning, contraindication, warnings and precautions, and adverse reactions sections of labeling are being updated to reflect that women should discontinue drinking alcohol at least two hours before taking Addyi® at bedtime or to skip the Addyi® dose that evening. Women should not consume alcohol at least until the morning after taking Addyi® at bedtime.
The FDA is ordering a safety labeling change requiring Sprout to make these changes because the agency was not able to reach an agreement with the company, which was continuing to request removal of the boxed warning and contraindication about alcohol completely from the product labeling. The FDA determined, based on a careful review of available data, that removing this important safety information was not acceptable for the protection of public health.
The FDA's decision to order modifications to the warnings about Addyi® and alcohol, instead of removing the boxed warning and contraindication completely, is based on two sets of postmarket research studies.
In the FDA-required postmarketing trial in women who took Addyi® and drank alcohol at the same time, there were missing or delayed measurements for blood pressure from when the women were first laying down to when they stood up that are critical in determining the risk of hypotension and syncope when taking Addyi® and alcohol together. The FDA's specific concerns with the trial included:

- While there were no reports of syncope or hypotension needing intervention amongst women in the trial, the safety precautions built into this trial did not allow for an adequate assessment of this risk. For example, women with low blood pressure while lying down or with symptoms that could be related to low blood pressure (such as dizziness) were not permitted to stand up to have blood pressure measurements taken or had to have repeated blood pressure measurements while lying down until

they were high enough for the women to safely stand up. As a result, the data collected had missing or delayed blood pressure measurements from these women while standing.

- Many more women had missing or delayed blood pressure measurements when they took Addyi® and alcohol together compared to when they received alcohol alone or Addyi® alone.
- The amount of missing blood pressure measurements peaked around the time when Addyi®'s blood levels were highest in those taking Addyi® with alcohol.

The pattern of the missing or delayed measurements provides further evidence of an interaction between Addyi® and alcohol that can increase the risk of hypotension and syncope. Given these results, the FDA has determined that the boxed warning and contraindication continue to be warranted. Women at home will not have the safety measures that were included in this trial or necessarily have access to immediate assistance if they were to experience severe hypotension or syncope, which can lead to serious outcomes including falls, accidents and bodily harm.

In other postmarketing trials, results showed that the risk of severe hypotension and syncope was reduced when women who consumed up to two alcoholic drinks waited at least two hours before taking Addyi®. The FDA has found these results sufficient to support a modification to the boxed warning and contraindication stating that Addyi® and alcohol must not be taken close in time (i.e. not within two hours).

Addyi® is a serotonin 1A receptor agonist and a serotonin 2A receptor antagonist, but the mechanism by which the drug improves sexual desire and related distress is not known. Addyi® is taken once daily. It is dosed at bedtime to help decrease the risk of adverse events occurring due to possible hypotension, syncope and central nervous system depression (such as sleepiness and sedation). Patients should discontinue treatment after eight weeks if they do not report an improvement in sexual desire and associated distress. The most common adverse reactions associated with the use of Addyi® are dizziness, somnolence (sleepiness), nausea, fatigue, insomnia and dry mouth.

The Food and Drug Administration Amendments Act of 2007 gave the FDA the authority to require and, when necessary, order safety labeling changes to reflect new safety information about an approved prescription drug. Failure to respond to the order as outlined may result in monetary fines and additional enforcement actions including seizure of the product and injunction.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

Current Drug Shortages Index (as of April 30th, 2019):

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

Abciximab (ReoPro) Injection	***Currently in Shortage***
Amino Acids	***Currently in Shortage***
Aminophylline Injection, USP	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Azithromycin (Azasite) Ophthalmic Solution 1%	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Bisoprolol Fumarate Tablets	***Currently in Shortage***
Bumetanide Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride and Epinephrine Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride Injection, USP	***Currently in Shortage***
Buspirone HCl Tablets	***Currently in Shortage***
Calcitriol Injection USP 1MCG /ML	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Carbidopa and Levodopa Extended Release Tablets	***Currently in Shortage***
Carisoprodol Tablets, USP	***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***
Dexamethasone Sodium Phosphate Injection	***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***
Dicyclomine Oral Tablets/Capsules	***Currently in Shortage***
Diltiazem Hydrochloride	***Currently in Shortage***
Diltiazem Hydrochloride ER (Twice-a-Day) Capsules	***Currently in Shortage***
Diphenhydramine Injection	***Currently in Shortage***
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***
Enalaprilat Injection, USP	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Epinephrine Injection, Auto-Injector	***Currently in Shortage***
Eprosartan Mesylate Tablets	***Currently in Shortage***
Erythromycin Lactobionate for Injection, USP	***Currently in Shortage***
Erythromycin Ophthalmic Ointment	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fludrocortisone Acetate Tablets	***Currently in Shortage***
Fluorescein Injection	***Currently in Shortage***
Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Fluorescein Strips	***Currently in Shortage***
Flurazepam Hydrochloride Capsules	***Currently in Shortage***
Fluvoxamine ER Capsules	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Guanfacine Hydrochloride Tablets	***Currently in Shortage***
Haloperidol Tablets	***Currently in Shortage***
Heparin Sodium and Sodium Chloride 0.9% Injection	***Currently in Shortage***
Hydromorphone Hydrochloride Injection, USP	***Currently in Shortage***
Hydroxyprogesterone Caproate Injection	***Currently in Shortage***
Hydroxyzine Pamoate Oral Capsules	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Isocarboxazid Tablets	***Currently in Shortage***
Ketamine Injection	***Currently in Shortage***
Ketoprofen Capsules	***Currently in Shortage***
Ketorolac Tromethamine Injection	***Currently in Shortage***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Latanoprost Ophthalmic Solution 0.005%	***Currently in Shortage***
Letermovir (Prevymis) Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Leuprolide Acetate Injection	***Currently in Shortage***
Levetiracetam Immediate-Release Oral Tablets, USP	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) and Dextrose Injection Solution-Premix Bags	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***

Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Lorazepam Injection, USP	***Currently in Shortage***
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 Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLIVANT XR) for Extended-Release Oral Susp	***Currently in Shortage***
Metoclopramide Injection, USP	***Currently in Shortage***
Metoprolol Tartrate Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Morphine Sulfate Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nelarabine (Arranon) Injection	***Currently in Shortage***
Nystatin Oral Suspension	***Currently in Shortage***
Olmesartan Medoxomil Tablets	***Currently in Shortage***
Ondansetron Hydrochloride Injection	***Currently in Shortage***
Penicillamine (Depen) Titratable Tablets	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Phenytoin Sodium Injection, USP	***Currently in Shortage***
Phosphate Injection Products	***Currently in Shortage***
Physostigmine Salicylate Injection, USP	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Prednisolone Acetate 1% Ophthalmic Suspension	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Progesterone Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	***Currently in Shortage***
Ropivacaine Hydrochloride Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine Transdermal System	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sodium Chloride Injection USP, 0.9% Vials and Syringes	***Currently in Shortage***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Sterile Water	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Thioridazine Hydrochloride Tablets	***Currently in Shortage***
Thiothixene Capsules	***Currently in Shortage***
Timolol Maleate Tablets	***Currently in Shortage***
Trifluoperazine Hydrochloride Tablets	***Currently in Shortage***
Valsartan Tablets	***Currently in Shortage***