Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
September 12, 2018
4:00pm

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

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review (DUR) Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for DUR Board Meeting – September 12, 2018

DATE: August 27, 2018

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

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

Call to Order

Public Comment Forum

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

Update on Medication Coverage Authorization Unit/Proton Pump Inhibitor (PPI) Deprescribing Mailing Update – Appendix B

Action Item – Vote to Prior Authorize Apadaz® [Benzhydrocodone/Acetaminophen (APAP)], Lucemyra™ (Lofexidine), and Sublocade™ [Buprenorphine Extended-Release (ER) Injection] – Appendix C

Action Item – Vote to Prior Authorize Jynarque™ (Tolvaptan) – Appendix D

Annual Review of Breast Cancer Medications and 30-Day Notice to Prior Authorize Verzenio™ (Abemaciclib), Ogivri™ (Trastuzumab-dkst), and Lynparza® (Olaparib) – Appendix E

Annual Review of Sickle Cell Disease (SCD) Medications and 30-Day Notice to Prior Authorize NutreStore® (L-Glutamine) and Siklos® (Hydroxyurea) – Appendix F

Annual Review of Phenylketonuria Medications and 30-Day Notice to Prior Authorize Palynziq™ (Pegvaliase-pqpz) – Appendix G

Annual Review of Synagis® (Palivizumab) – Appendix H

Annual Review of Fabry Disease Medications and 30-Day Notice to Prior Authorize Galafold™ (Migalastat) – Appendix I

30-Day Notice to Prior Authorize Qbrexza™ (Glycopyrronium) – Appendix J

Annual Review of Antihyperlipidemics and 30-Day Notice to Prior Authorize FloLipid® (Simvastatin Oral Suspension) – Appendix K

Annual Review of Parathyroid Medications – Appendix L

Annual Review of Growth Hormone – Appendix M

Industry News and Updates – Appendix N

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – September 12, 2018 @ 4:00pm

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call to Order

A. Roll Call – Dr. Cothran

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. July 11, 2018 DUR Minutes – Vote
B. July 11, 2018 DUR Recommendations Memorandum

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

4. Update on Medication Coverage Authorization Unit/Proton Pump Inhibitor (PPI) Deprescribing Mailing Update – See Appendix B

A. Medication Coverage Activity for July 2018
B. Pharmacy Helpdesk Activity for July 2018
C. Medication Coverage Activity for August 2018
D. Pharmacy Helpdesk Activity for August 2018
E. Proton Pump Inhibitor (PPI) Deprescribing Mailing Update

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

5. Action Item – Vote to Prior Authorize Apadaz® [Benzhydrocodone/Acetaminophen (APAP)], Lucemyra™ (Lofexidine), and Sublocade™ [Buprenorphine Extended-Release (ER) Injection] – See Appendix C

A. Introduction
B. College of Pharmacy Recommendations

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

6. Action Item – Vote to Prior Authorize Jynarque™ (Tolvaptan) – See Appendix D

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

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

7. Annual Review of Breast Cancer Medications and 30-Day Notice to Prior Authorize Verzenio™ (Abemaciclib), Ogivri™ (Trastuzumab-dkst), and Lynparza® (Olaparib) – See Appendix E

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

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

8. Annual Review of Sickle Cell Disease (SCD) Medications and 30-Day Notice to Prior Authorize NutreStore® (L-Glutamine) and Siklos® (Hydroxyurea) – See Appendix F

A. Current Prior Authorization Criteria
B. Utilization of SCD Medications
C. Prior Authorization of SCD Medications
D. Market News and Updates
E. Siklos® (Hydroxyurea) Product Summary
F. NutreStore® (L-Glutamine Powder for Oral Solution) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of SCD Medications

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

9. Annual Review of Phenylketonuria Medications and 30-Day Notice to Prior Authorize Palynziq™ (Pegvaliase-pqpz) – See Appendix G

A. Phenylketonuria Introduction
B. Current Prior Authorization Criteria
C. Utilization of Phenylketonuria Medications
D. Prior Authorization of Phenylketonuria Medications
E. Market News and Updates
F. Palynziq™ (Pegvaliase-pqpz) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Phenylketonuria Medications

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

10. Annual Review of Synagis® (Palivizumab) – See Appendix H

A. Current Prior Authorization Criteria
B. Utilization of Synagis® (Palivizumab)
C. Prior Authorization of Synagis® (Palivizumab)
D. Season Comparison
E. Market News and Updates
F. College of Pharmacy Recommendations

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

11. Annual Review of Fabry Disease Medications and 30-Day Notice to Prior Authorize Galafold™ (Migalastat) – See Appendix I

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Fabrazyme® (Agalsidase Beta)
D. Prior Authorization of Fabrazyme® (Agalsidase Beta)
E. Market News and Updates
F. Galafold™ (Migalastat) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Fabrazyme® (Agalsidase Beta)

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

12. 30-Day Notice to Prior Authorize Qbrexza™ (Glycopyrronium) – See Appendix J

A. Hyperhidrosis Introduction
B. Qbrexza™ (Glycopyrronium) Product Summary
C. Market News and Updates
D. College of Pharmacy Recommendations

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

13. Annual Review of Antihyperlipidemics and 30-Day Notice to Prior Authorize FloLipid® (Simvastatin Oral Suspension) – See Appendix K

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

Non-Presentation; Questions Only:

14. Annual Review of Parathyroid Medications – See Appendix L

A. Current Prior Authorization Criteria
B. Utilization of Parathyroid Medications
C. Prior Authorization of Parathyroid Medications
D. Market News and Updates
E. College of Pharmacy Recommendations
F. Utilization Details of Calcimimetics and Vitamin D Analogs
G. Utilization Details of Natpara® (Parathyroid Hormone Injection)

Non-Presentation; Questions Only:

15. Annual Review of Growth Hormone – See Appendix M

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

Non-Presentation; Questions Only:

16. Industry News and Updates – See Appendix N

A. Introduction
B. News and Updates

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

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

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

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

A. Targeted Immunomodulator Agents
B. Topical Corticosteroids
C. Constipation and Diarrhea Medications
D. Bladder Control Medications
E. Acute Lymphoblastic Leukemia and Chronic Myeloid Leukemia Medications
F. Skin Cancer Medications
G. Gonadotropin-Releasing Hormone Medications
H. Butalbital Medications

**Future business subject to change.*

19. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF JULY 11, 2018

BOARD MEMBERS:	PRESENT	ABSENT
Stephen Anderson, Pharm.D.	x	
Darlla D. Duniphin, MHS, PA-C	x	
Theresa Garton, M.D.	x	
Carla Hardzog-Britt, M.D.		x
Ashley Huddleston, Pharm.D., BCOP	x	
John Muchmore, M.D., Ph.D.; Chairman	x	
Lee Munoz, D.Ph.		x
James Osborne, Pharm.D.		x
Paul Louis Preslar, D.O., MBA; Vice Chairman	x	

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Melissa Abbott, Pharm.D.; Clinical Pharmacist	x	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Wendi Chandler, Pharm.D.; Clinical Pharmacist	x	
Sarai Connell, Pharm.D.; MBA; Resident	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Erin Ford, Pharm.D.; Clinical Pharmacist		x
Thomas Ha, Pharm.D.; Clinical Pharmacist	x	
Bethany Holderread, Pharm.D.; Clinical Coordinator	x	
Shellie Keast, Ph.D.; Assistant Professor	x	
Carol Moore, Pharm.D.; Clinical Pharmacist		x
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Timothy Pham, Ph.D.; Postdoctoral Research Fellow		x
Leslie Robinson, D.Ph.; PA Coordinator		x
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist	x	
Graduate Students: Christina Bulkley, Pharm.D.		x
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.; Assistant Pharmacy Director	x	
Kelli Brodersen, Marketing Coordinator		x
Robert Evans, M.D.; Sr. Medical Director		x
Michael Herndon, D.O.; Chief Medical Officer		x
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Thomas Nunn, D.O.; Medical Director	x	
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist		x
Joseph Young, J.D.; Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Jason Schwier, Juno	Charlie Collins, Sanofi Genzyme	Christina Heiner, Viking HCS
Jim Dunlap, PhRMA	Jon Maguire, GSK	Rhonda Clark, Indivior
John Kirby, Indivior	Eric Gardner, Vertex	Lisa Gilliam, Orexo
Megan Loftis, Ultragenx	Dan Doyle, Trividia	Terry McCurren, Otsuka
Sean George, Otsuka	Jane Stephen, Amgen	Audrey Ratten, Alkermes
Shelley Thompson, Alkermes	Valerie Ng, Indivior	Michael Boskello, Alkermes
Brian Buckles, Takeda	Amber Schrantz, Lilly	Travis Tate, Health Choice
Mai Duong, Novartis	Aaron Shaw, BI	Cris Valladares, Celgene
Brian Maves, Pfizer	Erica Brumleve, GSK	Dana Pipkin, Sarepta
Birqit Amann, Rhodes	Sean George, Otsuka	

PRESENT FOR PUBLIC COMMENT:	
Valerie Ng	Indivior
Michael Boskello	Alkermes
Birqit Amann	Rhodes
Sean George	Otsuka

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. 8 SPEAKER: BIRQIT AMANN
2B: AGENDA ITEM NO. 12 SPEAKER: VALERIE NG
2C: AGENDA ITEM NO. 12 SPEAKER: MICHAEL BOSKELLO
2D: AGENDA ITEM NO. 13 SPEAKER: SEAN GEORGE

ACTION: NONE REQUIRED

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

3A: JUNE 13, 2018 DUR MINUTES – VOTE
3B: JUNE 13, 2018 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Cothran
Dr. Preslar moved to approve; seconded by Dr. Anderson

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/SOONERCARE OPIOID INITIATIVE UPDATE

4A: MEDICATION COVERAGE ACTIVITY FOR JUNE 2018
4B: PHARMACY HELP DESK ACTIVITY FOR JUNE 2018
4C: SOONERCARE OPIOID INITIATIVE UPDATE – VOTE

Materials included in agenda packet; presented by Dr. Holderread
Dr. Anderson moved to approve; seconded by Dr. Garton

ACTION: MOTION CARRIED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE CRYSVITA® (BUROSUMAB-TWZA)

5A: INTRODUCTION
5B: MARKET NEWS AND UPDATES
5C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread
Dr. Huddleston moved to approve; seconded by Dr. Preslar

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE IMFINZI® (DURVALUMAB) AND TO UPDATE THE CURRENT LUNG CANCER MEDICATIONS PRIOR AUTHORIZATION CRITERIA

6A: INTRODUCTION

6B: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Medina

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE ERLEADA™ (APALUTAMIDE) AND YONSA® (ABIRATERONE)

7A: INTRODUCTION

7B: RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Medina

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE COTEMPLA XR-ODT™ [METHYLPHENIDATE EXTENDED-RELEASE (ER) ORALLY DISINTEGRATING TABLET (ODT)], MYDAYIS® (AMPHETAMINE/DEXTROAMPHETAMINE ER CAPSULE), AND ADZENYS ER™ (AMPHETAMINE ER SUSPENSION)

8A: INTRODUCTION

8B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Adams

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE BACLOFEN 5MG TABLET, ESOMEP-EZS™ (ESOMEPRAZOLE KIT), LYRICA® CR (PREGABALIN EXTENDED-RELEASE), RESTASIS MULTIDOSE® (CYCLOSPORINE 0.05% OPHTHALMIC EMULSION), SINUVA™ (MOMETASONE FUROATE SINUS IMPLANT), XEPI™ (OZENOXACIN 1% CREAM), XHANCE™ (FLUTICASONE PROPIONATE NASAL SPRAY), AND ZTLIDO™ (LIDOCAINE 1.8% TOPICAL SYSTEM)

9A: INTRODUCTION

9B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Chandler

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: ANNUAL REVIEW OF ATOPIC DERMATITIS (AD) MEDICATIONS

10A: CURRENT PRIOR AUTHORIZATION CRITERIA

10B: UTILIZATION OF AD MEDICATIONS

10C: PRIOR AUTHORIZATION OF AD MEDICATIONS

10D: MARKET NEWS AND UPDATES

10E: COLLEGE OF PHARMACY RECOMMENDATIONS

10F: UTILIZATION DETAILS OF AD MEDICATIONS

Materials included in agenda packet; presented by Dr. Abbott

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: ANNUAL REVIEW OF BOTULINUM TOXINS

11A: CURRENT PRIOR AUTHORIZATION CRITERIA

11B: UTILIZATION OF BOTULINUM TOXINS

11C: PRIOR AUTHORIZATION OF BOTULINUM TOXINS

11D: MARKET NEWS AND UPDATES

11E: COLLEGE OF PHARMACY RECOMMENDATIONS

11F: UTILIZATION DETAILS OF BOTULINUM TOXINS

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

AGENDA ITEM NO. 12: ANNUAL REVIEW OF OPIOID ANALGESICS AND OPIOID MEDICATION ASSISTED TREATMENT (MAT) MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE APADAZ® [BENZHYDROCODONE/ACETAMINOPHEN (APAP)], LUCEMYRA™ (LOFEXIDINE), AND SUBLOCADE™ [BUPRENORPHINE EXTENDED-RELEASE (ER) INJECTION]

12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF OPIOID ANALGESICS AND MAT MEDICATIONS
12C: PRIOR AUTHORIZATION OF OPIOID ANALGESICS AND MAT MEDICATIONS
12D: MARKET NEWS AND UPDATES
12E: APADAZ® (BENZHYDROCODONE/APAP TABLETS) PRODUCT SUMMARY
12F: LUCEMYRA™ (LOFEXIDINE TABLETS) PRODUCT SUMMARY
12G: SUBLOCADE™ (BUPRENORPHINE ER INJECTION) PRODUCT SUMMARY
12H: COLLEGE OF PHARMACY RECOMMENDATIONS
12I: UTILIZATION DETAILS OF OPIOID ANALGESICS
12J: UTILIZATION DETAILS OF MAT MEDICATIONS

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

AGENDA ITEM NO. 13: 30-DAY NOTICE TO PRIOR AUTHORIZE JYNARQUE™ (TOLVAPTAN)

13A: INTRODUCTION
13B: MARKET NEWS AND UPDATES
13C: JYNARQUE™ (TOLVAPTAN) PRODUCT SUMMARY
13D: COLLEGE OF PHARMACY RECOMMENDATIONS

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

AGENDA ITEM NO. 14: ANNUAL REVIEW OF VIMIZIM® (ELOSULFASE ALFA)

14A: INTRODUCTION
14B: CURRENT PRIOR AUTHORIZATION CRITERIA
14C: UTILIZATION OF VIMIZIM® (ELOSULFASE ALFA)
14D: PRIOR AUTHORIZATION OF VIMIZIM® (ELOSULFASE ALFA)
14E: COLLEGE OF PHARMACY RECOMMENDATIONS

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

AGENDA ITEM NO. 15: ANNUAL REVIEW OF BRINEURA® (CERLIPONASE ALFA)

15A: INTRODUCTION
15B: CURRENT PRIOR AUTHROZIATION CRITERIA
15C: UTILIZATION OF BRINEURA® (CERLIPONASE ALFA)
15D: PRIOR AUTHORIZATION OF BRINEURA® (CERLIPONASE ALFA)
15E: MARKET NEWS AND UPDATES
15F: COLLEGE OF PHARMACY RECOMMENDATIONS

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

AGENDA ITEM NO. 16: ANNUAL REVIEW OF RADICAVA® (EDARAVONE)

16A: INTRODUCTION
16B: CURRENT PRIOR AUTHORIZATION CRITERIA
16C: UTILIZATION OF RADICAVA® (EDARAVONE)
16D: PRIOR AUTHORIZATION OF RADICAVA® (EDARAVONE)
16E: MARKET NEWS AND UPDATES
16F: COLLEGE OF PHARMACY RECOMMENDATIONS

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

AGENDA ITEM NO. 17: INDUSTRY NEWS AND UPDATES

17A: INTRODUCTION

17B: NEWS AND UPDATES

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

AGENDA ITEM NO. 18: 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. 19: FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)

NO MEETING SCHEDULED FOR AUGUST

19A: ANTIHYPERLIPIDEMICS

19B: FABRAZYME® (AGALSIDASE BETA)

19C: GROWTH HORMONE

19D: BUTALBITAL MEDICATIONS

19E: SYNAGIS® (PALIVIZUMAB)

19F: BREAST CANCER MEDICATIONS

19G: SICKLE CELL MEDICATIONS

****FUTURE BUSINESS SUBJECT TO CHANGE***

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

AGENDA ITEM NO. 20: ADJOURNMENT

The meeting was adjourned at 5:25pm.

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

Memorandum

Date: July 12, 2018

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

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of July 11, 2018

Recommendation 1: SoonerCare Opioid Initiative Update

MOTION CARRIED by unanimous approval.

The College of Pharmacy in partnership with the OHCA recommends the implementation of a daily morphine milligram equivalent (MME) limit of 100 to coincide with the Oklahoma Bureau of Narcotics and Dangerous Drugs (OBNDD) clinical alert on the Oklahoma Prescription Monitoring Program (PMP) database.

1. Prior authorization would be required for members exceeding the 100 MME limit per day. Prior authorizations would require patient-specific, clinically significant reasoning for daily doses exceeding 100 MME. Prescribers must provide reasoning for why tapering to below the MME limit is not appropriate for the member.
2. Oncology diagnoses would be excluded from the MME limit.
3. The MME limit would be implemented in three phases (gradual lowering of the MME limit) with several months between each phase to allow for opioid taper.

Recommendation 2: Vote to Prior Authorize Crysvita® (Burosumab-twza)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Crysvita® (burosumab-twza) with the following criteria:

Crysvita® (Burosumab-twza) Approval Criteria:

1. An FDA approved indication for the treatment of X-linked hypophosphatemia (XLH) in adult and pediatric members 1 year of age and older. Diagnosis of XLH must be confirmed by one of the following:
    a. Genetic testing; or
    b. Elevated serum fibroblast growth factor 23 (FGF23) level; and
2. Member's serum phosphorus level must be below the normal range for member age; and
3. Member's XLH symptoms must not be adequately controlled on phosphate and calcitriol supplements. Members experiencing adverse effects related to these treatments may also be considered for approval. Detailed information regarding adverse effects must be documented on the prior authorization request; and
4. Member must not have any contraindications to taking Crysvita® including the following:
    a. Concomitant use with oral phosphate and active vitamin D analogs; and
    b. Serum phosphorus within or above the normal range for member age; and
    c. Severe renal impairment or end-stage renal disease; and
5. Crysvita® must be administered by a health care professional. Approvals will not be granted for self-administration. Prior authorization requests must indicate how Crysvita® will be administered; and
    a. Crysvita® must be shipped via cold chain supply to the facility where the member is scheduled to receive treatment; and
6. Member must have clinical signs and symptoms of XLH (symptoms beyond hypophosphatemia alone); and
7. Every two week dosing will not be approved for members 18 years of age or older; and
8. The prescriber must agree to assess serum phosphorus levels on a monthly basis for the first 3 months of treatment, and thereafter as appropriate; and
9. Crysvita® must be prescribed by a nephrologist, endocrinologist, or specialist with expertise in the treatment of XLH (or be an advanced care practitioner with a supervising physician who is a nephrologist, endocrinologist, or specialist with expertise in the treatment of XLH); and
10. Initial authorizations will be for the duration of 6 months, at which time the prescriber must verify the member is responding to the medication as demonstrated by serum phosphorus levels within the normal range for member age or clinically significant improvement in bone-related symptoms; and
11. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Recommendation 3: Vote to Prior Authorize Imfinzi® (Durvalumab) and to Update the Current Lung Cancer Medications Prior Authorization Criteria

MOTION CARRIED by unanimous approval.

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

1. Diagnosis of recurrent or metastatic NSCLC; and
2. Anaplastic lymphoma kinase (ALK) positivity; and
3. ~~Progressed on or intolerant to crizotinib; or~~
4. ~~Member has asymptomatic disease with rapid radiologic progression on crizotinib; and~~
5. Alectinib may be used in first-line or recurrent setting; and
6. Alectinib must be used as a single-agent only.

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

1. Diagnosis of stage III NSCLC; and
2. Disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.

Imfinzi® (Durvalumab) Approval Criteria [Urothelial Carcinoma Diagnosis]:

1. Diagnosis of locally advanced or metastatic urothelial carcinoma; and
2. Progressed on or following platinum-containing chemotherapy.

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

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

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

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

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

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

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

1. For nivolumab monotherapy:
    a. A diagnosis of relapsed or surgically unresectable stage IV disease; and
    b. Failed prior therapy with one of the following medications:
        i. Sunitinib; or
        ii. Sorafenib; or
        iii. Pazopanib; or

iv. Axitinib; or

2. For nivolumab use in combination with ipilimumab:
   a. A diagnosis of relapsed or surgically unresectable stage IV disease in the initial treatment of members with intermediate or poor risk, previously untreated, advanced RCC; and
3. The member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
4. Dose as follows:
   a. Single-agent: 240mg every two weeks or 480mg every four weeks; or
   b. In combination with ipilimumab: nivolumab 3mg/kg followed by ipilimumab 1mg/kg on the same day, every three weeks for a maximum of four doses, then nivolumab 240mg every two weeks or 480mg every four weeks.

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

1. Diagnosis of unresectable or metastatic melanoma; and
2. Nivolumab must be used as a single-agent, or in combination with ipilimumab:
   a. As first-line therapy for untreated melanoma; or
   b. As second-line or subsequent therapy for documented disease progression while receiving or since completing most recent therapy:
      i. If the member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
3. Dose as follows:
   a. Single-agent: 240mg every two weeks or 480mg every four weeks; or
   b. In combination with ipilimumab: 1mg/kg, followed by ipilimumab on the same day, every three weeks for four doses, then 240mg every two weeks or 480mg every four weeks.

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

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

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

1. A diagnosis of recurrent or metastatic head and neck cancer; and
2. Squamous cell histology; and
3. Member has received prior platinum-containing regimen (e.g., cisplatin, carboplatin); and
4. The member has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and

5. Dose as follows: ~~3mg/kg every two weeks~~ 240mg every two weeks or 480mg every four weeks.

Tagrisso™ (Osimertinib) Approval Criteria [Non-Small Cell Lung Cancer (NSCLC) Diagnosis]:

1. A diagnosis of metastatic NSCLC; and
    a. Epidermal growth factor receptor (EGFR) T790M mutation-positive disease and following progression on erlotinib, afatinib, or gefitinib for asymptomatic disease, symptomatic brain lesions, or multiple symptomatic systemic lesions; or
    b. First-line treatment of members with EGFR exon 19 deletions or exon 21 L858R mutations.
2. ~~Osimertinib must be used for subsequent therapy only.~~

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

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

Recommendation 4: Vote to Prior Authorize Erleada™ (Apalutamide) and Yonsa® (Abiraterone)

MOTION CARRIED by unanimous approval.

Erleada™ (Apalutamide) Approval Criteria:

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

Yonsa® (Abiraterone) Approval Criteria:

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

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

1. A diagnosis of metastatic, high-risk, CSPC; and
2. Member must have high-risk disease defined as having at least two of the following risk factors:
    a. Total Gleason score of ≥8; or

b. Presence of ≥3 lesions on bone scan; or
c. Evidence of measurable visceral metastases; and

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

Recommendation 5: Vote to Prior Authorize Cotempla XR-ODT™ [Methylphenidate Extended-Release (ER) Orally Disintegrating Tablet (ODT)], Mydayis® (Amphetamine/Dextroamphetamine ER Capsule), and Adzenys ER™ (Amphetamine ER Suspension)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the placement of Cotempla XR-ODT™ (methylphenidate ER ODT), Mydayis® (amphetamine/dextroamphetamine ER capsule), and Adzenys ER™ (amphetamine ER suspension) into the Special Prior Authorization (PA) Tier of the ADHD and Narcolepsy Medications Product Based Prior Authorization (PBPA) category, based on net costs, with the following criteria (changes noted in red):

ADHD Medications Tier-2 Approval Criteria:

1. A covered diagnosis; and
2. A previously failed trial with at least one long-acting Tier-1 stimulant that resulted in an inadequate response:
   a. Trials should have been within the last 180 days; and
   b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician; and
3. For Quillivant XR®, an age restriction of ten years and younger will apply. Members older than ten years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.

ADHD Medications Tier-3 Approval Criteria:

1. A covered diagnosis; and
2. A previously failed trial with at least one long-acting Tier-1 stimulant that resulted in an inadequate response; and
3. A previously failed trial with at least one long-acting Tier-2 stimulant that resulted in an inadequate response:
   a. Trials should have been within the last 365 days; and
   b. Trials should have been dosed up to maximum recommended dose or documented adverse effects at higher doses should be included; and
   c. If trials are not in member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician.
4. A clinical exception may apply for special formulation products when there is a patient-specific, clinically significant reason why the member cannot use the available long-acting lower tiered formulations.

5. Use of Kapvay® (clonidine extended-release tablets) requires:
    a. An FDA approved diagnosis; and
    b. Previously failed trials (within the last 180 days) with a long-acting Tier-1 stimulant, a long-acting Tier-2 stimulant, Intuniv®, and Strattera®, unless contraindicated, that did not yield adequate results; and
    c. A patient-specific, clinically significant reason why the member cannot use clonidine immediate-release tablets.

ADHD Medications Special Prior Authorization (PA) Approval Criteria:

1. Desoxyn®, Dexedrine®, Dexedrine Spansules®, Evekeo®, ProCentra®, and Zenzedi® Approval Criteria:
    a. A covered diagnosis; and
    b. A patient-specific, clinically significant reason why the member cannot use all other available stimulant medications.
2. Adzenys XR-ODT®, Adzenys ER™, Cotempla XR-ODT™, Daytrana®, Dyanavel® XR, and Methylin® Chewable Tablets and Solution Approval Criteria:
    a. A covered diagnosis; and
    b. A patient-specific, clinically significant reason why the member cannot use all other available formulations of stimulant medications that can be used for members who cannot swallow capsules or tablets; and
    c. An age restriction of ten years and younger will apply. Members older than ten years of age will require a patient-specific, clinically significant reason why a special formulation product is needed.
3. Mydayis® Approval Criteria:
    a. A covered diagnosis; and
    b. Member must be 13 years of age or older; and
    c. A patient-specific, clinically significant reason why the member cannot use all other available stimulant medications.

ADHD Medications Additional Criteria:

1. Doses exceeding 1.5 times the FDA maximum are not covered.
2. Prior authorization is required for all tiers for members older than 20 years of age and for members younger than 5 years of age. All prior authorization requests for members younger than 5 years of age must be reviewed by an Oklahoma Health Care Authority (OHCA)-contracted psychiatrist.
3. Vyvanse® (Lisdexamfetamine) Approval Criteria [Binge Eating Disorder (BED) Diagnosis]:
    a. An FDA approved diagnosis of moderate-to-severe binge eating disorder (BED); and
    b. Member must be 18 years of age or older; and
    c. Vyvanse® for the diagnosis of BED must be prescribed by a psychiatrist; and
    d. Authorizations will not be granted for the purpose of weight loss without the diagnosis of BED or for the diagnosis of obesity alone. The safety and effectiveness of Vyvanse® for the treatment of obesity have not been established; and
    e. A quantity limit of 30 capsules or chewable tablets per 30 days will apply; and
    f. Initial approvals will be for the duration of three months. Continued authorization will require prescriber documentation of improved response/effectiveness of Vyvanse®.

ADHD Medications			
Tier-1*	**Tier-2***	**Tier-3***	**Special PA**
Amphetamine			Adzenys ER™ (amphetamine ER susp) Adzenys XR-ODT® (amphetamine ER-ODT) Cotempla XR-ODT™ (methylphenidate ER ODT) Daytrana® (methylphenidate ER) Desoxyn® (methamphetamine) Dexedrine® (dextroamphetamine) Dexedrine Spansules® (dextroamphetamine ER) Dyanavel® XR (amphetamine ER susp) Evekeo® (amphetamine) Methylin® (methylphenidate soln & chew tabs) Mydayis® (amphetamine/ dextroamphetamine ER) ProCentra® (dextroamphetamine) Zenzedi® (dextroamphetamine)
Short-Acting			
Adderall® (amphetamine/ dextroamphetamine)			
Long-Acting			
Vyvanse® (lisdexamfetamine caps and chew tabs)+	Adderall XR® brand name only (amphetamine/ dextroamphetamine ER)	amphetamine/ dextroamphetamine ER (generic Adderall XR®)	
Methylphenidate			
Short-Acting			
Focalin® (dexmethylphenidate) Methylin® (methylphenidate) Ritalin® (methylphenidate)			
Long-Acting			
Aptensio XR® (methylphenidate ER) Focalin XR® brand name only (dexmethylphenidate ER) Metadate CD® (methylphenidate ER) QuilliChew ER® (methylphenidate ER chew tabs) Ritalin LA® (methylphenidate ER)	dexmethylphenidate ER (generic Focalin XR®) Quillivant XR® (methylphenidate ER susp)	Concerta® (methylphenidate ER) Metadate ER® (methylphenidate ER) Methylin ER® (methylphenidate ER) Ritalin SR® (methylphenidate ER)	
Non-Stimulants			
Intuniv® (guanfacine ER) Strattera® (atomoxetine)		Kapvay® (clonidine ER)Δ	

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable. Placement of products shown in blue is based on net cost after rebates, and products may be moved to a higher tier if the net cost changes in comparison to other available products.

+Unique criteria applies for the diagnosis of binge eating disorder (BED).

ΔUnique criteria applies in addition to tier trial requirements.

ER = extended-release, SR = sustained-release, caps = capsules, ODT = orally disintegrating tablet, chew tabs = chewable tablets, soln = solution, susp = suspension

Recommendation 6: Vote to Prior Authorize Baclofen 5mg Tablet, Esomep-EZS™ (Esomeprazole Kit), Lyrica® CR (Pregabalin Extended-Release), Restasis MultiDose® (Cyclosporine 0.05% Ophthalmic Emulsion), Sinuva™ (Mometasone Furoate Sinus Implant), Xepi™ (Ozenoxacin 1% Cream), Xhance™ (Fluticasone Propionate Nasal Spray), and ZTlido™ (Lidocaine 1.8% Topical System)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the placement of baclofen 5mg tablets into the Special Prior Authorization (PA) Tier of the Muscle Relaxant Medications Product Based Prior Authorization (PBPA) category with the following criteria:

Baclofen 5mg Tablet Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use other appropriate Tier-1 products including splitting a baclofen 10mg tablet to achieve a 5mg dose must be provided.

Muscle Relaxant Medications		
Tier-1	**Tier-2**	**Special PA***
baclofen 10mg, 20mg (Lioresal®)	metaxalone (Skelaxin®)	**baclofen 5mg (Lioresal®)**
chlorzoxazone (Parafon Forte®)		carisoprodol 250mg (Soma®)
cyclobenzaprine (Flexeril®)		carisoprodol 350mg (Soma®)
methocarbamol (Robaxin®)		carisoprodol/ASA
orphenadrine (Norflex®)		carisoprodol/ASA/codeine
tizanidine tablets (Zanaflex®)		chlorzoxazone (Lorzone®)
		cyclobenzaprine (Fexmid®)
		cyclobenzaprine ER (Amrix®)
		tizanidine capsules (Zanaflex®)

PA = prior authorization; ASA = aspirin; ER = extended-release
*Medications in the Special PA Tier have individual criteria.

The College of Pharmacy recommends the placement of Esomep-EZS™ (esomeprazole kit) into the Special PA Tier of the Anti-Ulcer Medications PBPA category with the following criteria:

Esomep-EZS™ (Esomeprazole Kit) Approval Criteria:

1. A previous 14-day trial of esomeprazole magnesium and a patient-specific, clinically significant reason why other lower tiered proton pump inhibitors including omeprazole and esomeprazole along with over-the-counter (OTC) pill swallowing spray are not appropriate for the member must be provided; and
2. Current Tier structure rules will also apply.

Anti-Ulcer Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA***
omeprazole (Prilosec® caps)	dexlansoprazole (Dexilant® caps)	esomeprazole (Nexium® caps, I.V.)	cimetidine tabs (Tagamet®)
pantoprazole (Protonix® tabs)	esomeprazole (Nexium® packets)	esomeprazole strontium caps	**esomeprazole kit (Esomep-EZS™)**
	lansoprazole (Prevacid® caps, ODT)	dexlansoprazole (Dexilant® SoluTab)	famotidine (Pepcid® susp)

Anti-Ulcer Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA***
	pantoprazole (Protonix® I.V.)	omeprazole (Prilosec® susp, powder)	nizatidine caps & sol (Axid®)
	rabeprazole sodium (Aciphex® tabs)	pantoprazole (Protonix® susp)	omeprazole/sodium bicarbonate (Zegerid®)
		rabeprazole sodium (Aciphex® Sprinkles)	ranitidine caps
			sucralfate susp unit dose cups

*Medications in the Special PA Tier have individual criteria.
PA = prior authorization; susp = suspension; I.V. = intravenous; tabs = tablets; caps = capsules; ODT = orally disintegrating tablet; sol = solution
Tier structure based on supplemental rebate participation, and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Additionally, the College of Pharmacy recommends the prior authorization of Lyrica® CR [pregabalin extended-release (ER)], Restasis MultiDose® (cyclosporine 0.05% ophthalmic emulsion), Sinuva™ (mometasone furoate sinus implant), and ZTlido™ (lidocaine 1.8% topical system) with the following criteria:

Lyrica® CR (Pregabalin Extended-Release) Approval Criteria:

1. An FDA approved diagnosis of one of the following:
   a. Neuropathic pain associated with diabetic peripheral neuropathy (DPN); or
   b. Neuropathic pain associated with postherpetic neuralgia (PHN); and
2. A patient-specific, clinically significant reason (beyond convenience) why the member cannot use the immediate-release formulation must be provided; and
3. For a diagnosis of DPN, current Lyrica® immediate-release criteria will also apply; and
4. Requests exceeding once daily dosing will not be approved.

Restasis MultiDose® (Cyclosporine 0.05% Ophthalmic Emulsion) Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use Restasis® in the individual dosage formulation (single-use vials) must be provided.

Sinuva™ (Mometasone Furoate Sinus Implant) Approval Criteria:

1. An FDA approved indication of nasal polyps in adults 18 years of age and older who have had ethmoid sinus surgery; and
2. Date of ethmoid sinus surgery must be provided; and
3. Sinuva™ must be prescribed and implanted by a physician specializing in otolaryngology; and
4. Failure of intranasal corticosteroids after at least a three month trial at the maximum recommended dose in combination with a 14-day trial of oral corticosteroids within the last six months (if not contraindicated); and
5. Prescriber must confirm the member has recurrent nasal obstruction/congestion symptoms and recurrent bilateral sinusitis or chronic sinusitis due to nasal polyps; and
6. A quantity limit of 2 implants per member will apply.

ZTlido™ (Lidocaine 1.8% Topical System) Approval Criteria:

1. An FDA approved diagnosis of pain due to postherpetic neuralgia (PHN); and

2. Documented treatment attempts, at recommended dosing, of at least one agent from two of the following drug classes that failed to provide adequate relief or contraindication(s) to all of the following classes:
    a. Tricyclic antidepressants; or
    b. Anticonvulsants; or
    c. Topical or oral analgesics; and
3. A patient-specific, clinically significant reason why the member cannot use lidocaine 5% topical patch(es), which are available without prior authorization, must be provided; and
4. A quantity limit of 3 patches per day with a maximum of 90 patches per month will apply.

The College of Pharmacy recommends the placement of Xhance™ (fluticasone propionate nasal spray) into Tier-3 of the Nasal Allergy Medications PBPA category with the following criteria:

Xhance™ (Fluticasone Propionate Nasal Spray) Approval Criteria:

1. An FDA approved diagnosis of nasal polyps; and
2. A patient-specific, clinically significant reason why the member cannot use intranasal fluticasone, budesonide, mometasone, and/or other cost-effective therapeutic equivalent medication(s) must be provided; and
3. Current Tier structure rules will also apply.

Nasal Allergy Medications		
Tier-1	**Tier-2**	**Tier-3**
beclomethasone (Beconase® AQ)	azelastine (Astelin®)	azelastine (Astepro®)
fluticasone (Flonase®)	beclomethasone (Qnasl® 80mcg)	azelastine/fluticasone (Dymista®)
		beclomethasone (Qnasl® 40mcg)
		budesonide (Rhinocort AQ®)
		ciclesonide (Omnaris®, Zetonna®)
		flunisolide (Nasalide®, Nasarel®)
		fluticasone (Veramyst®)
		fluticasone (Xhance™)
		mometasone (Nasonex®)
		olopatadine (Patanase®)

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

Finally, the College of Pharmacy recommends the placement of Xepi™ (ozenoxacin 1% cream) into Tier-2 of the Topical Antibiotic Products PBPA category. Current Tier-2 criteria will apply.

Topical Antibiotic Tier-2 Approval Criteria:

1. Documented five-day trial of a Tier-1 product within the last 30 days.
2. Clinical exceptions apply for adverse effects with all Tier-1 products, or a unique indication not covered by Tier-1 products.
3. Approvals will be for the duration of ten days.

Topical Antibiotics	
Tier-1	**Tier-2**
gentamicin cream 0.1% (Garamycin®)	mupirocin cream 2% (Bactroban®)
gentamicin ointment 0.1% (Garamycin®)	mupirocin kit 2% (Centany®)
gentamicin powder	mupirocin nasal ointment 2% (Bactroban®)

Topical Antibiotics	
Tier-1	**Tier-2**
neomycin/polymixin B sulfates/ bacitracin zinc/hydrocortisone ointment 1% (Cortisporin®)	**ozenoxacin 1% cream (Xepi™)**
neomycin/polymixin B sulfates/hydrocortisone cream 0.5% (Cortisporin®)	retapamulin ointment 1% (Altabax®)
mupirocin ointment 2% (Bactroban®)	

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

Recommendation 7: Annual Review of Atopic Dermatitis (AD) Medications

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes to the prior authorization criteria for Eucrisa® (crisaborole), as shown in red:

Eucrisa® (Crisaborole Ointment) Approval Criteria:

1. The manufacturer of Eucrisa® has currently provided a supplemental rebate to provide access to Eucrisa® without prior authorization for members 2 years of age and older; however, Eucrisa® will follow the original criteria and require trials with one topical corticosteroid and one topical calcineurin inhibitor if the manufacturer chooses not to participate in supplemental rebates.

Clinical Exceptions for Children Not Meeting Age Restriction:

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

Recommendation 8: Annual Review of Botulinum Toxins

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends updating the current prior authorization criteria for Botox® (onabotulinumtoxinA) for the prevention of migraine headaches, based on the FDA approved indication, the International Classification of Headache Disorders (ICHD-3) diagnostic criteria for chronic migraine and for medication overuse headache (MOH), and current net costs (changes noted in red):

Approval Criteria for Botox® for Prevention of Migraine Headaches *(other botulinum toxins will not be approved for this diagnosis)*:

1. Non-migraine medical conditions known to cause headache have been ruled out and/or have been treated. This includes, but is not limited to:
   a. Increased intracranial pressure (e.g., tumor, pseudotumor cerebri, central venous thrombosis); or
   b. Decreased intracranial pressure (e.g., post-lumbar puncture headache, dural tear after trauma); and

2. Migraine headache exacerbation secondary to other medical conditions or medication therapies have been ruled out and/or treated. This includes, but is not limited to:
    a. Hormone replacement therapy or hormone-based contraceptives; and
    b. Chronic insomnia; and
    c. Obstructive sleep apnea; and
3. Member has no contraindications to Botox® injections; and
4. FDA indications are met:
    a. Member is 18 years of age or older; and
    b. Member has documented chronic migraine headaches:
        i. Frequency of 15 or more headache days per month with 8 or more migraine days per month and occurring for more than 3 months; and
        ii. Duration of four hours of headache per day or longer; and
5. The member has failed medical migraine preventative therapy including at least ~~three~~ two agents ~~in three or more categories~~ with different mechanisms of action. This includes, but is not limited to:
    a. Select antihypertensive therapy (e.g., beta-blockers); or
    b. Select anticonvulsant therapy; or
    c. Select antidepressant therapy [e.g., tricyclic antidepressants (TCA), serotonin and norepinephrine reuptake inhibitors (SNRI)]; and
6. Member is not frequently taking medications which are known to cause medication overuse headaches (MOH or rebound headaches) in the absence of intractable conditions known to cause chronic pain. MOH are a frequent cause of chronic headaches. A list of prescription or non-prescription medications known to cause MOH includes, but is not limited to:
    a. Decongestants (alone or in combination products) (≥10 days/month for >3 months); and
    b. Combination analgesics containing caffeine and/or butalbital (~~>5~~ ≥10 days/month for >3 months); and
    c. Opioids (≥10 days/month for >3 months); and
    d. Analgesic medications including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs) (≥15 days/month for >3 months); and
    e. Ergotamine-containing medications (~~>8~~ ≥10 days/month for >3 months); and
    f. Triptans (~~>8~~ ≥10 days/month for >3 months); and
7. Member is not taking any medications that are likely to be the cause of the headaches; and
8. Member must have been evaluated within the last six months by a neurologist for chronic migraine headaches and Botox® recommended as treatment (not necessarily prescribed or administered by a neurologist); and
9. Members who smoke or use tobacco products will not be approved.

Recommendation 9: Annual Review of Opioid Analgesics and Opioid Medication Assisted Treatment (MAT) Medications and 30-Day Notice to Prior Authorize Apadaz® [Benzhydrocodone/Acetaminophen (APAP)], Lucemyra™ (Lofexidine), and Sublocade™ [Buprenorphine Extended-Release (ER) Injection]

NO ACTION REQUIRED.

Recommendation 10: 30-Day Notice to Prior Authorize Jynarque™ (Tolvaptan)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Vimizim® (Elosulfase Alfa)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Brineura® (Cerliponase Alfa)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Radicava® (Edaravone)

NO ACTION REQUIRED.

Recommendation 14: Industry News and Updates

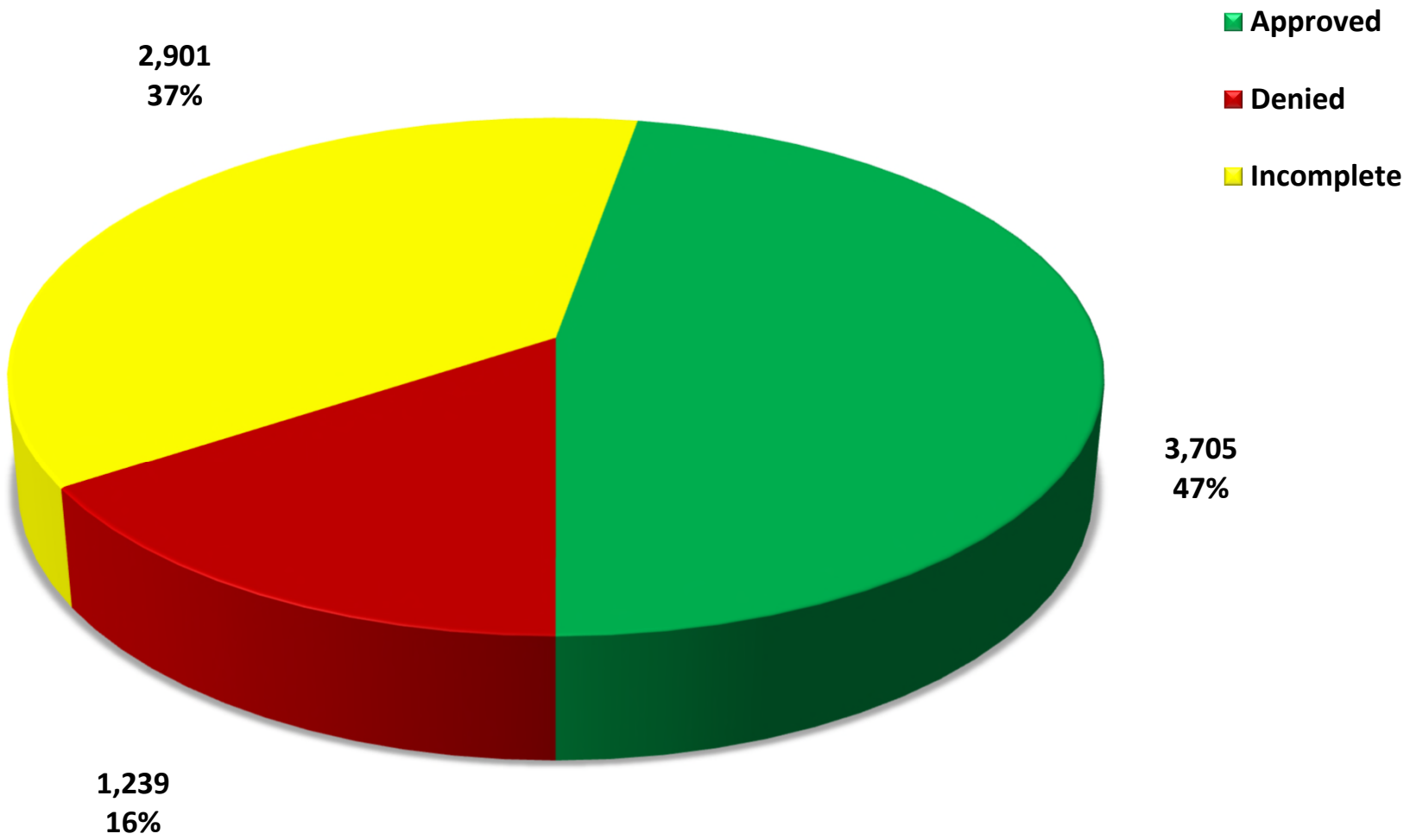
NO ACTION REQUIRED.

Recommendation 15: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

NO ACTION REQUIRED.

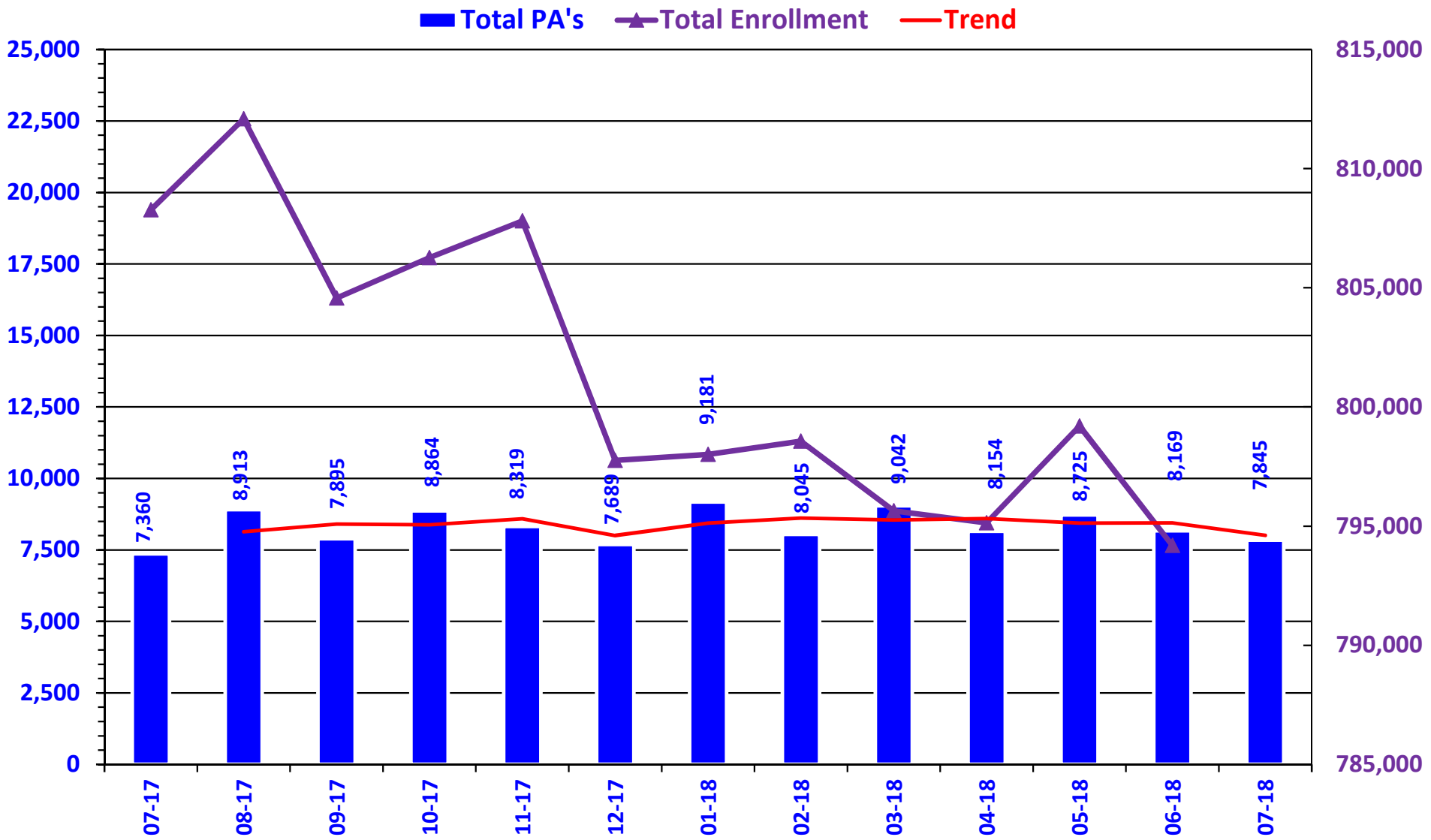
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: JULY 2018



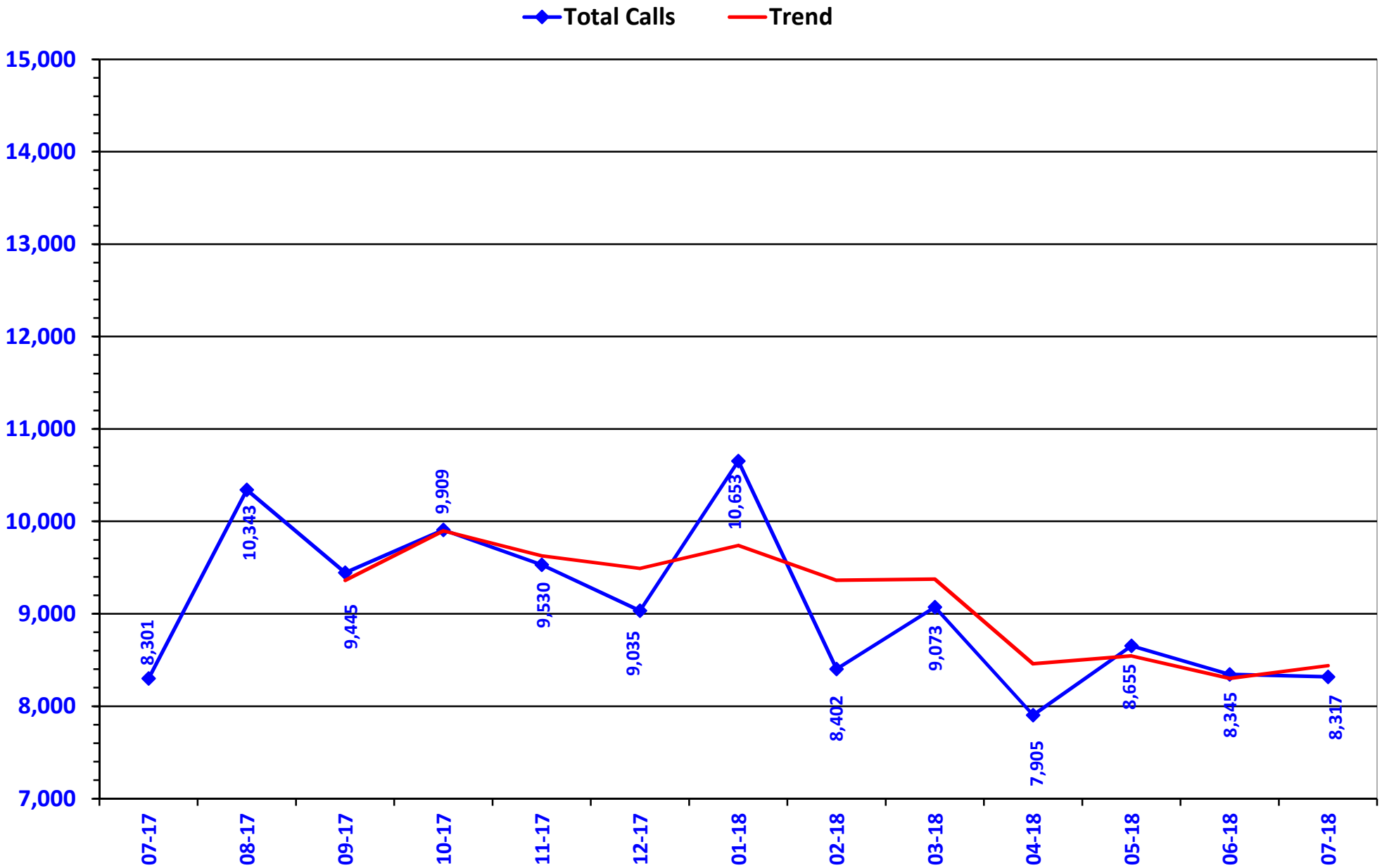
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: JULY 2017 – JULY 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
JULY 2017 – JULY 2018



Prior Authorization Activity

7/1/2018 Through 7/31/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	217	20	63	134	358
Analgesic - NonNarcotic	27	0	9	18	0
Analgesic, Narcotic	399	203	50	146	162
Antiasthma	60	19	15	26	284
Antibiotic	40	24	1	15	280
Anticonvulsant	166	67	28	71	301
Antidepressant	156	36	25	95	307
Antidiabetic	243	82	44	117	343
Antihistamine	13	3	7	3	358
Antimigraine	30	5	6	19	165
Antineoplastic	57	44	6	7	162
Antiparasitic	25	6	7	12	11
Antiulcers	131	32	40	59	106
Anxiolytic	62	30	7	25	252
Atypical Antipsychotics	190	103	14	73	333
Biologics	152	82	20	50	275
Bladder Control	64	16	20	28	342
Blood Thinners	239	147	17	75	334
Botox	42	30	11	1	324
Buprenorphine Medications	338	249	17	72	78
Cardiovascular	91	43	9	39	310
Chronic Obstructive Pulmonary Disease	170	30	42	98	308
Constipation/Diarrhea Medications	129	20	52	57	210
Contraceptive	19	15	1	3	312
Dermatological	138	22	50	66	196
Diabetic Supplies	429	252	28	149	214
Endocrine & Metabolic Drugs	109	77	6	26	143
Erythropoietin Stimulating Agents	17	8	1	8	108
Fibromyalgia	220	36	97	87	321
Fish Oils	10	2	1	7	359
Gastrointestinal Agents	116	26	24	66	216
Growth Hormones	118	83	5	30	153
Hematopoietic Agents	11	6	3	2	111
Hepatitis C	154	95	24	35	8
HFA Rescue Inhalers	42	3	8	31	243
Insomnia	39	6	11	22	151
Insulin	151	48	28	75	316
Miscellaneous Antibiotics	20	4	5	11	96
Multiple Sclerosis	86	45	13	28	142
Muscle Relaxant	47	7	10	30	126
Nasal Allergy	48	8	19	21	116
Neurological Agents	101	35	31	35	203
NSAIDs	152	28	41	83	221
Ocular Allergy	22	6	6	10	120
Osteoporosis	19	6	6	7	333
Other*	295	76	68	151	254
Otic Antibiotic	29	0	6	23	0
Respiratory Agents	24	14	1	9	110
Statins	24	5	11	8	360
Stimulant	630	326	64	240	343

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

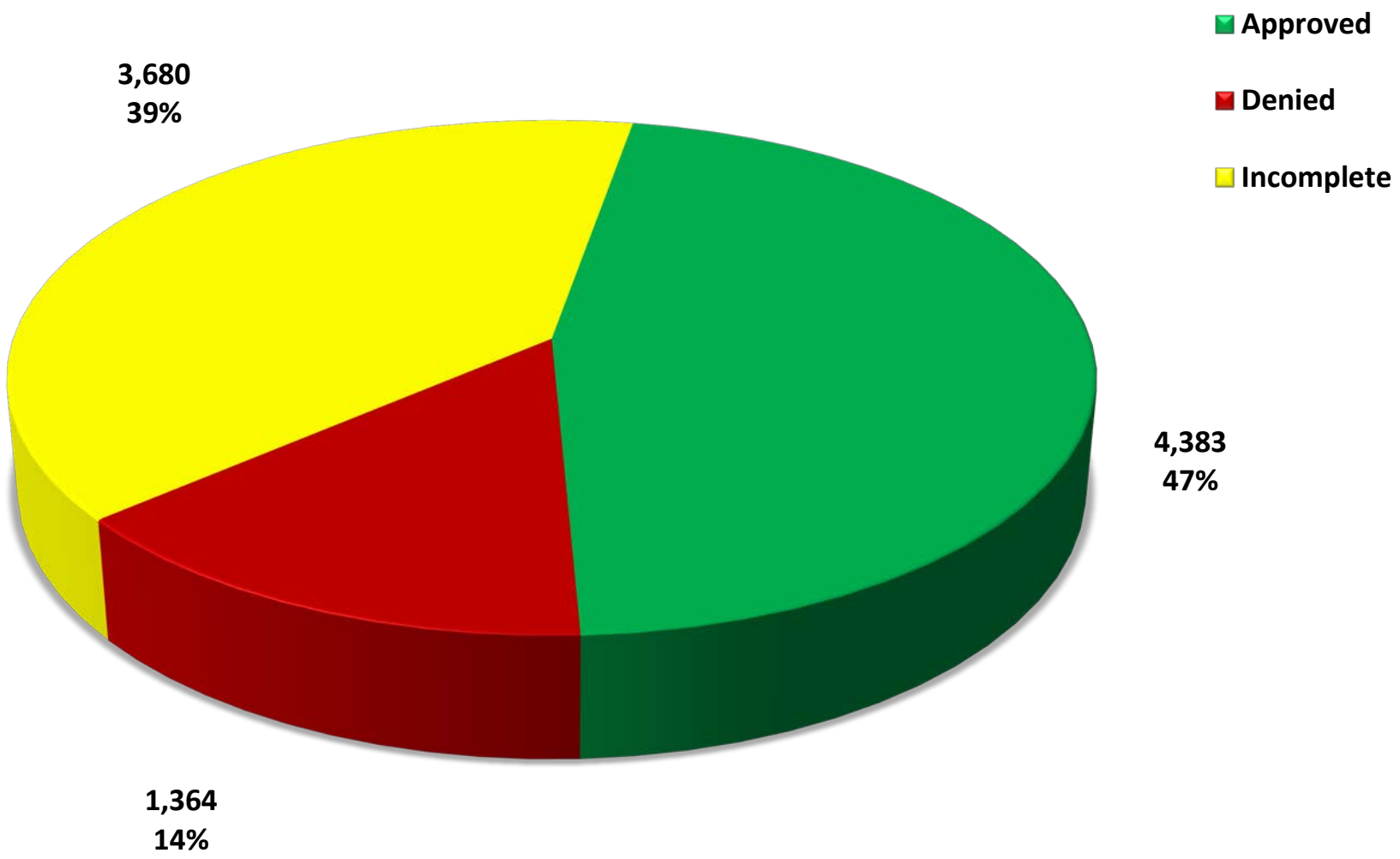
	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Testosterone	46	10	16	20	357
Topical Antifungal	26	5	7	14	40
Topical Corticosteroids	67	0	28	39	0
Vitamin	82	33	29	20	168
Pharmacotherapy	80	64	1	15	265
Emergency PAs	0	0	0	0	
Total	**6,412**	**2,642**	**1,159**	**2,611**	
Overrides					
Brand	38	24	2	12	304
Compound	12	12	0	0	53
Cumulative Early Refill	1	0	0	1	0
Diabetic Supplies	32	15	0	17	263
Dosage Change	270	247	1	22	12
High Dose	6	6	0	0	257
Ingredient Duplication	18	10	2	6	11
Lost/Broken Rx	84	80	0	4	11
NDC vs Age	264	163	32	69	226
Nursing Home Issue	31	28	2	1	10
Opioid Quantity	24	21	2	1	147
Other*	38	34	0	4	17
Prescriber Temp Unlock	2	2	0	0	359
Quantity vs. Days Supply	553	377	33	143	231
STBS/STBSM	20	12	4	4	74
Stolen	4	4	0	0	12
Temporary Unlock	1	0	0	1	0
Third Brand Request	35	28	2	5	20
Overrides Total	**1,433**	**1,063**	**80**	**290**	
Total Regular PAs + Overrides	**7,845**	**3,705**	**1,239**	**2,901**	

Denial Reasons	
Unable to verify required trials.	2,283
Does not meet established criteria.	1,257
Lack required information to process request.	579
Ingredient Duplication Override	2

Other PA Activity	
Duplicate Requests	543
Letters	9,215
No Process	14
Changes to existing PAs	700
Helpdesk Initiated Prior Authorizations	632
PAs Missing Information	38

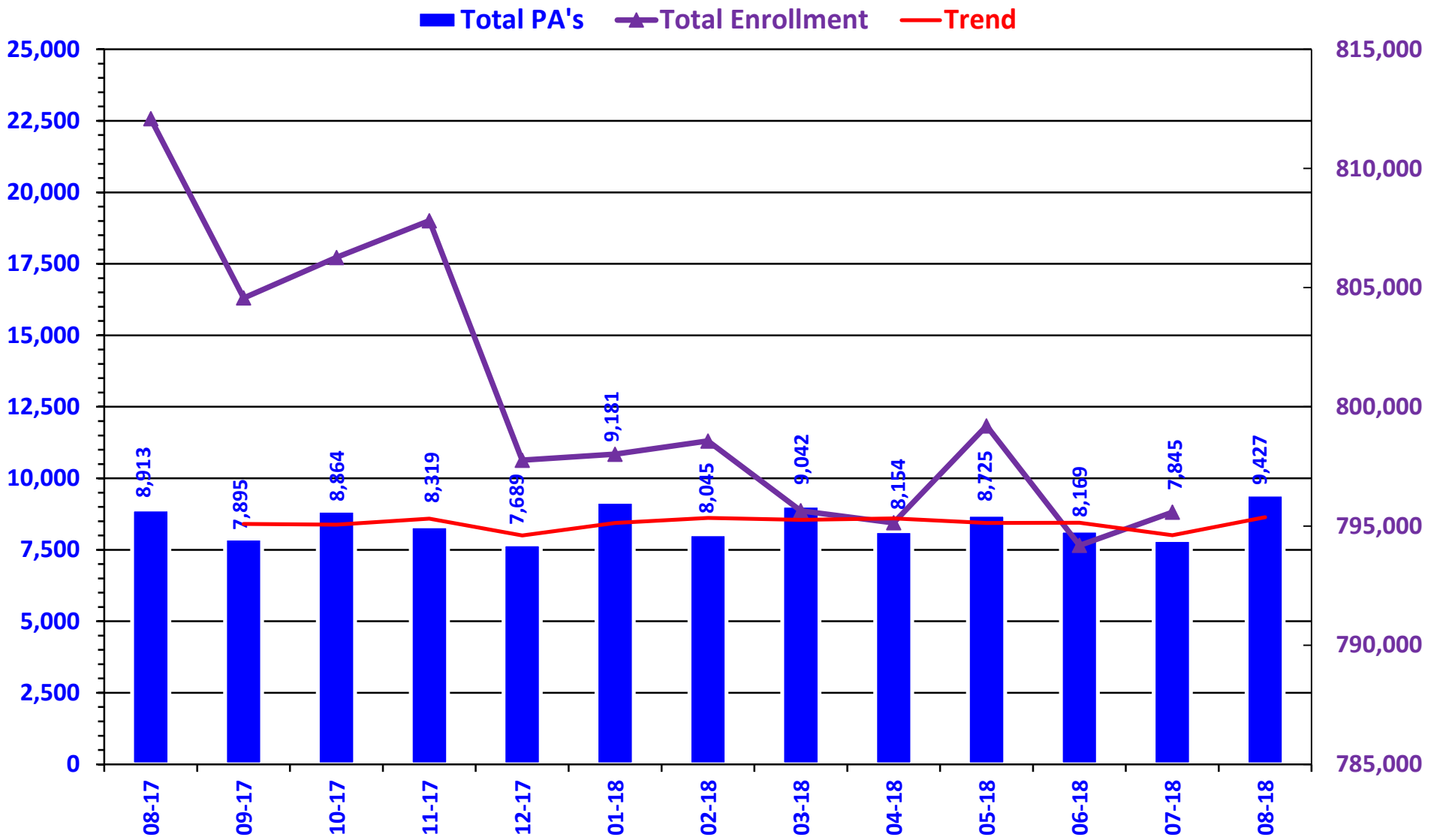
* Includes any therapeutic category with less than 10 prior authorizations for the month.

PRIOR AUTHORIZATION ACTIVITY REPORT: AUGUST 2018



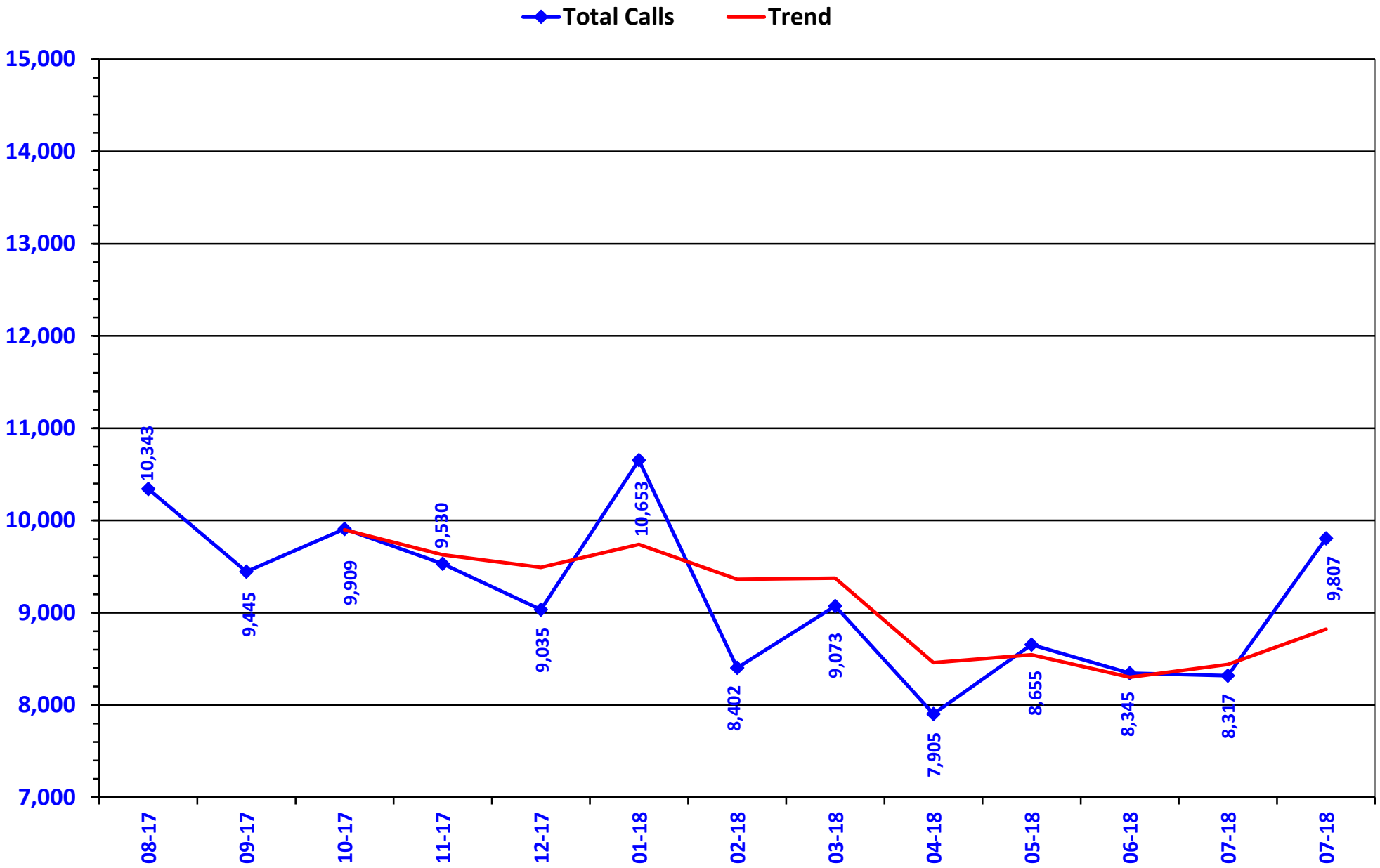
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: AUGUST 2017 – AUGUST 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
AUGUST 2017 – AUGUST 2018



Prior Authorization Activity

8/1/2018 Through 8/31/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	262	28	78	156	325
Analgesic - NonNarcotic	30	0	5	25	0
Analgesic, Narcotic	407	207	40	160	165
Angiotensin Receptor Antagonist	20	5	5	10	359
Antiasthma	72	17	15	40	331
Antibiotic	30	16	2	12	305
Anticonvulsant	175	77	18	80	318
Antidepressant	197	44	31	122	281
Antidiabetic	292	109	55	128	352
Antigout	11	7	1	3	316
Antihistamine	36	10	13	13	347
Antimigraine	42	3	11	28	247
Antineoplastic	89	59	3	27	153
Antiparasitic	19	0	3	16	0
Antiulcers	170	49	45	76	126
Anxiolytic	74	38	6	30	272
Atypical Antipsychotics	216	102	21	93	354
Biologics	152	86	16	50	259
Bladder Control	65	7	25	33	358
Blood Thinners	263	163	15	85	328
Botox	52	37	7	8	358
Buprenorphine Medications	543	388	21	134	73
Cardiovascular	138	59	26	53	304
Chronic Obstructive Pulmonary Disease	185	39	47	99	313
Constipation/Diarrhea Medications	137	22	48	67	205
Contraceptive	21	15	1	5	335
Corticosteroid	10	1	0	9	51
Dermatological	156	25	65	66	150
Diabetic Supplies	517	313	13	191	180
Endocrine & Metabolic Drugs	168	104	9	55	139
Erythropoietin Stimulating Agents	19	9	1	9	108
Fibric Acid Derivatives	13	0	1	12	0
Fibromyalgia	221	30	112	79	340
Gastrointestinal Agents	120	27	31	62	134
Growth Hormones	82	55	7	20	165
Hematopoietic Agents	12	6	2	4	68
Hepatitis C	177	116	16	45	9
HFA Rescue Inhalers	51	1	11	39	241
Insomnia	30	7	7	16	163
Insulin	154	40	22	92	291
Miscellaneous Antibiotics	25	3	5	17	89
Multiple Sclerosis	94	41	12	41	191
Muscle Relaxant	39	5	7	27	120
Nasal Allergy	56	8	13	35	154
Neurological Agents	136	41	41	54	198
NSAIDs	194	32	53	109	207
Ocular Allergy	42	3	10	29	86
Ophthalmic Corticosteroid	13	1	5	7	25
Osteoporosis	19	9	0	10	356
Other*	350	64	87	199	280

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Otic Antibiotic	23	3	3	17	10
Respiratory Agents	47	30	4	13	171
Statins	25	4	7	14	354
Stimulant	845	427	69	349	344
Testosterone	51	13	16	22	340
Topical Antifungal	30	4	8	18	20
Topical Corticosteroids	102	0	45	57	0
Vitamin	98	39	31	28	154
Pharmacotherapy	150	142	0	8	306
Emergency PAs	1	1	0	0	
Total	**7,768**	**3,191**	**1,271**	**3,306**	
Overrides					
Brand	48	25	4	19	285
Compound	21	17	0	4	39
Cumulative Early Refill	5	3	0	2	180
Diabetic Supplies	23	12	3	8	78
Dosage Change	320	294	5	21	12
High Dose	6	5	0	1	237
Ingredient Duplication	22	14	2	6	6
Lost/Broken Rx	88	82	3	3	9
NDC vs Age	260	176	20	64	245
Nursing Home Issue	56	56	0	0	12
Opioid Quantity	29	20	2	7	139
Other	50	42	2	6	9
Quantity vs. Days Supply	654	391	48	215	231
STBS/STBSM	24	12	3	9	57
Stolen	14	13	0	1	10
Third Brand Request	39	30	1	8	34
Overrides Total	**1,659**	**1,192**	**93**	**374**	
Total Regular PAs + Overrides	**9,427**	**4,383**	**1,364**	**3,680**	

Denial Reasons	
Unable to verify required trials.	2,847
Does not meet established criteria.	1,396
Lack required information to process request.	778
Other PA Activity	
Duplicate Requests	648
Letters	10,354
No Process	8
Changes to existing PAs	790
Helpdesk Initiated Prior Authorizations	685
PAs Missing Information	45

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

Proton Pump Inhibitor (PPI) Deprescribing Mailing Update

Oklahoma Health Care Authority
September 2018

Introduction[1,2,3]

The use of proton pump inhibitors (PPIs) in non-institutionalized adults in the United States has doubled between 1999 and 2012 (3.9% to 7.8%), and during that same period, the number of studies reporting PPI-related adverse reactions also doubled. Several studies have also found that approximately 50% of chronic PPI users do not have an indication for use. The American Gastroenterological Association (AGA) recently released a clinical practice update reviewing the risks and benefits of long-term use of PPIs and provided best practice recommendations. Although generally considered safe, several studies have shown evidence of uncommon but potentially serious adverse reactions associated with long-term PPI use including increased risk of kidney disease, dementia, bone fractures, infections, micronutrient deficiencies, and gastrointestinal malignancies. Long-term PPI best practices cited by the AGA include:

- Stop or reduce PPIs in patients with uncomplicated gastroesophageal reflux disease (GERD).
- Patients with Barrett's esophagus and patients at high-risk for ulcer-related bleeding from nonsteroidal anti-inflammatory drugs (NSAIDs) who continue to take NSAIDs are candidates for long-term PPI use.
- The dose of long-term PPIs should be periodically reevaluated so that the lowest effective PPI dose can be prescribed to manage the condition.

Due to the increased utilization of PPIs and reports of serious adverse effects as a result of long-term use, a Canadian guideline for deprescribing PPIs has been developed to assist prescribers in safely tapering or discontinuing PPIs in patients where appropriate.

Prescriber Mailing Summary[4]

In February 2018, the College of Pharmacy and the Oklahoma Health Care Authority (OHCA) sent an educational letter to 2,018 prescribers of 7,307 unique adult members who had paid claims for more than a 90-day supply of PPIs during the analysis period of September 27, 2017 through January 24, 2018.

The educational mailing contained information on the type of patient who should be considered for deprescribing including those taking PPIs continuously for more than 4 weeks for the treatment of GERD or mild-to-moderate esophagitis and patients who have completed short-term treatment of stress ulcer prophylaxis or *Helicobacter pylori* eradication. In addition, prescribers were provided methods or opportunities for deprescribing including decreasing the daily dose, changing to on-demand use, and considering histamine (H_2) receptor blockers as an alternative to PPIs. Patients for whom long-term PPI use is appropriate (e.g., Barrett's esophagus, documented history of bleeding gastrointestinal ulcer) were also highlighted. A similar notification was included in the Fall 2017 SoonerCare Provider Newsletter, released mid-September.

PPI Deprescribing Mailing Results

Of the 7,307 members included in the mailing, 25.7% were 18 to 40 years of age, 34.4% were 41 to 55 years of age, 38.0% were 56 years of age or older, and 66.3% were female. The majority of patients (55.5%) had 100-day supply or less of medication over the 120-day study period.

The post-analysis of the mailing reviewed claims from February 19, 2018 to June 18, 2018. Results found 2,047 prescribers accounting for 7,439 unique adult members with more than a 90-day supply of PPIs during the analysis period. While the number of members on chronic PPI therapy increased, 34.7% of members included in the original mailing no longer had more than a 90-day supply during the post mailing analysis. Similarly, while the number of prescribers with chronic PPI members increased, 23.2% of the prescribers included in the mailing no longer had members using PPIs chronically in the post mailing analysis. The majority of chronic PPI members in the post mailing analysis (56.6%) had 100-day supply or less of medication over the 120-day analysis period. The member demographic break down among chronic PPI users was similar to prior to the mailing with 65.6% of members being female, 28.4% age 19 to 40 years, 33.6% age 41 to 55 years, and 37.9% age 56 years or older.

Conclusions

Analysis of the period following the educational mailing revealed a modest change in chronic PPI utilization for members included in the mailing despite an overall increase in the number of members utilizing PPIs for more than 90 days. Additionally, approximately one-fourth of the prescribers who received an educational letter no longer had members receiving chronic PPI therapy in the post-mailing analysis. These results indicate the intervention may have been somewhat effective; however, additional educational efforts may be warranted to produce a lasting effect and additional impact. Some effect from the educational mailing may have been negated by the prescriber notification in the provider newsletter. This occurred prior to the pre-analysis period and may have encouraged prescribers to discontinue chronic PPI utilization for those where it was appropriate prior to the analysis period thereby potentially leaving a group of members not appropriate for discontinuation in the analysis. As the provider notification came out approximately two weeks prior to the analysis period, it may not have been a feasible period to alter chronic PPI utilization and therefore impact may have been minimal on the analysis. The College of Pharmacy and OHCA will continue to monitor chronic PPI use, with potential intervention opportunities brought to the Drug Utilization Review (DUR) Board where appropriate.

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[1] Freedberg DE, Kim LS, Yang YX. The Risks and Benefits of Long-Term Use of Proton Pump Inhibitors: Expert Review and Best Practice Advice from The American Gastroenterological Association. *Gastroenterology*. 2017; 152:706-15.

[2] Farrell B, Pottie K, Thompson W, Boghossian T, et al. Deprescribing proton pump inhibitors: Evidence-based clinical practice guidelines. *Can Fam Physician*. 2017; 63:354-65.

[3] Hochman M. Slow Medicine: Discontinuing PPIs. *Medpage Today*. Available online at: https://www.medpagetoday.com/blogs/slowmedicine/74475. Issued 08/08/2018. Last accessed 08/09/2018.

[4] Oklahoma Health Care Authority (OHCA). What's the word about GERD? Provider Checkup Fall 2017, Vol. 1. Available online at: https://content.govdelivery.com/accounts/OKHCA/bulletins/1b11ce1?reqfrom=share#link_1462991543646. Issued 09/19/2017. Last accessed 09/04/2018.

Appendix C

Vote to Prior Authorize Apadaz® [Benzhydrocodone/ Acetaminophen (APAP)], Lucemyra™ (Lofexidine), and Sublocade™ [Buprenorphine Extended-Release (ER) Injection]

Oklahoma Health Care Authority
September 2018

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

- **Apadaz® [benzhydrocodone/APAP immediate-release (IR) tablets]:** In February 2018, the U.S. Food and Drug Administration (FDA) approved Apadaz®, a combination of benzhydrocodone, a prodrug of the opioid agonist hydrocodone, and APAP. Apadaz® is indicated for the short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. Apadaz® is available as IR oral tablets containing 6.12mg benzhydrocodone (equivalent to 6.67mg benzhydrocodone hydrochloride) and 325mg APAP. Initial recommended dosing is 1 or 2 tablets every 4 to 6 hours as needed for pain. Dosages should not exceed 12 tablets in a 24-hour period. It is recommended that if switching from IR hydrocodone bitartrate/APAP, 6.12mg/325mg Apadaz® should be substituted for 7.5mg/325mg hydrocodone bitartrate/APAP. The approval of Apadaz® was based on pharmacokinetic studies with hydrocodone/ibuprofen, tramadol/APAP, and hydrocodone/ APAP in which Apadaz® demonstrated exposure to hydrocodone and APAP that is expected to result in therapeutic effects equivalent to currently approved IR hydrocodone/APAP combination products.[3] The results of abuse-deterrent studies do not support a finding that Apadaz® can be expected to deter abuse by the oral or intranasal route of administration. Cost information for Apadaz® is not yet available.
- **Lucemyra™ (lofexidine tablets):** In May 2018, the FDA approved Lucemyra™, a central alpha-2 adrenergic agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. Lucemyra™ is supplied as oral tablets containing 0.18mg lofexidine. The usual recommended dosage of Lucemyra™ is 3 tablets taken orally 4 times daily at 5- to 6-hour intervals. Lucemyra™ treatment may be continued for up to 14 days with dosing guided by symptoms. Dosage adjustments are recommended based on the degree of renal or hepatic impairment. The efficacy of Lucemyra™ was evaluated in two randomized, double-blind, placebo-controlled trials in patients meeting Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) criteria for opioid dependence who were physically dependent on short-acting opioids (e.g., heroin, hydrocodone, oxycodone). The wholesale acquisition cost (WAC) per tablet of Lucemyra™ is $20.69, resulting in a daily cost of $248.28 and a 14-day cost of $3,475.92 at maximum dosing.
    - Alpha-2 adrenergic agonists including clonidine (tablets or patches) and Lucemyra™ have been shown to reduce symptoms of opioid withdrawal and have shown comparable efficacy to reducing doses of methadone. Many times alpha-2 adrenergic agonists are used as adjuncts to treatment with buprenorphine or methadone.

Hypotension and sedation may limit use of clonidine or Lucemyra™ for opioid withdrawal, though Lucemyra™ is thought to result in less hypotension than clonidine. A meta-analysis of three clinical trials with a total of 148 opioid dependent patients found that alpha-2 adrenergic agonists were superior to placebo for treatment completion [55% vs. 29%; risk ratio 1.95 (1.34, 2.84)]. Additionally, a meta-analysis of multiple randomized trials found alpha-2 adrenergic agonists to be comparable to reducing doses of methadone in ameliorating opioid withdrawal symptoms in DSM-IV opioid dependent patients. No differences were seen between the treatments in severe withdrawal symptoms [risk ratio 1.18 (0.81, 1.73)], peak withdrawal score, overall withdrawal severity, and rate of treatment completion. The duration of treatment was longer with reducing doses of methadone. Hypotension and other adverse effects were more likely with alpha-2 adrenergic agonists. Direct comparison research of Lucemyra™ and clonidine does not suggest superior efficacy of one alpha-2 adrenergic agonist in place of the other.

- **Sublocade™ (buprenorphine ER injection):** In November 2017, the FDA approved Sublocade™, a partial opioid agonist indicated for the treatment of moderate-to-severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days. Sublocade™ is supplied as ER buprenorphine prefilled-syringes in the following strengths: 100mg/0.5mL and 300mg/1.5mL. Under the Drug Addiction Treatment Act (DATA), prescription use of Sublocade™ in the treatment of opioid dependence is limited to healthcare providers who meet certain qualifying requirements, and who have notified the Secretary of Health and Human Services (HHS) of their intent to prescribe Sublocade™ for the treatment of opioid dependence and have been assigned a unique identification number that must be included on every prescription. Sublocade™ is distributed through a restricted distribution system, which is intended to prevent the direct distribution to a patient. Sublocade™ should only be dispensed directly to a healthcare provider for administration by a healthcare provider. Sublocade™ treatment should only be initiated following induction and dose-adjustment with a transmucosal buprenorphine-containing product delivering the equivalent of 8 to 24mg of buprenorphine daily for a minimum of 7 days. Sublocade™ is administered monthly by subcutaneous (sub-Q) injection in the abdominal region. The recommended dose is two monthly initial doses of 300mg followed by 100mg monthly maintenance doses. Increasing the maintenance dose to 300mg monthly may be considered for patients who tolerate the 100mg dose, but do not demonstrate a satisfactory clinical response, as evidenced by self-reported illicit opioid use or urine drug screens positive for illicit opioid use. The efficacy of Sublocade™ was established in a Phase 3 double-blind efficacy and safety study and an opioid blockade study. The WAC of either strength of Sublocade™ per syringe is $1,580.00.

Recommendations

The College of Pharmacy recommends the following:

1. The placement of Apadaz® (benzhydrocodone/APAP) into Tier-3 of the Opioid Analgesics Product Based Prior Authorization (PBPA) category. Current short-acting Tier-3 criteria will apply.

2. The prior authorization of Lucemyra™ (lofexidine) and Sublocade™ (buprenorphine ER injection) with the following criteria:

Lucemyra™ (Lofexidine) Approval Criteria:

1. An FDA approved indication for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults; and
2. Date of opioid discontinuation must be listed on the prior authorization request; and
3. Prescriber must verify member has been screened for hepatic and renal impairment and that dosing is appropriate for the member's degree of hepatic and renal function; and
4. Prescriber must verify member's vital signs have been monitored and that the member is capable of and has been instructed on self-monitoring for hypotension, orthostasis, bradycardia, and associated symptoms; and
5. Member must not have severe coronary insufficiency, a recent myocardial infarction, cerebrovascular disease, chronic renal failure, or marked bradycardia; and
6. Member must not have congenital long QT syndrome; and
7. Prescriber must verify Lucemyra™ will be used in conjunction with a comprehensive management program for the treatment of opioid use disorder; and
8. A patient-specific, clinically significant reason why clonidine tablets or patches cannot be used in place of Lucemyra™ to mitigate opioid withdrawal symptoms must be provided; and
9. Approvals will be for a maximum duration of 14 days; and
10. A quantity limit of 12 tablets daily will apply.

Sublocade™ [Buprenorphine Extended-Release (ER) Injection] Approval Criteria:

1. Sublocade™ must be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a Drug Enforcement Agency (DEA) X number; and
2. An FDA approved diagnosis of moderate-to-severe opioid use disorder; and
3. Member must have initiated treatment with a transmucosal buprenorphine-containing product for a minimum of seven days; and
4. Concomitant treatment with opioids (including tramadol) will be denied; and
5. Sublocade™ should only be prepared and administered by a health care provider; and
6. A patient-specific, clinically significant reason why the member cannot use the preferred buprenorphine product(s) (Suboxone®) must be provided; and
7. Approvals will be for the duration of 90 days to allow for concurrent medication monitoring; and
8. A quantity limit of one dose (300mg or 100mg) per 28 days will apply.

Opioid Analgesics*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Long-Acting: oxycodone ER 10mg, 15mg, 20mg only (Oxycontin®)◊ **Short-Acting:** ASA/butalbital/caff/cod (Fiorinal with Codeine®) codeine codeine/APAP dihydrocodone/ASA/caff (Synalgos-DC®) hydrocodone/APAP (Norco®) hydrocodone/IBU (Vicoprofen®, Ibudone®, Reprexain™) hydromorphone (Dilaudid®) morphine IR (MSIR®) oxycodone IR (Oxy IR®) oxycodone/APAP (Percocet®) oxycodone/ASA (Percodan®) oxycodone/IBU (Combunox®) tramadol (Ultram®) tramadol/APAP (Ultracet®)	**Long-Acting:** buprenorphine patch (Butrans®) fentanyl patch (Duragesic®) hydrocodone ER (Hysingla® ER) morphine ER tab (MS Contin®) morphine/naltrexone (Embeda®) oxycodone ER 30mg, 40mg, 60mg, 80mg (Oxycontin®)◊ tramadol ER tab (Ultram ER®, Ryzolt®) **Short-Acting:** oxymorphone IR (Opana®) tapentadol IR (Nucynta®)	**Long-Acting:** buprenorphine ER buccal film (Belbuca®) hydrocodone ER (Vantrela™ ER) hydrocodone ER (Zohydro® ER) hydromorphone ER (Exalgo®) methadone (Dolophine®) morphine ER (Arymo® ER) morphine ER (Kadian®) morphine ER (MorphaBond™) morphine/naltrexone (Troxyca® ER) oxycodone ER (Xtampza® ER) tapentadol ER (Nucynta® ER) **Short-Acting:** **benzhydrocodone/APAP (Apadaz®)** dihydrocodeine/APAP/caff (Trezix®) hydrocodone/APAP (Xodol®, Zamicet®, Liquicet®) oxycodone (Oxaydo®) oxycodone (Oxecta®) oxycodone (RoxyBond™) oxycodone/APAP (Primlev™, Xolox®)	**Long-Acting:** oxycodone/APAP ER (Xartemis® XR) tramadol ER cap (ConZip®) **Oncology Only:** fentanyl transmucosal lozenge (Actiq®) fentanyl buccal tab (Fentora®) fentanyl buccal film (Onsolis®) fentanyl SL tab (Abstral®) fentanyl nasal spray (Lazanda®) fentanyl SL spray (Subsys®)

PA = prior authorization; APAP = acetaminophen; ASA = aspirin; IR = immediate-release; ER = extended-release; IBU = ibuprofen; cod = codeine; caff = caffeine; tab = tablet; cap = capsule; SL = sublingual

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

◊Brand name preferred.

- Tier-1 products are covered with no prior authorization necessary.
- Members with an oncology-related diagnosis are exempt from the prior authorization process, and do not require pain contracts.
- Only one long-acting and one-short acting agent can be used concurrently. Short-acting, solid dosage formulation products are limited to a quantity of four units per day or a quantity of 120 units per 30 days.
- An age restriction applies on oral liquid narcotic analgesic products for all members older than 12 years of age and oral solid dosage forms for all members younger than 10 years of age.
- An age restriction for all tramadol and codeine products (both liquid and solid dosage formulations) for members younger than 12 years of age applies. Members younger than 12 years of age require prior authorization approval for reimbursement of these products. Authorization requires a patient-specific, clinically significant reason for use of these products despite the medication being contraindicated for the member's age.

Opioid Analgesics Tier-2 Approval Criteria:

1. A documented 30-day trial/titration period with at least one Tier-1 medication within the last 90 days is required for a Tier-2 long-acting medication; or
2. A documented 30-day trial with at least two Tier-1 short-acting medications within the last 90 days is required for a Tier-2 short-acting medication; or
3. A chronic pain diagnosis requiring time-released medication (for long-acting medications).

Opioid Analgesics Tier-3 Approval Criteria:

1. A documented 30-day trial with at least two Tier-2 long-acting medications within the last 90 days is required for approval of a long-acting Tier-3 medication; or
2. A documented 30-day trial with at least two Tier-2 short-acting medications within the last 90 days is required for approval of a Tier-3 short-acting medication; or
3. A documented allergy or contraindication(s) to all available Tier-2 medications.

Opioid Analgesics Special Prior Authorization (PA) Approval Criteria:

1. Actiq®, Fentora®, Onsolis®, Abstral®, Lazanda®, and Subsys® are approved for oncology-related diagnoses only.
2. Unique Strengths of Hydrocodone/Acetaminophen (APAP) Approval Criteria:
    a. A patient-specific, clinically significant reason why the member cannot use generic Norco® (hydrocodone/APAP 5/325mg, 7.5/325mg, or 10/325mg).
3. ConZip® [Tramadol Extended-Release (ER) Capsules] Approval Criteria:
    a. A patient-specific, clinically significant reason why the member cannot use the ER tablet formulation. Tier structure rules apply.
4. Xartemis® XR (Oxycodone/APAP ER Tablets) Approval Criteria:
    a. An acute pain condition requiring around-the-clock opioid treatment; and
    b. A patient-specific, clinically significant reason for all of the following:
        i. Why the member cannot use any other opioid medication for treatment of acute pain; and
        ii. Why the member requires a long-acting medication for an acute pain condition; and
        iii. Why the member cannot use Oxycontin® (oxycodone ER) and over-the-counter (OTC) APAP individual products in place of this combination product; and
    c. A quantity limit of four tablets per day will apply with a maximum approval duration of 10 days; and
    d. The member must not exceed 3,250mg of APAP per day from all sources; and
    e. Tier structure rules still apply.

Approval Criteria for Greater than 12 Claims Per Year of Hydrocodone Products:

1. Members may be approved for greater than 12 claims per year of hydrocodone products if the member has a pain contract with a single prescriber. A copy of the pain contract should be submitted with the prior authorization request. Requests outside of the plan outlined in the contract will not be approved.
2. Members with a current oncology-related diagnosis do not require a pain contract for additional approvals.

Suboxone® [Buprenorphine/Naloxone Sublingual (SL) Tablets and Films], Subutex® (Buprenorphine SL Tablets), Zubsolv® (Buprenorphine/Naloxone SL Tablets), and Bunavail® (Buprenorphine/Naloxone Buccal Films) Approval Criteria:

1. Suboxone® is the preferred product. Bunavail® and Zubsolv® authorization requires a patient-specific, clinically significant reason why Suboxone® is not appropriate.
2. Subutex® (buprenorphine) 2mg and 8mg tablets will only be approved if the member is pregnant or has a documented serious allergy or adverse reaction to naloxone.
3. Buprenorphine products FDA approved for a diagnosis of opioid abuse/dependence must be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a Drug Enforcement Agency (DEA) X number; and
4. Member must have an FDA approved diagnosis of opioid abuse/dependence; and
5. Concomitant treatment with opioids (including tramadol) will be denied; and
6. Approvals will be for the duration of 90 days to allow for concurrent medication monitoring; and
7. The following limitations will apply:
    a. **Suboxone®** 2mg/0.5mg, 4mg/1mg, and 8mg/2mg SL tablets and films: A quantity limit of 90 SL units per 30 days will apply.
    b. **Suboxone®** 12mg/3mg SL films: A quantity limit of 60 SL films per 30 days will apply.
    c. **Subutex®** 2mg and 8mg SL tablets: A quantity limit of 90 SL tablets per 30 days will apply.
    d. **Zubsolv®** 0.7mg/0.18mg, 1.4mg/0.36mg, 2.9mg/0.71mg, and 5.7mg/1.4mg SL tablets: A quantity limit of 90 SL tablets per 30 days will apply.
    e. **Zubsolv®** 8.6mg/2.1mg SL tablets: A quantity limit of 60 SL tablets per 30 days will apply.
    f. **Zubsolv®** 11.4mg/2.9mg SL tablets: A quantity limit of 30 SL tablets per 30 days will apply.
    g. **Bunavail®** 2.1mg/0.3mg and 4.2mg/0.7mg buccal films: A quantity limit of 90 buccal films per 30 days will apply.
    h. **Bunavail®** 6.3mg/1mg buccal films: A quantity limit of 60 buccal films per 30 days will apply.

High-Dose Buprenorphine Products Approval Criteria:

1. Each request for greater than 24mg bioequivalent buprenorphine per day will be evaluated on a case-by-case basis.
2. A taper schedule, dates of an attempted taper with reason for failure, or a patient-specific, clinically significant reason why a taper schedule or attempt is not appropriate for the member should be documented on the prior authorization request; and
3. Opioid urine drug screens should be submitted with high-dose requests that plan to continue high-dose treatment longer than the duration of one month.
    a. Urine drug screens must show the absence of opioid medications other than buprenorphine products for continued approval; or

    b. Prescriber must document a patient-specific reason the member should continue therapy, reason for opioid use, and document a plan for member to discontinue opioid use; and
4. Symptoms associated with withdrawal at lower doses or symptoms requiring high doses should be listed on the prior authorization request; and
5. Each approval will be for the duration of one month. If urine drug screen and other documentation are submitted indicating high-dose therapy is necessary, an approval can be granted for the duration of three months.
6. Continued high-dose authorization after the three-month approval will require a new (recent) urine drug screen.

Probuphine® (Buprenorphine Implant) Approval Criteria:

1. An FDA approved indication of maintenance treatment of opioid dependence; and
2. Members must be currently on a maintenance dose of 8mg per day or less of a Subutex® or Suboxone® sublingual tablet or its transmucosal buprenorphine product equivalent; and
3. Member must have been stable on current transmucosal buprenorphine dose (of 8mg per day or less) for three months or longer without any need for supplemental dosing or adjustments; and
4. Members must have had no positive urine toxicology results or paid claims for opioids within the last three months. Concomitant treatment with opioids (including tramadol) will be denied; and
5. Probuphine® must be prescribed by a licensed physician who qualifies for a waiver under the Drug Addiction Treatment Act (DATA) and has notified the Center for Substance Abuse Treatment of the intention to treat addiction patients and has been assigned a Drug Enforcement Agency (DEA) X number; and
6. Prescribers must verify they have considered the following factors in determining clinical stability and suitability for Probuphine®:
    a. Period free from illicit opioid drug use
    b. Stability of living environment
    c. Participation in a structured activity/job
    d. Consistency in participation in recommended behavioral therapy/peer support program
    e. Consistency in compliance with clinic visit requirements
    f. Minimal to no desire or need to use illicit opioids
    g. Period without episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions
    h. Social support system
7. The prescriber must verify enrollment in the Probuphine® Risk Evaluation and Mitigation Strategy (REMS) program; and
8. Approvals will be for one kit (four implants) per six months. Reauthorizations for an additional six months may be granted if the member does not have ongoing use of supplemental dosing with transmucosal buprenorphine or opioid analgesics while utilizing Probuphine®.

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Appendix D

Vote to Prior Authorize Jynarque™ (Tolvaptan)

Oklahoma Health Care Authority
September 2018

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 two known (and possibly more unknown) 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* [end-stage renal disease (ESRD) mean age 54.3 years vs. 74.0 years in *PKD1* vs. *PKD2*, respectively].

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. Patients with ADPKD can present with hypertension, proteinuria, renal insufficiency, and flank pain due to renal hemorrhage, calculi, or urinary tract infection. The major extrarenal manifestations can include hepatic and pancreatic cysts, cerebral aneurysms, cardiac valve disease, colonic diverticula, abdominal wall and inguinal hernia, and seminal vesical cysts. The age at which individuals have clinical manifestations such as renal failure or hypertension 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 hypertension, 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 glomerular filtration rate (GFR) starts to decline, the average GFR 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. In one study, patients diagnosed before 30 years of age had a mean survival that was 10 years or less than those diagnosed after age 30. Most patients with ADPKD die from cardiac causes, particularly myocardial infarction (MI) or congestive heart failure (CHF).

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 mortality. Hypertension 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 cardiovascular 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. 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) was approved by the U.S. Food and Drug Administration (FDA) as an Orphan Drug for the treatment of ADPKD. 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 five 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. Samsca® 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 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™.

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

News:

- **August 2018:** Results from an 11-year follow-up reviewing data from 97 patients with ADPKD enrolled in the 3-year Tolvaptan Efficacy and Safety in Management of ADPKD and its Outcomes (TEMPO) 3:4 clinical trial and the 1-year Replicating Evidence of Preserved Renal Function: An Investigation of Tolvaptan Safety and Efficacy in ADPKD (REPRISE) trial were published in the August 2018 issue of the *Clinical Journal of the American Society of Nephrology*. The results suggest that tolvaptan might delay the need for dialysis or kidney transplantation, provided that its effect on kidney function decline is sustained and cumulative over time, beyond the relatively short duration of TEMPO 3:4 and REPRISE. Because all patients participating in the clinical trials were given the opportunity of continuing tolvaptan in an open-label extension study, investigators gathered information on the efficacy of tolvaptan for up to 11.2 years (average 4.6 years). Kidney function was measured as estimated glomerular filtration rate (eGFR). Investigators found that patients treated with tolvaptan had lower eGFR declines compared with controls (-1.97 vs. -3.50mL/min/1.73m^2/year) and a lower risk of a 33% reduction in eGFR from baseline compared with controls. Also, the annualized

eGFR declines of patients treated with tolvaptan did not change with the duration of follow-up. The follow-up study showed a sustained reduction in the annual rate of eGFR decline in patients treated with tolvaptan compared with controls and an increasing separation of eGFR values over time between the two groups.

Pipeline:

- **July 2018:** Reata Pharmaceuticals, Inc. announced positive final results for the Phase 2 ADPKD study of bardoxolone methyl (bardoxolone) in patients with CKD. The Phase 2 PHOENIX program is studying bardoxolone in patients with ADPKD, immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis, and CKD associated with type 1 diabetes. Patients received bardoxolone open-label, orally, once-daily for 12 weeks, and the primary efficacy endpoint was change from baseline in eGFR after 12 weeks of treatment. Endpoints were assessed for each cohort separately. In the Phase 2 ADPKD cohort of the PHOENIX study, bardoxolone significantly increased eGFR at Week 12 from baseline, [9.3mL/min/1.73m^2 ($P<0.0001$) improvement was observed in bardoxolone-treated patients]. Reata collected historical eGFR data for 29 of the 31 Phase 2 study patients. The historical eGFR data demonstrated that these patients' kidney function was declining at an average annual rate of 4.8mL/min/1.73m^2 prior to study entry. The observed 9.3mL/min/1.73m^2 improvement after 12 weeks of treatment with bardoxolone represents a recovery of approximately two years of average eGFR loss.
- **August 2018:** XORTX Therapeutics Inc. announced with its collaborative partner, Cato Clinical Research, the filing of its pre-Investigational New Drug (IND) meeting documents with the FDA regarding development of XRx-008 for the treatment of ADPKD. XORTX's meeting with the FDA is scheduled for September 20, 2018. The company's ADPKD program is a fast track approach to reposition a new formulation of oxypurinol. Oxypurinol is a drug that has been extensively studied and characterized as safe and effective for decreasing uric acid in a patient's blood. Evidence from a variety of recent studies supports the concept that serum uric acid (SUA), when increased above the upper limit of normal, is a "causative" mediator of hypertension, and decreasing uric acid has the potential to lower this risk factor potentially slowing deterioration of kidney function.

Recommendations

The College of Pharmacy recommends the prior authorization of Jynarque™ (tolvaptan) with the following 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.

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Appendix E

Fiscal Year 2018 Annual Review of Breast Cancer Medications and 30-Day Notice to Prior Authorize Verzenio™ (Abemaciclib), Ogivri™ (Trastuzumab-dkst), and Lynparza® (Olaparib)

Oklahoma Health Care Authority
September 2018

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

According to the National Cancer Institute, in 2018 there will be an estimated 266,120 new cases of breast cancer, making it the most common cancer found in women, and an estimated 40,920 breast cancer deaths. The most common type of breast cancer is ductal carcinoma, which begins in the cells of the ducts. Breast cancer can also begin in the cells of the lobules and in other tissues in the breast. Invasive breast cancer is breast cancer that has spread from where it began in the ducts or lobules to surrounding tissues. Traditional chemotherapy has long been used to treat breast cancer, but in more recent years, targeted chemotherapy is being developed to take advantage of gene changes in cells that cause cancer [e.g., drugs that target human epidermal receptor type 2 (HER2), anti-angiogenesis drugs, cyclin-dependent kinase inhibition].

Use of evidence-based expert consensus guidelines is imperative in the treatment of cancers. The National Comprehensive Cancer Network (NCCN) Compendium contains authoritative, scientifically derived information designed to support decision making about the appropriate use of drugs and biologics in patients with cancer. These evidence-based guidelines should be used for optimal outcomes of cancer patients.

Current Prior Authorization Criteria

Afinitor® (Everolimus) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced breast cancer; and
2. Negative expression of human epidermal receptor type 2 (HER2); and
3. Hormone receptor positive; and
4. Used in combination with exemestane; and
5. Member must have failed treatment with, have a contraindication to, or be intolerant to letrozole or anastrozole.

Afinitor® (Everolimus) Approval Criteria [Neuroendocrine Tumors of Pancreatic Origin (PNET) or Neuroendocrine Tumors (NET) of Gastrointestinal or Lung Origin Diagnosis]:

1. Diagnosis of unresectable, locally advanced, or metastatic neuroendocrine tumors (NET) of pancreatic (PNET), gastrointestinal, or lung origin; and
2. Progressive disease from a previous treatment.

Afinitor® (Everolimus) Approval Criteria [Renal Cell Carcinoma (RCC) Diagnosis]:

1. Diagnosis of advanced RCC; and

2. Failure of treatment with sunitinib or sorafenib; and
3. Everolimus may also be approved to be used in combination with lenvatinib for advanced renal cell carcinoma.

Afinitor® (Everolimus) Approval Criteria [Renal Angiomyolipoma and Tuberous Sclerosis Complex (TSC) Diagnosis]:

1. Diagnosis of renal angiomyolipoma and tuberous sclerosis complex (TSC); and
2. Not requiring immediate surgery; and
3. Used in pediatric and adult members with 1 year of age and older.

Afinitor® (Everolimus) Approval Criteria [Subependymal Giant Cell Astrocytoma (SEGA) with Tuberous Sclerosis Complex (TSC) Diagnosis]:

1. Diagnosis of SEGA with TSC; and
2. Requires therapeutic intervention but cannot be curatively resected.

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

1. Diagnosis of metastatic breast cancer; and
2. Previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting.

Halaven® (Eribulin) Approval Criteria [Liposarcoma Diagnosis]:

1. Diagnosis of unresectable or metastic liposarcoma; and
2. Previously received an anthracycline-containing chemotherapy regimen.

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

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

Ixempra® (Ixabepilone) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of metastatic or locally advanced breast cancer; and
2. Usage as either:
    a. In combination with capecitabine after failure of an anthracycline and a taxane (must have failed combination taxane and anthracycline therapy unless anthracyclines not indicated); or
    b. Monotherapy after failure of an anthracycline, a taxane, and capecitabine.

Kadcyla® (Ado-Trastuzumab) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of metastatic breast cancer; and
2. Positive expression of human epidermal receptor type 2 (HER2); and
3. Member has previously received trastuzumab and a taxane, separately or in combination; and
4. Member should also have either:

a. Received prior therapy for metastatic disease; or
b. Developed disease recurrence during or within six months of completing adjuvant therapy.

Kisqali® (Ribociclib) Approval Criteria [Breast Cancer Diagnosis]:

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

Kisqali® Femara® Co-Pack (Ribociclib/Letrozole) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced or metastatic breast cancer, initial therapy; and
2. Member must be hormone receptor positive; and
3. Member must be human epidermal receptor type 2 (HER2)-negative; and
4. Must be used in postmenopausal women only.

Nerlynx® (Neratinib) Approval Criteria [Breast Cancer Diagnosis]:

1. For adjuvant treatment in early stage breast cancer; and
2. Member must have human epidermal receptor type 2 (HER2)-overexpressed breast cancer; and
3. Neratinib must be used to follow adjuvant trastuzumab-based therapy.

Perjeta® (Pertuzumab) Approval Criteria [Breast Cancer Diagnosis]:

1. Positive expression of human epidermal receptor type 2 (HER2); and
2. Usage for either:
    a. Metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease; or
    b. Neoadjuvant treatment of patients with locally advanced, inflammatory, or early stage breast cancer (either greater than 2cm in diameter or node positive); and
3. Used in combination with trastuzumab and docetaxel (neoadjuvant treatment may also contain other agents in addition to trastuzumab and docetaxel).

Tykerb® (Lapatinib) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of metastatic or recurrent breast cancer; and
2. Positive expression of human epidermal receptor type 2 (HER2); and
3. Lapatinib must be used in combination with one of the following:
    a. Trastuzumab; or
    b. Capecitabine; or
    c. An aromatase inhibitor (e.g., exemestane, letrozole, anastrozole) if also estrogen receptor positive.

Utilization of Breast Cancer Medications: Fiscal Year 2018

Breast Cancer Medications Fiscal Year Comparison: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	38	176	$2,077,442.66	$11,803.65	$413.09	4,957	5,029
2018	62	321	$3,835,500.82	$11,948.60	$417.54	13,680	9,186
% Change	**63.20%**	**82.40%**	**84.60%**	**1.20%**	**1.10%**	**176.00%**	**82.70%**
Change	**24**	**145**	**$1,758,058.16**	**$144.95**	**$4.45**	**8,723**	**4,157**

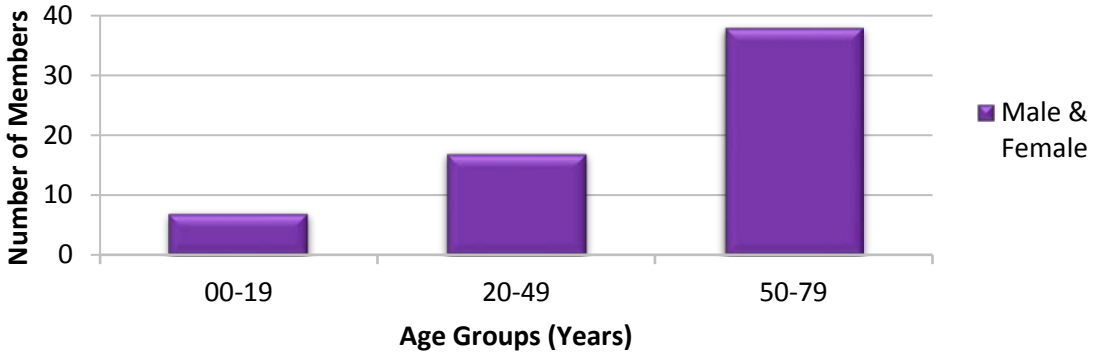
*Total number of unduplicated members.
Cost do not reflect rebated prices or net costs.

Breast Cancer Medications Fiscal Year Comparison: Medical Claims

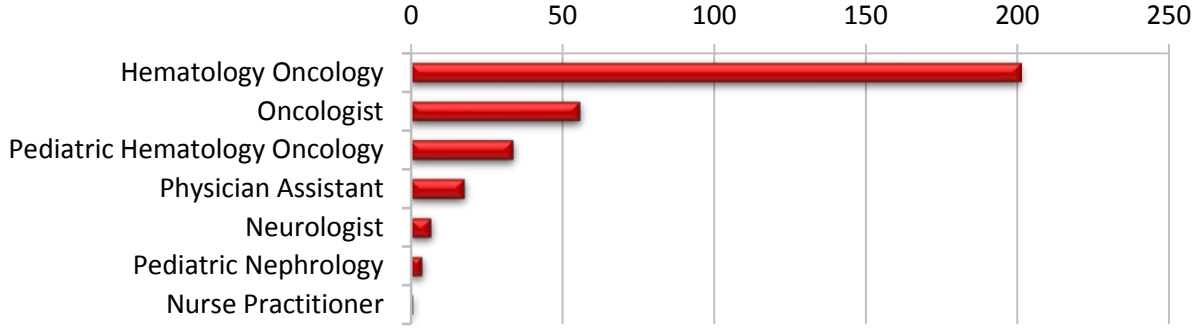
Fiscal Year	*Total Members	+Total Claims	Total Cost	Cost/ Claim	Total Units
2017	127	822	$4,039,116.14	$4,913.77	125,695
2018	84	549	$4,311,703.46	$7,853.74	149,656
% Change	**-33.86%**	**-33.21%**	**6.75%**	**59.83%**	**19.06%**
Change	**-43**	**-273**	**$272,587.32**	**$2,939.97**	**23,961**

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

Demographics of Members Utilizing Breast Cancer Medications: Pharmacy Claims

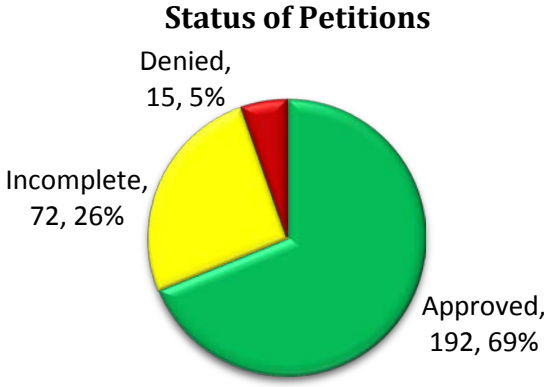


Top Prescriber Specialties of Breast Cancer Medications By Number of Claims: Pharmacy Claims



Prior Authorization of Breast Cancer Medications

There were 279 prior authorization requests submitted for breast cancer medications during fiscal year 2018. The following chart shows the status of the submitted petitions.



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

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

- **September 2017:** The FDA approved Verzenio™ (abemaciclib) in combination with fulvestrant for women with hormone receptor (HR)-positive, HER2-negative, advanced or metastatic breast cancer with disease progression following endocrine therapy.
- **December 2017:** Perjeta® (pertuzumab) was granted regular approval by the FDA for use in combination with Herceptin® (trastuzumab) and chemotherapy as adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence.
- **December 2017:** The FDA approved Ogivri™ (trastuzumab-dkst) as a biosimilar to Herceptin® (trastuzumab) for the treatment of patients with HER2-overexpressing breast or metastatic stomach cancer (gastric or gastroesophageal junction adenocarcinoma).
- **January 2018:** The FDA granted regular approval to Lynparza® (olaparib), a poly (ADP-ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative, metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting. Lynparza® was previously approved for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- **February 2018:** The FDA approved Verzenio™ (abemaciclib) for use in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer.
- **April 2018:** The FDA approved Afinitor® (everolimus) tablets for oral suspension for the adjunctive treatment of adult and pediatric patients 2 years of age and older with tuberous sclerosis complex (TSC)-associated partial-onset seizures. Everolimus was previously approved for two other manifestations of TSC: TSC-associated subependymal giant cell astrocytoma (SEGA) and TSC-associated renal angiomyolipoma.

- **July 2018:** The FDA expanded the indication for Kisqali® (ribociclib) for use in combination with an aromatase inhibitor for pre/perimenopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer, as initial endocrine-based therapy.

Guideline Updates:

- **Perjeta® (Pertuzumab):** Perjeta® received additional recommendations to be used as adjuvant, systemic therapy for patients with node positive, HER2-positive tumors, or high-risk, node negative breast cancer patients.
- **Afinitor® (Everolimus):** Afinitor® received additional recommendations to be used in combination with exemestane, fulvestrant, or tamoxifen for the treatment of HER2-negative, HR-positive, advanced breast cancer.

Pipeline:

- **Sacituzumab Govitecan:** While there are numerous ongoing trials in both early and late phases focused on breast cancer treatment, there is only one agent currently on the FDA calendar to review in the upcoming year. The FDA is scheduled to make its decision on the Biologics License Application (BLA) for sacituzumab govitecan for the treatment of metastatic, triple-negative breast cancer by January 2019.

Product Summaries[10,11,12]

Lynparza® (Olaparib):

- **Therapeutic Class:** PARP inhibitor
- **Indication(s):**
  - For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy
  - For the treatment of adult patients with deleterious or suspected deleterious gBRCAm, advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy
  - In patients with deleterious or suspected deleterious gBRCAm, HER2-negative, metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting; patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy
- **How Supplied:** 100mg and 150mg oral tablets
- **Dose:** 300mg orally twice daily with or without food
- **Cost:** $115.72 per tablet; 300mg twice daily for 30 days (120 tablets): $13,886.40

Ogivri™ (Trastuzumab-dkst):

- **Therapeutic Class:** HER2/neu receptor antagonist; biosimilar to Herceptin® (trastuzumab)
- **Indication(s):**
  - Treatment of HER2-overexpressing breast cancer

- Treatment of HER2-overexpressing, metastatic gastric or gastroesophageal junction adenocarcinoma

- **How Supplied:** 420mg lyophilized powder in a multiple-dose vial for reconstitution
- **Dose:**
  - Adjuvant Treatment of HER2-Overexpressing Breast Cancer:
    - Recommended initial dose of 4mg/kg over 90 minutes via intravenous (IV) infusion, then 2mg/kg over 30 minutes weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin); 1 week after the last weekly dose of trastuzumab-dkst, 6mg/kg should be administered as an IV infusion over 30 to 90 minutes every 3 weeks to complete a total of 52 weeks of therapy; or
    - Recommended initial dose of 8mg/kg over 90 minutes via IV infusion, then 6mg/kg over 30 to 90 minutes via IV infusion every 3 weeks for 52 weeks
  - Metastatic HER2-Overexpressing Breast Cancer:
    - Initial dose of 4mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2mg/kg as 30 minute IV infusions
  - Metastatic HER2-Overexpressing Gastric Cancer:
    - Initial dose of 8mg/kg over 90 minutes via IV infusion, followed by 6mg/kg over 30 to 90 minutes via IV infusion every 3 weeks
- **Cost:** Cost information for Ogivri™ is not yet available.

Verzenio™ (Abemaciclib):

- **Therapeutic Class:** Kinase inhibitor
- **Indication(s):**
  - In combination with an aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with HR-positive, HER2-negative, advanced or metastatic breast cancer
  - In combination with fulvestrant for the treatment of women with HR-positive, HER2-negative, advanced or metastatic breast cancer with disease progression following endocrine therapy
  - As monotherapy for the treatment of adult patients with HR-positive, HER2-negative, advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting
- **How Supplied:** 50mg, 100mg, 150mg, and 200mg oral tablets
- **Dose:** The recommended starting dose when used in combination with fulvestrant or an aromatase inhibitor is 150mg twice daily. The recommended starting dose when used as monotherapy is 200mg twice daily. Dosing interruption and/or dose reductions may be required based on individual safety and tolerability.
- **Cost:** $201.45 per tablet; $12,087 per month based on recommended dose of 1 tablet twice daily

Recommendations

Afinitor® (Everolimus) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced breast cancer; and
2. Negative expression of human epidermal receptor type 2 (HER2); and
3. Hormone receptor positive; and
4. Used in combination with exemestane, fulvestrant, or tamoxifen; and
5. Member must have failed treatment with, have a contraindication to, or be intolerant to letrozole or anastrozole.

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

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

Kisqali® (Ribociclib) Approval Criteria [Breast Cancer Diagnosis]:

1. ~~A patient-specific, clinically significant reason why the member cannot use the co-packaged formulation with letrozole; and~~
2. ~~A diagnosis of advanced or metastatic breast cancer, initial therapy; and~~
3. Member must be hormone receptor positive; and
4. Member must be human epidermal receptor type 2 (HER2)-negative; and
5. If used in combination with an aromatase inhibitor:
    a. Diagnosis of advanced or metastatic breast cancer, initial therapy; or
6. If used in combination with fulvestrant:

a. Diagnosis of advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy; and
b. Must be used in postmenopausal women only.

~~7. Ribociclib must be given in combination with an aromatase inhibitor; and~~
~~8. Ribociclib must be used in postmenopausal women only.~~

Kisqali® Femara® Co-Pack (Ribociclib/Letrozole) Approval Criteria [Breast Cancer Diagnosis]:

1. Diagnosis of advanced or metastatic breast cancer, initial therapy; and
2. Member must be hormone receptor positive; and
3. Member must be human epidermal receptor type 2 (HER2)-negative; and
4. ~~Ribociclib must be used in postmenopausal women only.~~

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

1. Diagnosis of deleterious or suspected deleterious germline BRCA mutated, advanced gBRCAm ovarian cancer; and
2. The member must have been treated with three or more prior lines of chemotherapy. Prior chemotherapy regimens should be documented on the prior authorization request; and
3. A quantity limit based on FDA approved dosing will apply.

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

1. Diagnosis of metastatic breast cancer; and
2. Member must have shown progression on previous chemotherapy in any setting; and
3. Human epidermal receptor 2 (HER2)-negative; and
4. Positive test for a germline BRCA-mutation; and
5. Members with hormone receptor positive disease must have failed prior endocrine therapy or are considered to not be a candidate for endocrine therapy.

Ogivri™ (Trastuzumab-dkst) Approval Criteria [Breast Cancer Diagnosis]:

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

Ogivri™ (Trastuzumab-dkst) Approval Criteria [Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma Diagnosis]:

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

Perjeta® (Pertuzumab) Approval Criteria [Breast Cancer Diagnosis]:

1. Positive expression of human epidermal receptor type 2 (HER2); and
2. Used in one of the following settings:
   a. Metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease:
      i. Used in combination with trastuzumab and docetaxel; or

b. Neoadjuvant treatment of members with locally advanced, inflammatory, or early stage breast cancer (either >2cm in diameter or node positive):
    i. Used in combination with trastuzumab and docetaxel (neoadjuvant treatment may also contain other agents in addition to trastuzumab and docetaxel); or
c. Adjuvant systemic therapy for patients with node positive, HER2-positive tumors or high-risk node negative members [tumor >1cm; tumor 0.5 to 1cm with histologic or nuclear grade 3; estrogen receptor (ER)/progesterone receptor (PR) negative; or age <35]:
    i. Used in combination with trastuzumab and paclitaxel following AC (doxorubicin/cyclophosphamide); or
    ii. Used in combination with trastuzumab and docetaxel following AC; or
    iii. Used in combination with TCH (docetaxel/carboplatin/trastuzumab).

Verzenio™ (Abemaciclib) Approval Criteria [Breast Cancer Diagnosis]:

1. Used in one of the following settings:
    a. In combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women; or
    b. In combination with fulvestrant with disease progression following endocrine therapy in advanced or metastatic breast cancer; or
    c. As monotherapy for disease progression following endocrine therapy and prior chemotherapy in metastatic breast cancer; and
2. All the following criteria must be present:
    a. Advanced or metastatic breast cancer; and
    b. Progressed after endocrine therapy when used with fulvestrant or as initial therapy in combination with an aromatase inhibitor; and
    c. Hormone receptor positive; and
    d. Human epidermal receptor 2 (HER2)-negative.

Utilization Details of Breast Cancer Medications: Fiscal Year 2018

Pharmacy Claims: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
PALBOCICLIB PRODUCTS					
IBRANCE CAP 125MG	90	22	$1,004,593.78	4.09	$11,162.15
IBRANCE CAP 100MG	43	10	$477,400.43	4.3	$11,102.34
IBRANCE CAP 75MG	33	5	$304,152.61	6.6	$9,216.75
SUBTOTAL	**166**	**37**	**$1,786,146.82**	**4.49**	**$10,759.92**
EVEROLIMUS PRODUCTS					
AFINITOR TAB 10MG	35	7	$490,124.17	5	$14,003.55
AFINITOR TAB 7.5MG	18	2	$254,059.12	9	$14,114.40
AFINITOR DIS TAB 5MG	17	2	$239,554.12	8.5	$14,091.42
AFINITOR TAB 5MG	15	2	$314,383.59	7.5	$20,958.91
AFINITOR DIS TAB 2MG	5	2	$83,060.17	2.5	$16,612.03

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
AFINITOR TAB 2.5MG	4	1	$55,657.84	4	$13,914.46
SUBTOTAL	**94**	**16**	**$1,436,839.01**	**5.88**	**$15,285.52**
NERATINIB PRODUCTS					
NERLYNX TAB 40MG	18	5	$193,822.30	3.6	$10,767.91
SUBTOTAL	**18**	**5**	**$193,822.30**	**3.6**	**$10,767.91**
LAPATINIB PRODUCTS					
TYKERB TAB 250MG	15	4	$101,376.15	3.75	$6,758.41
SUBTOTAL	**15**	**4**	**$101,376.15**	**3.75**	**$6,758.41**
RIBOCICLIB PRODUCTS					
KISQALI 600 PAK FEMARA	9	2	$101,260.95	4.5	$11,251.22
KISQALI TAB 400DOSE	4	1	$36,129.40	4	$9,032.35
KISQALI TAB 600DOSE	2	2	$22,249.60	1	$11,124.80
SUBTOTAL	**15**	**5**	**$159,639.95**	**3.75**	**$10,642.66**
ABEMACICLIB PRODUCTS					
VERZENIO TAB 150MG	8	1	$88,604.00	8	$11,075.50
SUBTOTAL	**8**	**1**	**$88,604.00**	**8**	**$11,075.50**
OLAPARIB PRODUCTS					
LYNPARZA TAB 150MG	5	2	$69,072.59	2.5	$13,814.52
SUBTOTAL	**5**	**2**	**$69,072.59**	**2.5**	**$13,814.52**
TOTAL	**321**	**62***	**$3,835,500.82**	**5.18**	**$11,948.600**

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

Medical Claims: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS[+]	TOTAL MEMBERS*	TOTAL COST	COST/ CLAIM
J9355 TRASTUZUMAB INJECTION	475	76	$2,561,569.48	$5,392.78
J9306 PERTUZUMAB INJECTION	223	42	$1,230,129.60	$5,516.28
J9354 ADO-TRASTUZUMAB INJECTION	35	7	$409,894.40	$11,711.27
J9179 ERIBULIN MESYLATE INJECTION	36	4	$110,109.98	$3,058.61
TOTAL	**549[+]**	**84***	**$4,311,703.46**	**$7,853.74**

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

[1] National Cancer Institute. SEER Cancer Statistics. Available online at: https://seer.cancer.gov/statfacts/html/breast.html. Last accessed 08/20/2018.
[2] American Cancer Society. What's new in breast cancer research and treatment? Available online at: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-new-research. Last revised 02/01/2018. Last accessed 08/20/2018.
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[5] Ramsey SD, Ganz PA, Shankaran V, et al. Addressing the American health-care cost crisis: Role of the oncology community. *J Natl Cancer Inst* 2013; 105:1777-8.
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[7] Von Minckwitz G, Procter MJ, De Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. *N Engl J Med* 2017; 377:122-131.
[8] Kornblum N, Zhao F, Manola J, et al. Randomized Phase II Trial of Fulvestrant Plus Everolimus or Placebo in Postmenopausal Women With Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer Resistant to Aromatase Inhibitor Therapy: Results of PrE0102. *JCO* 2018; 36(16):1556-1563.
[9] Broderick JM. FDA Grants Sacituzumab Govitecan Priority Review for Triple-Negative Breast Cancer. *OncLive*. Available online at: https://www.onclive.com/web-exclusives/fda-grants-sacituzumab-govitecan-priority-review-for-triplenegative-breast-cancer. Issued 07/18/2018. Last accessed 08/21/2018.
[10] Verzenio™ (abemaciclib) Prescribing Information. Eli Lilly and Company. Available online at: http://uspl.lilly.com/verzenio/verzenio.html#pi. Last revised 02/2018. Last accessed 07/25/2018.
[11] Ogivri™ (trastuzumab-dkst) Prescribing Information. Mylan. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761074s000lbl.pdf. Last revised 12/2017. Last accessed 08/22/2018.
[12] Lynparza® (olaparib) Prescribing Information. AstraZeneca Pharmaceuticals. Available online at: https://www.azpicentral.com/lynparza_tb/pi_lynparza_tb.pdf#page=1. Last revised 01/2018. Last accessed 07/25/2018.

Appendix F

Fiscal Year 2018 Annual Review of Sickle Cell Disease (SCD) Medications and 30-Day Notice to Prior Authorize NutreStore® (L-Glutamine) and Siklos® (Hydroxyurea)

Oklahoma Health Care Authority
September 2018

Current Prior Authorization Criteria

Endari™ (L-Glutamine Oral Powder) Approval Criteria:

1. An FDA approved diagnosis of sickle cell disease (SCD); and
2. Member must be at least 5 years of age or older; and
3. A trial of hydroxyurea or documentation why hydroxyurea is not appropriate for the member; and
4. Endari™ must be prescribed by, or in consultation with, a hematologist or a specialist with expertise in treatment of SCD (or in consultation with an advanced care practitioner with a supervising physician who is a hematologist or specialist with expertise in treating SCD); and
5. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.
6. Initial approvals will be for a duration of six months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

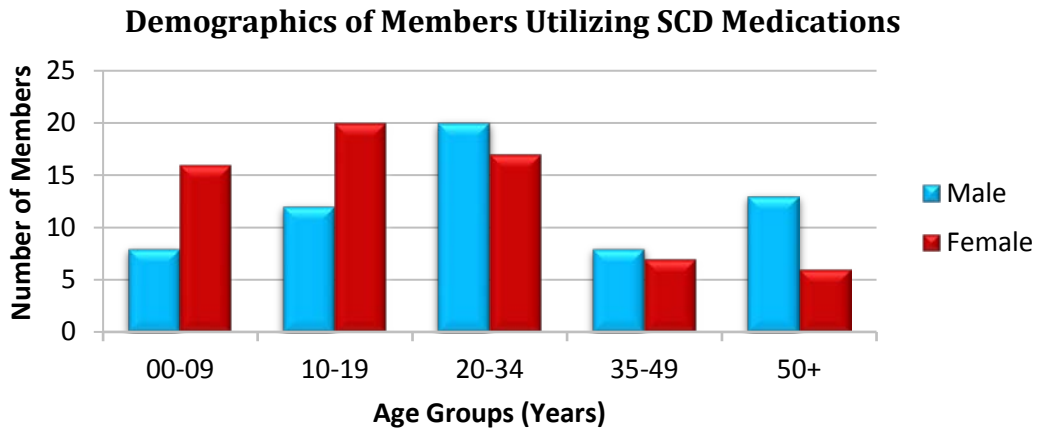
Utilization of SCD Medications: Fiscal Year 2018

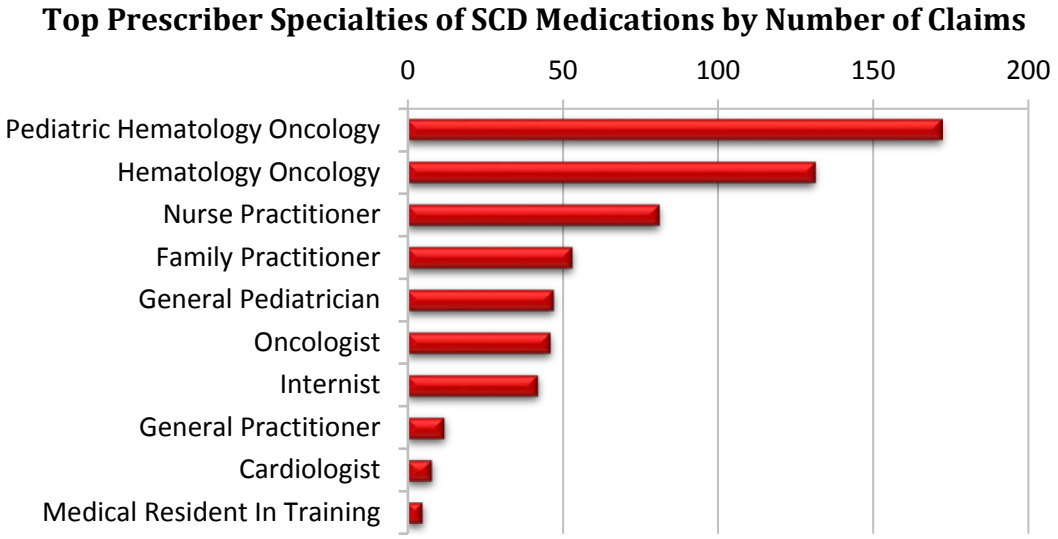
Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	120	560	$17,613.10	$31.45	$1.08	44,124	16,307
2018	127	605	$21,267.23	$35.15	$1.15	52,373	18,445
% Change	**5.80%**	**8.00%**	**20.70%**	**11.80%**	**6.50%**	**18.70%**	**13.10%**
Change	**7**	**45**	**$3,654.13**	**$3.70**	**$0.07**	**8,249**	**2,138**

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

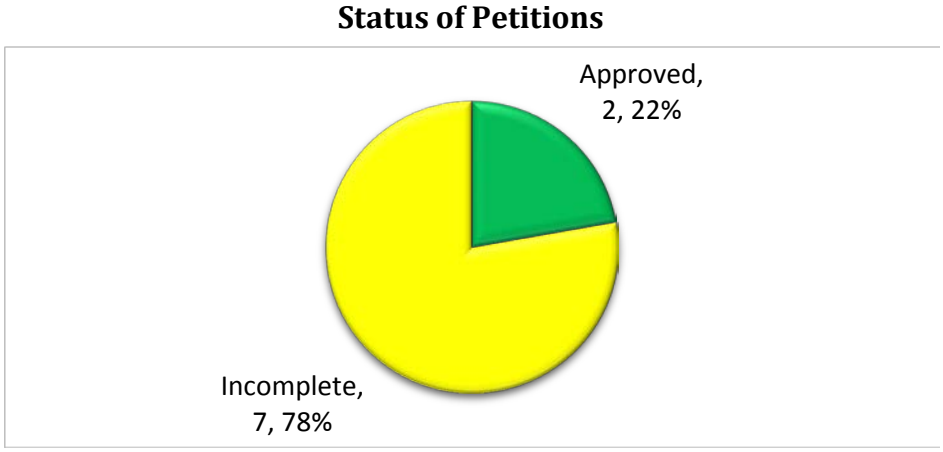
- This utilization data includes SCD medications (e.g., hydroxyurea) used for all diagnoses and does not differentiate between SCD and other diagnoses for which use may be appropriate.





Prior Authorization of SCD Medications

There were 9 prior authorization requests submitted for SCD medications during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.



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

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

- **December 2017:** The FDA approved Siklos® (hydroxyurea tablets) to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients 2 years of age and older with sickle cell anemia (SCA) with recurrent, moderate-to-severe, painful crises. This is the first FDA approval of hydroxyurea for use in pediatric patients with SCD.

Pipeline:

- **Crizanlizumab:** Results from a post hoc subgroup analysis of the Phase 2 SUSTAIN study were featured at the 59th American Society of Hematology Annual Meeting in December 2017. The study showed that crizanlizumab, an investigational, humanized anti-P-selectin monoclonal antibody, delayed the time to first sickle cell pain crisis (SCPC) in patients versus placebo in key subgroups of adult patients with SCD. The data from a subgroup analysis showed that crizanlizumab dosed at 5mg/kg per month increased the time to SCPC in patients on treatment, including those in high-risk subpopulations and with hydroxyurea use. The analysis looked at the following subgroups of patients with SCD: patients with 2 to 4 or 5 to 10 SCPC events in the year before the study; patients with HbSS genotypes and non-HbSS genotypes; patients who were or were not taking hydroxyurea. In all of the subgroups analyzed, crizanlizumab increased the estimated median time to first SCPC versus placebo by approximately two-fold or more. Results of the SUSTAIN trial were originally published in *The New England Journal of Medicine (NEJM)*, which showed that crizanlizumab reduced the median annual rate of SCPCs by 45% compared to placebo (1.6 vs. 3.0, P=0.01) in patients with or without hydroxyurea therapy. Filing with the FDA is anticipated by the end of 2018.
- **Rivipansel:** Rivipansel is a pan-selectin inhibitor and a potential new treatment for the pain of vaso-occlusive crises associated with SCA. The Phase 3 RESET clinical trial began in June 2015, and is assessing the effectiveness and safety of rivipansel for the treatment of pain crisis in hospitalized SCA patients. Patients who complete this study will have the chance to enter a Phase 3 extension study to evaluate the long-term safety and efficacy of rivipansel. Rivipansel received Orphan Drug and Fast Track designation from the FDA.
- **Voxelotor:** Global Blood Therapeutics, Inc. announced in January 2018 it had received Breakthrough Therapy designation from the FDA for voxelotor (previously known as GBT440) for the treatment of SCD. Voxelotor is being developed as a disease-modifying therapy for SCD. It is an oral, once-daily therapy and works by increasing hemoglobin's affinity for oxygen. With the potential to restore normal hemoglobin function and improve oxygen delivery, it is thought that voxelotor may potentially modify the course of SCD. The FDA has also granted voxelotor Fast Track, Orphan Drug, and Rare Pediatric Disease designations for the treatment of SCD. Voxelotor is being evaluated in the HOPE (Hemoglobin Oxygen Affinity Modulation to Inhibit HbS PolymErization) study, a Phase 3 clinical study in patients 12 years of age and older with SCD. Voxelotor is also being studied in the ongoing Phase 2a HOPE-KIDS 1 study, an open-label, single- and multiple-dose study in pediatric patients 6 to 17 years of age with SCD.

- **Sevuparin:** The FDA granted Modus Therapeutics' sevuparin Rare Pediatric Disease designation for the treatment of SCD. Sevuparin is a polysaccharide drug with anti-adhesive, anti-aggregate, and anti-inflammatory effects. Modus states that sevuparin has the potential to restore blood flow and prevent further microvascular obstructions in patients with SCD.
- **LentiGlobin Gene Therapy:** Bluebird Bio published interim data from studies showing that its lentiviral-based gene therapy eliminated or reduced the need for blood transfusions in patients with transfusion-dependent beta-thalassemia. The findings were published in *NEJM* in April 2018. The trial involved 22 patients who received a one-time treatment of LentiGlobin therapy, which involves harvesting blood stem cells from a patient, inserting a functional human beta-globin gene into them, and then transplanting them back into the patient's bone marrow. Patients were followed for at least two years and investigators found that 15 of the 22 patients no longer needed transfusions. Most of the other seven patients had a more severe form of the disease and they still needed transfusions; however, they required fewer transfusions, with a median decrease in transfusion volume of 73%.

Siklos® (Hydroxyurea) Product Summary[7]

Indication(s): Siklos® (hydroxyurea) is an antimetabolite indicated to reduce the frequency of painful crises and to reduce the need for blood transfusions in pediatric patients 2 years of age and older with SCA with recurrent, moderate-to-severe, painful crises.

Dosing:

- Siklos® (hydroxyurea) is supplied as film-coated tablets in 100mg and 1,000mg strengths. The 1,000mg tablet is functionally triple-scored which can be divided into four equal parts. The 100mg tablet should not be split into smaller parts.
- The recommended initial dose is 20mg/kg once daily based on the patient's actual or ideal body weight, whichever is less. The dose may be increased by 5mg/kg/day every 8 weeks, or sooner if a severe painful crisis occurs, until a maximum tolerated dose or 35mg/kg/day is reached (if blood counts are in an acceptable range).
- For patients who are not able to swallow the tablet, the tablet can be dispersed immediately before use in a small quantity of water in a teaspoon.
- Hydroxyurea is a cytotoxic drug. Applicable special handling and disposal procedures should be followed.
- Blood counts should be monitored every 2 weeks and Siklos® should be discontinued until hematologic recovery if blood counts are considered toxic. Treatment may be resumed after reducing the dose by 5mg/kg/day from the dose associated with hematological toxicity. Please refer to the prescribing information for detailed information on dose modification criteria and monitoring parameters.
- For patients with renal impairment, it is recommended to reduce the dose by 50% in patients with creatinine clearance (CrCl) <60mL/min or with end-stage renal disease (ESRD).

Boxed Warning: Myelosuppression and Malignancies

- Siklos® (hydroxyurea) may cause severe myelosuppression. If bone marrow function is markedly depressed, Siklos® should not be given. Blood counts should be monitored at baseline and throughout treatment. It is recommended to interrupt treatment and reduce the dose as necessary.
- Hydroxyurea is carcinogenic. Patients should be advised on sun protection, and patients should be monitored for malignancies.

Mechanism of Action: The precise mechanism of action by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known. Various studies have supported the hypothesis that hydroxyurea causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor, without interfering with the synthesis of ribonucleic acid or of protein. The mechanism by which Siklos® produces its beneficial effects in patients with SCA are uncertain. The known pharmacologic effects of Siklos®, which may contribute to its beneficial effects, include increasing hemoglobin F levels in red blood cells (RBCs), decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium.

Contraindication(s):

- Previous hypersensitivity to hydroxyurea or any other component of its formulation

Warnings and Precautions:

- Embryo-Fetal Toxicity: Hydroxyurea can cause fetal harm. Patients should be advised of the potential risk to a fetus. Males and females of reproductive potential should be advised to use effective contraception during and after treatment with Siklos® for at least 6 months after therapy.
- Vasculitic Toxicities (Including Leg Ulcers): Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease (a condition for which Siklos® is not approved), Siklos® treatment should be discontinued and/or its dose reduced if cutaneous vasculitic ulcerations develop. Siklos® should be avoided in patients with wounds on the legs (leg ulcers).
- Risks with Concomitant Use of Antiretroviral Drugs: Pancreatitis, hepatotoxicity, and peripheral neuropathy have occurred when hydroxyurea was administered concomitantly with antiretroviral drugs, including didanosine and stavudine.
- Concomitant Use with Live Virus Vaccine(s): Live virus vaccines should be avoided in patients taking Siklos®. Concomitant use of hydroxyurea with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reactions of the vaccine virus and result in severe infections. It is recommended to consider consultation with a specialist.

- Macrocytosis: Siklos® may cause macrocytosis, which is self-limiting, and is often seen early in the course of treatment. Prophylactic administration of folic acid is recommended.
- Test Interference: Interference with uric acid, urea, or lactic acid assays is possible, rendering falsely elevated results of these tests in patients treated with hydroxyurea.

Use in Specific Populations:

- Pregnancy: Hydroxyurea can cause fetal harm based on findings from animal studies and the drug's mechanism of action. There are no studies with the use of hydroxyurea in pregnant women, and limited available data on hydroxyurea use during pregnancy are insufficient to inform drug-associated risks.
- Lactation: It is not known whether hydroxyurea is excreted in human milk, the effects of hydroxyurea on the breastfed child, or the effects of hydroxyurea on milk production. Based on the potential for serious adverse reactions in a breastfed child from hydroxyurea, including carcinogenicity, patients should be advised not to breastfeed during treatment with hydroxyurea.
- Females and Males of Reproductive Potential: The pregnancy status of females of reproductive potential should be verified prior to initiating hydroxyurea therapy. Females of reproductive potential should be advised to use effective contraception during and after treatment with hydroxyurea for at least 6 months after therapy. Males with female sexual partners of reproductive potential should use effective contraception during and after treatment with hydroxyurea for at least 6 months after therapy. Based on findings in animals and humans, male fertility may be compromised by treatment with hydroxyurea. Before the start of therapy, male patients should be informed about the possibility of sperm conservation.
- Pediatric Use: The safety and effectiveness of Siklos® have been established in pediatric patients 2 to 18 years of age with SCA with recurrent, moderate-to-severe, painful crises. Continuous follow-up of the growth of the treated child is recommended. Patients between 2 to 16 years of age had a higher risk of neutropenia than patients older than 16 years of age.
- Renal Impairment: The exposure to hydroxyurea is higher in patients with CrCl of <60mL/min. It is recommended to reduce the dose and closely monitor hematologic parameters when hydroxyurea is to be administered to these patients.
- Hepatic Impairment: In patients with hepatic impairment receiving hydroxyurea, it is recommended to closely monitor hematologic parameters.

Adverse Reactions: The most common adverse reactions to Siklos® (incidence >10%) include infections and neutropenia.

Efficacy: The efficacy of Siklos® was assessed in the European Sickle Cell Disease Cohort study (ESCORT HU). It was an open-label, single-arm study of 405 pediatric patients with SCD between the ages of 2 and 18 years, of which 141 had not been previously treated with hydroxyurea prior to enrollment. Evaluable patients had at least 12 months follow-up [median (range) 23 months (12, 80)]. Median (range) hemoglobin F percentages were 5.6% (1.3, 15.0) at baseline and 12.8% (2.1, 37.2) at least 6 months (the value closest to 6 months collected

between 5 and 14 months) after initiation of Siklos® treatment, with a median change of 5.9% (-2.2, 34.7) in 47 patients. Median (range) hemoglobin levels were 8.2g/dL (3.7, 14.2) at baseline, 8.8g/dL (0.7, 13.1) at 6 months (the value closest to 6 months collected between 5 and 7 months), and 8.9g/dL (5.5, 13.2) at 12 months (the value closest to 12 months collected between 10 and 14 months) after initiation of Siklos® treatment. The median (range) change was 0.5g/dL (-4.6, 6.1) in 63 patients at 6 months (the post-baseline value closest to 6 months collected between 5 and 7 months) and 0.7g/dL (-6.4, 6.0) in 83 patients at 12 months (the post-baseline value closest to 12 months collected between 10 and 14 months) after initiation of Siklos® treatment. Among pediatric patients not previously treated with hydroxyurea prior to enrollment and analyzable for efficacy (N=141), the percentage of patients with at least one vaso-occlusive episode, one episode of acute chest syndrome, one hospitalization due to SCD, or one blood transfusion decreased after 12 months of Siklos® treatment.

SCD Events	Patients younger than 18 years of age not previously treated with hydroxyurea with at least 12 months follow-up data available for clinical efficacy (N=141)		
	In the 12 months prior to enrollment	After 12 months of Siklos® treatment	Change
Number of patients with at least one vaso-occlusive episode (in 120 evaluable patients)			
No	37 (30.8%)	69 (57.5%)	
Yes	83 (69.2%)	51 (42.5%)	
Number of vaso-occlusive episodes over 12 months (in 113 evaluable patients)			
Median (range)	2.0 (0.0, 10.0)	0.0 (0.0, 7.0)	-1.0 (-10.0, 5.0)
Number of patients with at least one episode of acute chest syndrome (in 123 evaluable patients)			
No	94 (76.4%)	116 (94.3%)	
Yes	29 (23.6%)	7 (5.7%)	
Number of episodes of acute chest syndrome over 12 months (in 123 evaluable patients)			
Median (range)	0.0 (0.0, 2.0)	0.0 (0.0, 1.0)	0.0 (-2.0, 1.0)
Number of patients with at least one hospitalization related to SCD (in 110 evaluable patients)			
No	27 (24.5%)	64 (58.2%)	
Yes	83 (75.5%)	46 (41.8%)	
Number of hospitalizations related to SCD over 12 months (in 106 evaluable patients)			
Median (range)	2.0 (0.0, 6.0)	0.0 (0.0, 7.0)	-1.0 (-6.0, 6.0)
Number of days of hospitalizations related to SCD over 12 months (in 100 evaluable patients)			
Median (range)	8.0 (0.0, 58.0)	0.0 (0.0, 100.0)	-3.0 (-58.0, 86.0)
Number of patients with at least one blood transfusion (in 122 evaluable patients)			
No	66 (54.1%)	94 (77.0%)	
Yes	56 (45.9%)	28 (23.0%)	

Cost Comparison:

Product	Cost Per Unit	Cost Per 30 Days*
Siklos® (hydroxyurea) 100mg tablet	**$5.00**	**$150.00**
Droxia® (hydroxyurea) 200mg capsule	$0.76	$22.80
Droxia® (hydroxyurea) 300mg capsule	$0.76	$22.80
Droxia® (hydroxyurea) 400mg capsule	$0.89	$26.70
hydroxyurea 500mg capsule	$0.43	$12.90

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.
*Cost based on one tablet or capsule per day.

NutreStore® (L-Glutamine Powder for Oral Solution) Product Summary[8,9]

Indication(s): NutreStore® (L-glutamine power for oral solution) is indicated for the treatment of Short Bowel Syndrome (SBS) in patients receiving specialized nutritional support when used in conjunction with a recombinant human growth hormone (rh-GH) that is approved for this indication. Glutamine and rh-GH therapy should be used in conjunction with optimal management of SBS. Optimal management of SBS may include a specialized oral diet, enteral feedings, parenteral nutrition, and fluid and micronutrient supplements. A specialized oral diet (SOD) may consist of a low-fat, high-carbohydrate diet, adjusted for individual patient preferences and requirements.

Dosing:

- NutreStore® should be administered as a co-therapy with rh-GH (please refer to the package insert for somatotropin for injection for full prescribing information) followed by continued NutreStore® for up to 16 weeks.
- The recommended dosage of NutreStore® is 30g daily in divided doses (5g taken 6 times each day orally) for up to 16 weeks. Each dose of NutreStore® should be reconstituted in 8 ounces of water prior to consumption.
- NutreStore® should be taken with meals or snacks at 2- to 3-hour intervals while awake. The volume of water may be varied according to the patient's preference. In the event of a patient's transient intolerance to oral intake, a dose may be delayed for up to 2 hours.
- The safety and efficacy of NutreStore® have not been studied beyond 16 weeks of treatment.
- NutreStore® is supplied in preprinted, paper-foil-plastic laminate packets containing 5g of L-glutamine powder.

Contraindication(s):

- None

Warnings and Precautions:

- In patients with SBS, NutreStore® should only be taken under the direction of a physician, registered dietician, or nutritionist. NutreStore® is not for parenteral use.
- Laboratory Tests: Routine monitoring of renal and hepatic function is recommended in patients receiving intravenous (IV) parenteral nutrition (IPN), particularly in those with

renal or hepatic impairment. Glutamine is metabolized to glutamate and ammonia, which may increase in patients with hepatic dysfunction.

- Drug Interactions: Formal drug interaction studies have not been conducted.
- Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic potential of L-glutamine. Studies to evaluate the potential for impairment of fertility or the mutagenic potential of L-glutamine have not been conducted.

Use in Specific Populations:

- Pregnancy: L-glutamine is a Pregnancy Category C. Animal reproduction studies have not been conducted with glutamine. It is not known whether glutamine can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Glutamine should be given to a pregnant women only if clearly needed.
- Labor and Delivery: The effect of L-glutamine on labor and delivery is unknown.
- Nursing Mothers: It is not known whether L-glutamine is excreted in human milk. Many drugs are excreted in human milk, therefore caution should be exercised when L-glutamine is administered to a nursing woman.
- Pediatric Use: The safety and effectiveness of L-glutamine in pediatric patients has not been established.
- Geriatric Use: The clinical trial enrolled SBS patients between the ages of 20 and 75 years. Of the 41 subjects evaluated, only 8 were 65 years of age and older. The clinical trial of oral glutamine did not include sufficient numbers of subjects 65 years of age and older to determine if they respond differently than younger subjects. In general, dose selection for an elderly patient should be individualized, because of the greater frequency of decreased hepatic, renal, or cardiac function, as well as concomitant disease(s) in this population.

Adverse Reactions: The safety profile in patients taking oral glutamine with growth hormone was similar to the safety profile in patients taking growth hormone without glutamine. During the initial 4-week treatment period, all patients receiving growth hormone with and without glutamine reported at least one adverse event, whereas 89% of patients receiving growth hormone placebo with glutamine reported at least one adverse event. During weeks 5 through 18, 81% of patients receiving growth hormone with glutamine, 80% of patients receiving growth hormone without glutamine, and 78% of patients receiving growth hormone placebo with glutamine experienced at least one adverse event. There were no deaths in the study. Some of the most frequently reported adverse events included flatulence, abdominal pain, and vomiting.

Efficacy: A randomized, controlled, 3-arm, double-blind, parallel-group clinical study evaluated the efficacy and safety of oral glutamine as a co-therapy with rh-GH in patients with SBS who were dependent on IPN for nutritional support. The primary endpoint was the change in weekly total IPN volume defined as the sum of the volumes of IPN, supplemental lipid emulsion (SLE), and IV hydration fluid. The secondary endpoints were the change in weekly IPN caloric content and the change in the frequency of IPN administration per week. All subjects received a specialized oral diet (SOD) for the duration of the study. Following a two-week equilibration

period, treatment was administered in a double-blind manner. Group A (N=16) received rh-GH for 4 weeks plus oral glutamine placebo for 16 weeks, Group B (N=16) received rh-GH for 4 weeks plus oral glutamine for 16 weeks, and Group C (N=9) received rh-GH placebo for 4 weeks plus oral glutamine for 16 weeks. The efficacy of glutamine was assessed by comparing the co-therapy (rh-GH and oral glutamine) to rh-GH alone. After 4 weeks of treatment with subcutaneous (Sub-Q) rh-GH (0.1mg/kg/day) and oral glutamine (30g/day), subjects with SBS reduced their requirement for IPN volume (-7.7L/week), IPN caloric content (-5,751kcal/week), and weekly frequency of IPN administration (-4.2 days/week). IPN volume requirements were significantly reduced in subjects receiving Sub-Q rh-GH and oral glutamine when compared with IPN volume requirements in subjects receiving either treatment alone.

L-Glutamine Product Comparison: L-glutamine is also FDA approved as an oral powder formulation (Endari™) to reduce the acute complications of SCD in patients 5 years of age and older. Endari™ is supplied in packets containing 5 grams of L-glutamine powder. The recommended dose is 5g in patients who weigh <30kg, 10g in patients who weigh 30 to 65kg, and 15g in patients who weigh >65kg, each given twice daily. The powder is mixed in 8 ounces of cold or room-temperature liquid, such as water, milk, or apple juice, or in 4 to 6 ounces of soft food, such as applesauce or yogurt, and consumed immediately. L-glutamine is also available over-the-counter (OTC) as a dietary supplement.

Product	Cost Per Unit	Cost Per 30 Days*
NutreStore® (L-glutamine 5g powder for oral solution)	**$5.92**	**$1,065.60**
Endari™ (L-glutamine 5g oral powder)	$18.50	$3,330.00

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.
*Costs based on dose of 15g orally twice daily, which is the recommended dose to reduce acute complications of SCD in a patient weighing >65kg.

Recommendations

The College of Pharmacy recommends the prior authorization of Siklos® (hydroxyurea) and NutreStore® (L-glutamine) with the following criteria:

Siklos® (Hydroxyurea Tablets) Approval Criteria:

1. An FDA approved indication of sickle cell anemia; and
2. Member must be 2 years of age or older; and
3. Member must have a history of moderate-to-severe painful crises; and
4. A trial of hydroxyurea capsules or a patient-specific, clinically significant reason why hydroxyurea capsules are not appropriate for the member; and
5. Prescriber must agree to monitor blood counts every 2 weeks throughout therapy; and
6. Prescriber must agree to monitor the patient for the development of secondary malignancies; and
7. Female members must not be pregnant and must have a negative pregnancy test prior to therapy initiation; and

8. Male and female members of reproductive potential must be willing to use effective contraception during and after treatment with Siklos® for at least 6 months after therapy; and
9. Member must not be given live vaccines while on Siklos® therapy; and
10. Initial approvals will be for the duration of 12 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

NutreStore® (L-Glutamine) Approval Criteria [Short Bowel Syndrome (SBS) Diagnosis]:

1. An FDA approved diagnosis of SBS; and
2. NutreStore® must be used in conjunction with a recombinant human growth hormone product that is approved for this indication; and
3. Member must be receiving optimal management of SBS (e.g., specialized oral diet, enteral feedings, parenteral nutrition, fluid and micronutrient supplements); and
4. Approvals will be for up to 16 weeks.

NutreStore® (L-Glutamine) Approval Criteria [Sickle Cell Disease (SCD) Diagnosis]:

1. A diagnosis of SCD; and
2. Member must be 5 years of age or older; and
3. A trial of hydroxyurea or documentation why hydroxyurea is not appropriate for the member; and
4. NutreStore® must be prescribed by, or in consultation with, a hematologist or a specialist with expertise in treatment of SCD (or in consultation with an advanced care practitioner with a supervising physician who is a hematologist or specialist with expertise in treating SCD); and
5. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required.
6. Initial approvals will be for a duration of six months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

The College of Pharmacy recommends updating the prior authorization criteria for Endari™ (L-glutamine) with the changes noted in red:

Endari™ (L-Glutamine) Approval Criteria:

1. An FDA approved diagnosis of sickle cell disease (SCD); and
2. Member must be at least 5 years of age or older; and
3. A trial of hydroxyurea or documentation why hydroxyurea is not appropriate for the member; and
4. Endari™ must be prescribed by, or in consultation with, a hematologist or a specialist with expertise in treatment of SCD (or in consultation with an advanced care practitioner with a supervising physician who is a hematologist or specialist with expertise in treating SCD); and
5. A patient-specific, clinically significant reason why NutreStore® (L-glutamine powder for oral solution) cannot be used must be provided; and

6. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.
7. Initial approvals will be for a duration of six months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Utilization Details of SCD Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
HYDROXYUREA CAP 500MG	569	125	$19,451.48	$1.13	$34.19	91.46%
DROXIA CAP 200MG	18	6	$961.79	$1.39	$53.43	4.52%
DROXIA CAP 400MG	16	6	$791.46	$1.68	$49.47	3.72%
DROXIA CAP 300MG	2	2	$62.50	$1.04	$31.25	0.29%
TOTAL	**605**	**127***	**$21,267.23**	**$1.15**	**$35.15**	**100%**

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

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Appendix G

Fiscal Year 2018 Annual Review of Phenylketonuria Medications and 30-Day Notice to Prior Authorize Palynziq™ (Pegvaliase-pqpz)

Oklahoma Health Care Authority
September 2018

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

Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) deficiency, is a genetic, metabolic disorder that causes phenylalanine (Phe), an essential amino acid found in protein-containing foods, to build up in the blood due to lack of PAH, a hepatic enzyme that breaks down Phe. Elevated blood Phe levels can cause serious health problems including severe brain damage resulting in intellectual disability. Other symptoms include seizures, delayed mental and social skills, behavioral problems including hyperactivity, eczematous rash, lighter pigmentation (Phe plays a role in melanin production), and decreased motor coordination. PKU is estimated to occur in 1 in 13,500 to 19,000 births in the United States; however, it is less common in African-Americans with an estimated incidence of 1 in 50,000.

PKU newborn screening is implemented in hospitals across the United States so treatment can be initiated as early as possible and many symptoms can be prevented with early, continuous, and lifelong treatment. The diagnosis of PKU is based on an elevated serum concentration of Phe. Complete enzyme deficiency results in classic PKU, in which serum Phe concentration exceeds 20mg/dL (1,200µmol/L). Residual enzyme activity causes moderate PKU (Phe concentrations 900 to 1,200µmol/L), mild PKU (Phe concentrations 600 to 900µmol/L), mild hyperphenylalaninemia (HPA; Phe concentrations 360 to 600µmol/L), and benign mild HPA, which may not require treatment (Phe concentrations 120 to 360µmol/L).

PKU treatment guidelines recommend starting dietary treatment with a low-Phe diet within the first week of life. Phe is found in high protein foods such as meat, eggs, dairy, nuts, and legumes. Artificial sweeteners containing aspartame must be avoided as they also contain Phe. Phe-free formula for newborns, medical foods including Phe-free protein substitutes, and low-protein foods such as vegetables, fruits, and some grains are recommended. The National Institutes of Health (NIH) Consensus Development Conference on PKU recommends maintaining a Phe blood concentration of 2 to 6mg/dL (120 to 360µmol/L) for affected children through 12 years of age and 2 to 15mg/dL (120 to 900µmol/L) after 12 years of age; however, the American College of Medical Genetics and Genomics (ACMG) recommends maintaining a Phe blood concentration of 2 to 6mg/dL (120 to 360µmol/L) in patients of all ages throughout life.

Kuvan® (sapropterin) is a PAH activator indicated to reduce blood Phe levels in patients with HPA due to tetrahydrobiopterin- (BH4-) responsive PKU in conjunction with a Phe-restricted diet. Sapropterin was approved by the U.S. Food and Drug Administration (FDA) in December

2007. BH4 is a cofactor required for PAH activity. This pathway accounts for most of Phe catabolism and is responsible for the disposal of approximately 75% of dietary Phe, with the remainder used for protein synthesis. Treatment guidelines recommend that all PKU diagnosed patients, except for those with two null mutations in *trans*, be offered a trial of sapropterin to determine if the therapy is efficacious in lowering Phe blood levels. In clinical trials, approximately 20 to 56% of PKU patients responded to treatment with sapropterin.

In May 2018, the FDA approved Palynziq™ (pegvaliase-pqpz) for adults with PKU whose uncontrolled blood Phe concentration is >600µmol/L on current therapy. Palynziq™, a PEGylated recombinant Phe ammonia lyase (PAL) enzyme, is the first FDA approved enzyme substitution therapy to target the underlying cause of PKU by helping the body break down Phe. Palynziq™ has a boxed warning for the risk of anaphylaxis and is only available through the Palynziq™ Risk Evaluation and Mitigation Strategy (REMS) program.

Current Prior Authorization Criteria

Kuvan® (Sapropterin) Approval Criteria:

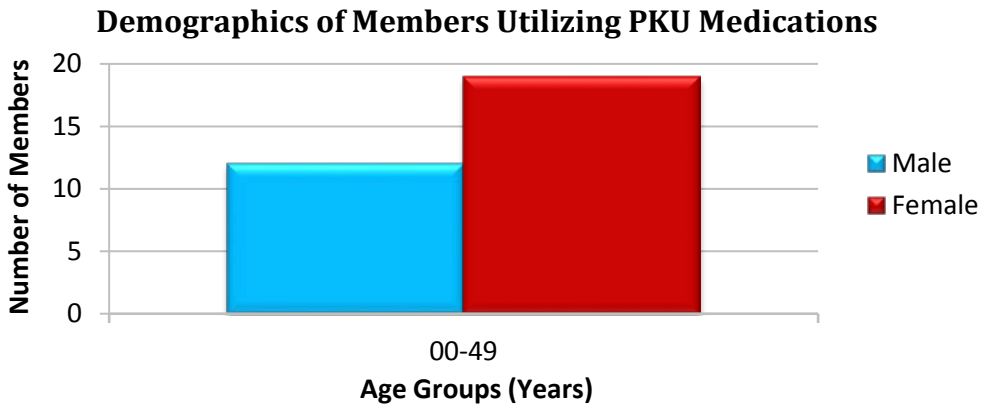
1. An FDA approved diagnosis of phenylketonuria; and
2. Documentation of active management with a phenylalanine restricted diet; and
3. Member must not have two null mutations in *trans*; and
4. Initial approvals will be for the duration of 30 days. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
    a. If the member was initiated at 10mg/kg/day dose, then a subsequent trial of 20mg/kg/day for a duration of 30 days can be approved. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
    b. If the member was initiated at 20mg/kg/day dose, then no additional approvals will be granted after a trial period of 30 days if the member did not respond to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
5. Subsequent approvals will be for the duration of one year.

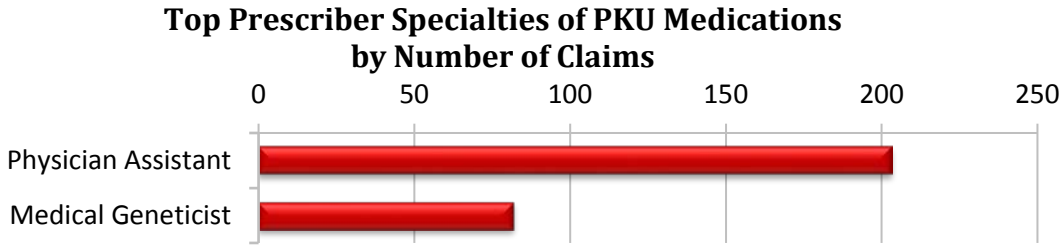
Utilization of PKU Medications: Fiscal Year 2018

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	27	287	$1,872,591.33	$6,524.71	$217.64	43,680	8,604
2018	31	285	$1,981,912.60	$6,954.08	$232.54	44,955	8,523
% Change	**14.80%**	**-0.70%**	**5.80%**	**6.60%**	**6.80%**	**2.90%**	**-0.90%**
Change	**4**	**-2**	**$109,321.27**	**$429.37**	**$14.90**	**1,275**	**-81**

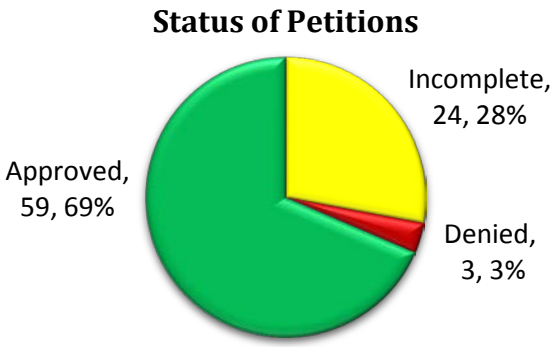
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.





Prior Authorization of PKU Medications

There were 86 prior authorization requests submitted for PKU medications during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.



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

Anticipated Patent Expiration(s):

- Kuvan® tablets (sapropterin): May 2026
- Kuvan® powder (sapropterin): November 2032

New FDA Approval(s):

- **May 2018:** The FDA approved Palynziq™ (pegvaliase-pqpz), a Phe-metabolizing enzyme, indicated to reduce blood Phe concentrations in adult patients with PKU who have uncontrolled blood Phe concentrations >600µmol/L on existing management.

Pipeline:

- **April 2018:** BioMarin announced that a gene therapy product will be the company's next Investigational New Drug (IND) candidate for the treatment of PKU in 2019. In preclinical models, BioMarin's PKU gene therapy product candidate (BMN 307) demonstrated sustained, normalized Phe levels without hypophenylalanemia in an ongoing study and out to 53 weeks at the last observation. The gene therapy candidate is an adeno-associated virus (AAV) vector containing the DNA sequence that codes for the PAH enzyme that is deficient in people with PKU.
- **August 2018:** Synlogic, Inc., a clinical stage company applying synthetic biology to probiotics to develop novel, living medicines, announced the publication of data from preclinical studies of SYNB1618, the company's Synthetic Biotic development program targeting PKU, in *Nature Biotechnology*. The data demonstrate that oral administration of SYNB1618 significantly reduced blood Phe levels in mouse models of PKU and resulted in dose-dependent pharmacodynamics in healthy non-human primates. Synlogic's Synthetic Biotic platform leverages the tools and principles of synthetic biology to engineer a strain of probiotic bacteria (*Escherichia coli* Nissle) to perform or deliver specific functions lost or damaged due to disease. SYNB1618 is designed to metabolize Phe and was engineered by inserting specific genetic circuits including a bacterial gene that encodes PAL. PAL is an enzyme that breaks down Phe to generate *trans*-cinnamic acid (TCA), which is converted to hippuric acid (HA) in the liver and is excreted in the urine. Plasma TCA and urinary HA levels can serve as biomarkers of PAL, and therefore, of SYNB1618 activity *in vivo*. Synlogic is currently evaluating SYNB1618 in a Phase 1/2a clinical trial for the management of PKU and expects to report interim data from healthy volunteers in 2018 and full data, including cohorts of patients with PKU, in 2019.

Palynziq™ (Pegvaliase-pqpz) Product Summary[11]

Indication(s): Palynziq™ (pegvaliase-pqpz) is a Phe-metabolizing enzyme indicated to reduce blood Phe concentrations in adult patients with PKU who have uncontrolled blood Phe concentrations >600µmol/L on existing management.

Dosing:

- Palynziq™ (pegvaliase-pqpz) is available as single-dose prefilled syringes in the following strengths: 2.5mg/0.5mL, 10mg/0.5mL, and 20mg/mL.
- Baseline blood Phe concentration should be obtained before initiating treatment.
- The recommended initial dosage is 2.5mg subcutaneously (sub-Q) once weekly for 4 weeks. The dosage should then be titrated in a step-wise manner over at least 5 weeks based on tolerability to achieve a dosage of 20mg sub-Q once daily. Please see full prescribing information for the recommended titration regimen.
- The patient should be assessed for tolerability, blood Phe concentration, and dietary protein and Phe intake throughout treatment.
- Consideration should be given to increasing the dosage to a maximum of 40mg sub-Q once daily in patients who have been on 20mg once daily continuously for at least 24

weeks and who have not achieved either a 20% reduction in blood Phe concentration from pre-treatment baseline or a blood Phe concentration ≤600µmol/L.

- Palynziq™ should be discontinued in patients who have not achieved at least a 20% reduction in blood Phe concentration from pre-treatment baseline or a blood Phe concentration ≤600µmol/L after 16 weeks of continuous treatment with the maximum dosage of 40mg once daily.
- The dosage should be reduced and/or dietary protein and Phe intake modified, as needed, to maintain blood Phe concentrations within a clinically acceptable range and above 30µmol/L.
- Blood Phe concentrations should be obtained every 4 weeks until a maintenance dosage is established. After a maintenance dosage is established, blood Phe concentrations should be periodically monitored.
- Patients should be counseled to monitor dietary protein and Phe intake, and adjust as directed by their healthcare provider.
- Premedication should be considered for hypersensitivity reactions.
- Injection sites should be rotated. If more than one injection is needed for a single dose, the injection sites should be at least 2 inches away from each other.

Mechanism of Action: Pegvaliase-pqpz is a PEGylated PAL enzyme that converts Phe to ammonia and TCA. Pegvaliase-pqpz substitutes for deficient PAH enzyme activity in patients with PKU and reduces blood Phe concentrations.

Boxed Warning: Risk of Anaphylaxis

- Anaphylaxis has been reported after administration of pegvaliase-pqpz and may occur at any time during treatment.
- The initial dose of pegvaliase-pqpz should be administered under the supervision of a healthcare provider equipped to manage anaphylaxis, and patients should be closely observed for at least 60 minutes following injection.
- Pegvaliase-pqpz is available only through a restricted distribution program called the Palynziq™ REMS Program.

Contraindication(s): None

Safety:

- Hypersensitivity Reactions Other than Anaphylaxis: Management of hypersensitivity reactions other than anaphylaxis should be based on the severity of the reaction, recurrence, and clinical judgement. Management may include dosage adjustment, temporary drug interruption, or treatment with antihistamines, antipyretics, and/or corticosteroids.

Use in Specific Populations:

- Pregnancy: Based on findings in studies of pregnant animals without PKU who were treated with pegvaliase-pqpz, pegvaliase-pqpz may cause fetal harm when administered to a pregnant woman. Limited available data with pegvaliase-pqpz use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental

outcomes. There are risks to the fetus associated with poorly controlled Phe concentrations in women with PKU during pregnancy including increased risk for miscarriage, major birth defects (e.g., microcephaly, major cardiac malformations), intrauterine fetal growth retardation, and future intellectual disability with low IQ. Phe concentrations should be closely monitored in women with PKU during pregnancy. Pregnant women should be advised of the potential risks to the fetus.

- Lactation: There are no data on the presence of pegvaliase-pqpz in human milk, the effects on the breastfed infant, or the effects on milk production. A pre-/post-natal study in rats showed that pegvaliase-pqpz is present in rat milk and that administration of pegvaliase-pqpz during lactation decreased pup weight and survival. However, systemic absorption of pegvaliase-pqpz was not detected in the rat pups. Pegvaliase-pqpz may cause low Phe concentrations in human milk. The developmental and health benefits of breastfeeding should be considered along with the clinical need for pegvaliase-pqpz treatment.
- Pediatric Use: The safety and effectiveness of pegvaliase-pqpz in pediatric patients have not been established.
- Geriatric Use: Clinical studies of pegvaliase-pqpz did not include patients 65 years of age and older.

Drug Interactions:

- Effect of Pegvaliase-pqpz on Other PEGylated Products: Patients should be monitored for hypersensitivity reactions, including anaphylaxis, when undergoing concomitant treatment with other PEGylated products.

Adverse Reactions: The most common adverse reactions (at least 20% in either treatment phase) experienced during pegvaliase-pqpz trials included the following: injection site reactions, arthralgia, hypersensitivity reactions, headache, generalized skin reactions lasting at least 14 days, pruritus, nausea, abdominal pain, oropharyngeal pain, vomiting, cough, diarrhea, and fatigue.

Efficacy: The safety and efficacy of pegvaliase-pqpz were studied in two clinical studies in adult patients with PKU with blood Phe concentrations >600µmol/L on existing management. The first study was a randomized, open-label study where patients were treated with a target dose of 20mg or 40mg pegvaliase-pqpz once daily. The second study was a placebo-controlled, randomized withdrawal trial in patients who were previously treated with pegvaliase-pqpz.

Study 301: Induction/Titration/Maintenance Treatment:

- Study 301 was an open-label, randomized, multi-center study of adults with PKU to assess the safety and tolerability of self-administered pegvaliase-pqpz in an induction/ titration/maintenance regimen with a target maintenance dose of 20mg sub-Q once daily or 40mg sub-Q once daily.
- At pegvaliase-pqpz treatment initiation, 253 patients demonstrated inadequate blood Phe control (blood Phe concentration >600µmol/L) on existing management, and 8 patients had blood Phe concentrations ≤600µmol/L. Existing management options included prior or current restriction of dietary Phe and protein intake and/or prior

treatment with sapropterin dihydrochloride. Patients previously treated with sapropterin dihydrochloride were required to discontinue use at least 14 days prior to the first dose.

- The 261 enrolled patients were 16 to 55 years of age (mean: 29 years) and had a baseline mean (range) blood Phe of 1,233µmol/L (285 to 2,330µmol/L). A total of 149 out of 261 (57%) patients were taking medical food at baseline and 41 out of 261 patients (16%) were on a protein-restricted diet at baseline (defined as receiving >75% of total protein intake from medical food). Patients were randomized (1:1) to one of two target maintenance dosage arms: 20mg once daily or 40mg once daily. Patients were titrated to reach their randomized target dosage of 20mg once daily or 40mg once daily. The duration of titration varied among patients and was based on patient tolerability.
- Of the 261 enrolled patients, 195 (75%) patients reached their randomized maintenance dosage (103 in the 20mg once daily arm, 92 in the 40mg once daily arm). Among the patients who reached their randomized maintenance dosage, patients in the 20mg once daily randomized arm reached their maintenance dosage at a median time of 10 weeks (range: 9 to 29 weeks), and patients in the 40mg once daily arm reached their maintenance dosage at a median time of 11 weeks (range: 10 to 33 weeks).
- Of the 261 patients who enrolled in Study 301, 54 (21%) patients discontinued treatment during the study, 4 patients completed the study and did not continue to Study 302, 152 patients continued to the eligibility period of Study 302, and 51 patients continued directly from Study 301 into the long-term treatment period of Study 302.

<u>Study 302: Efficacy Assessment:</u>

- A total of 164 adult patients with PKU who were previously treated with pegvaliase-pqpz (152 patients from Study 301 and 12 patients from other pegvaliase-pqpz trials) enrolled in Study 302 and continued treatment with pegvaliase-pqpz in Study 302 for up to 13 weeks to assess eligibility for randomized withdrawal period.
- Following this period of up to 13 weeks of additional pegvaliase-pqpz treatment in Study 302, eligibility for entry into the efficacy assessment period (randomized withdrawal period) was determined by whether a patient achieved at least a 20% reduction in blood Phe concentration from pre-treatment baseline (when in previous studies). A total of 86 out of 164 patients (52%) met this response target and continued into the randomized withdrawal period.
- In the double-blind, placebo-controlled, randomized withdrawal period, patients were randomized in a 2:1 ratio to either continue their maintenance pegvaliase-pqpz dosage or to receive matching placebo for a total of 8 weeks.
- At Study 302 randomized withdrawal week 8, pegvaliase-pqpz-treated patients (20mg once daily or 40mg once daily) maintained their blood Phe concentrations as compared to baseline, whereas patients randomized to matching placebo returned to their pretreatment baseline blood Phe concentrations.

<u>Study 301 and 302 Continuous Treatment:</u>

- Of 118 patients from Study 301 with a pre-treatment baseline blood Phe concentration >600µmol/L who were randomized to and received at least one dose of 20mg once daily

pegvaliase-pqpz, 108 patients, 98 patients, and 51 patients were treated for at least 24 weeks, 48 weeks, and 96 weeks, respectively.

- Of the 118 patients, 53 patients reached their first response (at least a 20% reduction in blood Phe concentration from pre-treatment baseline or a blood Phe concentration ≤600µmol/L) by 4 weeks of treatment with 20mg once daily, and 28 patients reached their first response between weeks 4 and 24 with 20mg once daily.
- Of the 118 patients, 25 patients escalated their dosage from 20mg once daily to 40mg once daily before reaching a first response. Of those 25 patients, 8 patients reached their first response by 4 weeks of treatment with 40mg once daily, and 6 patients reached their first response between weeks 4 and 16 with 40mg once daily.

Cost:

Medication	Cost Per Unit	Cost Per 28 Days	Cost Per Year
Palynziq™ (pegvaliase-pqpz) 2.5mg/0.5mL	**$488.00**	**$1,952.00***	**$25,376.00***
Palynziq™ (pegvaliase-pqpz) 10mg/0.5mL	**$488.00**	**$13,664.00***	**$177,632.00***
Palynziq™ (pegvaliase-pqpz) 20mg/mL	**$488.00**	**$13,664.00-$27,328.00***	**$177,632.00-$355,264.00***
Kuvan® (sapropterin) all strengths/formulations	$36.90-$184.50	$15,498.00¥	$201,474.00¥

Unit = single-dose pre-filled syringe, tablet, or single-dose unit of powder for oral solution
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.
*The FDA approved starting dose is 2.5mg sub-Q once weekly for 4 weeks. Dosage should be titrated in a step-wise manner, based on tolerability, over at least 5 weeks, to achieve a dosage of 20mg once daily. Once the 20mg daily dose is maintained over at least 24 weeks, the dose may be increased to a maximum of 40mg daily in patients who have not achieved either a 20% reduction in blood Phe concentration from pre-treatment baseline or a blood Phe concentration ≤600 µmol/L.
¥Kuvan® costs based on a maximum dose of 20mg/kg once daily for a 75kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Palynziq™ (pegvaliase-pqpz) and updating the current Kuvan® (sapropterin) prior authorization criteria. The following criteria would apply:

Palynziq™ (Pegvaliase-pqpz) Approval Criteria:

1. An FDA approved diagnosis to reduce blood phenylalanine concentrations in patients with phenylketonuria who have uncontrolled blood phenylalanine concentrations >600µmol/L on existing management; and
2. Documentation of active management with a phenylalanine restricted diet; and
3. Phenylalanine concentration must be documented on the prior authorization request and must be drawn within the last 30 days; and
4. Documentation the member's average blood phenylalanine concentration over the last 6 months is >600µmol/L on existing management; and
5. Concomitant use with Kuvan® (sapropterin) will not be approved; and

6. Initial approvals will be for the duration of 33 weeks to allow for initial titration and for 24 weeks of maintenance treatment with 20mg once daily dosing. Patients should then be assessed for a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600µmol/L.
    a. If member has not achieved a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600µmol/L, approvals may be granted for the 40mg once daily dosing for a duration of 16 weeks; or
    b. If member has achieved a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600µmol/L, subsequent approvals will be for the duration of one year; and
7. Members who do not achieve at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration ≤600µmol/L after 16 weeks of continuous treatment with the maximum dosage of 40mg once daily will not be approved for subsequent approvals; and
8. Subsequent approvals will be for the duration of one year.
9. Reauthorization will require the following:
    a. Documentation of active management with a phenylalanine restricted diet; and
    b. Verification from prescriber of continued response to therapy.

Kuvan® (Sapropterin) Approval Criteria:

1. An FDA approved diagnosis of phenylketonuria; and
2. Documentation of active management with a phenylalanine restricted diet; and
3. Member must not have two null mutations in *trans*; and
4. Phenylalanine concentration must be documented on the prior authorization request and must be drawn within the last 30 days; and
5. Initial approvals will be for the duration of 30 days. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
    a. If the member was initiated at 10mg/kg/day dose, then a subsequent trial of 20mg/kg/day for a duration of 30 days can be approved. After which time, the prescriber must verify that the member responded to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
    b. If the member was initiated at 20mg/kg/day dose, then no additional approvals will be granted after a trial period of 30 days if the member did not respond to treatment as defined by laboratory documentation of ≥30% decrease in blood phenylalanine levels from baseline.
6. Subsequent approvals will be for the duration of one year.
7. Reauthorization will require the following:
    a. Documentation of active management with a phenylalanine restricted diet; and
    b. Verification from prescriber of continued response to therapy.

Utilization Details of PKU Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
SAPROPTERIN PRODUCTS						
KUVAN TAB 100MG	142	18	$1,268,099.10	$303.88	$8,930.28	63.98%
KUVAN POW 100MG	78	13	$218,087.80	$93.20	$2,796.00	11.00%
KUVAN POW 500MG	65	9	$495,725.70	$246.63	$7,626.55	25.01%
TOTAL	**285**	**31***	**$1,981,912.60**	**$232.54**	**$6,954.08**	**100%**

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

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Appendix H

Fiscal Year 2018 Annual Review of Synagis® (Palivizumab)

Oklahoma Health Care Authority
September 2018

Current Prior Authorization Criteria

A prior authorization is required for all members who receive palivizumab in an outpatient setting. Palivizumab is approved for members who meet the established prior authorization criteria, which is based on a modified version of the American Academy of Pediatrics (AAP) 2014 guidelines for palivizumab prophylaxis.

Synagis® (Palivizumab) Approval Criteria:

A. Member Selection:
   1. Infants less than 12 months of age at the start of respiratory syncytial virus (RSV) season:
      a. Born before 29 weeks, 0 days gestation; or
      b. Born before 32 weeks, 0 days gestation and develop chronic lung disease (CLD) of prematurity (require >21% oxygen supplementation for at least 28 days after birth); or
      c. Have hemodynamically significant congenital heart disease [acyanotic heart disease and receiving medication to control congestive heart failure (CHF) and will require surgical procedures, or have moderate-to-severe pulmonary hypertension]; or
      d. May be considered for:
         i. Infants with neuromuscular disease or a congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough; or
         ii. Infants who undergo cardiac transplantation during RSV season; or
         iii. Infants who are profoundly immunocompromised during RSV season; or
         iv. Infants with cystic fibrosis with clinical evidence of CLD and/or are nutritionally compromised
   2. Infants 12 to 24 months of age at the start of RSV season:
      a. Born before 32 weeks, 0 days gestation and have CLD of prematurity (required at least 28 days of oxygen after birth) and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6 months before the start of the RSV season; and

B. Length of Treatment: Palivizumab is approved for use only during RSV season. Approval dates will be November 1st through March 31st.

C. Units Authorized: The maximum duration of therapy is five (5) doses, with a dose to be administered no more often than every 30 days. Members given doses more frequently than every 30 days will not be authorized for additional doses. Doses administered prior to the member's discharge from a hospital will be counted as one of the approved total.

D. Dose-Pooling: To avoid unnecessary risk to the patient, multiple patients are not to be treated from a single vial. Failure to follow this recommendation will result in referral of the provider to the Quality Assurance Committee of the Oklahoma Health Care Authority.

Utilization of Synagis® (Palivizumab): Fiscal Year 2018

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	281	1,223	$2,785,035.85	$2,277.22	$75.92	1,046	36,686
2018	265	1,157	$2,737,006.44	$2,365.61	$78.88	1,000	34,698
% Change	**-5.70%**	**-5.40%**	**-1.70%**	**3.90%**	**3.90%**	**-4.40%**	**-5.40%**
Change	**-16**	**-66**	**-$48,029.41**	**$88.39**	**$2.96**	**-46**	**-1,988**

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

Pharmacy Claim Details for Respiratory Syncytial Virus (RSV) Season 2017-2018

Product Utilized	Total Claims	Total Members	Total Cost	Claims/ Member	Cost/ Day	Cost/ Claim
SYNAGIS INJ 100MG/ML	790	252	$2,208,929.49	3.13	$93.24	$2,796.11
SYNAGIS INJ 50MG/0.5ML	367	163	$528,076.95	2.25	$47.98	$1,438.90
Total	**1,157**	**265***	**$2,737,006.44**	**4.37**	**$78.88**	**$2,365.61**

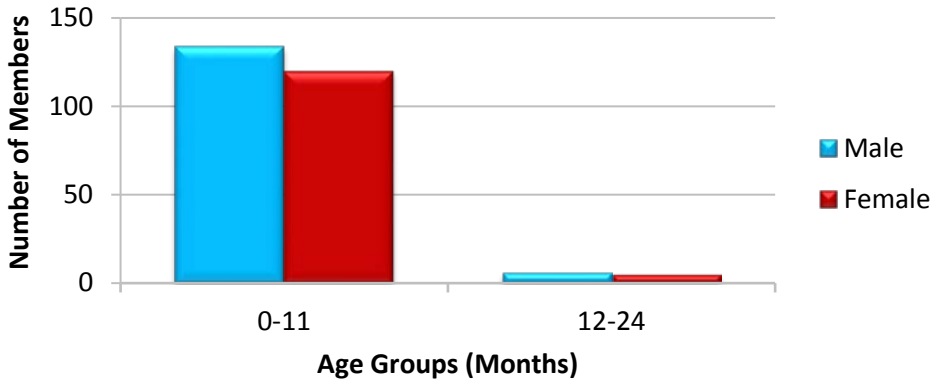
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Cost per Vial

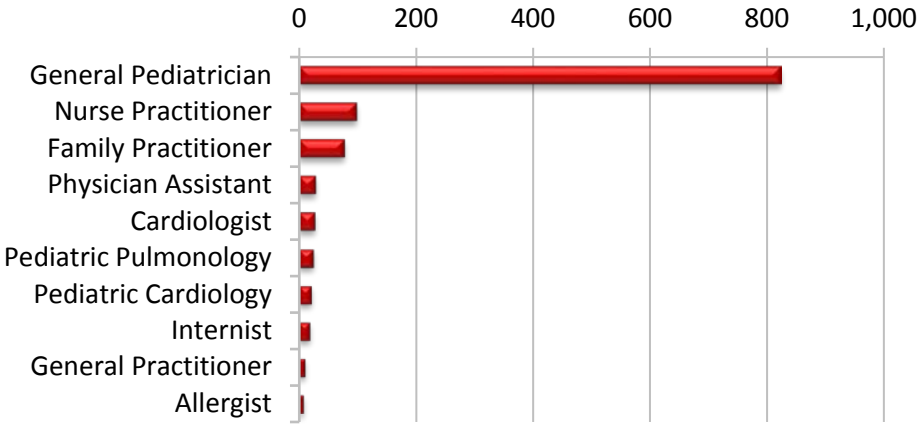
Vial Size	Cost Per Vial
Synagis® (palivizumab) 100mg/mL vial	$2,764.02
Synagis® (palivizumab) 50mg/0.5mL vial	$1,463.28

Costs do not reflect rebated prices or net costs.
Costs based on state maximum allowable cost (SMAC).

Demographics of Members Utilizing Synagis® (Palivizumab)



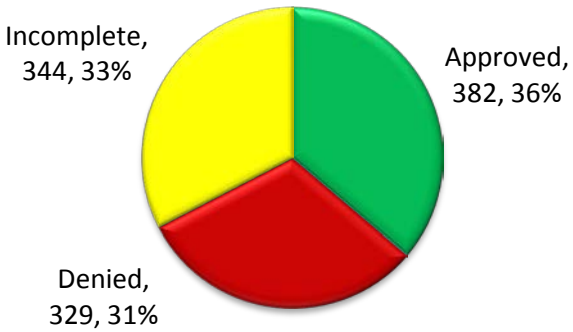
Top Prescriber Specialties of Synagis® (Palivizumab) by Number of Claims



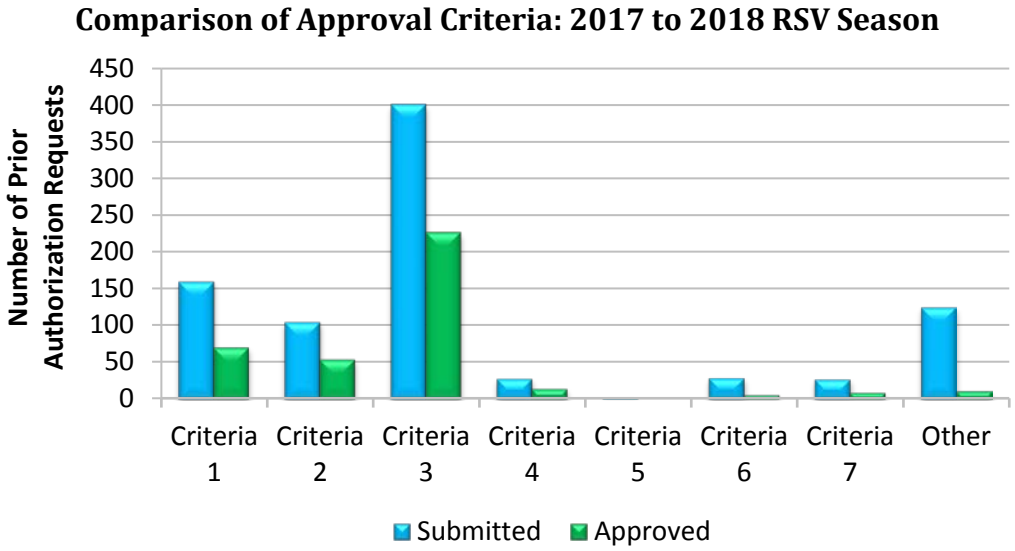
Prior Authorization of Synagis® (Palivizumab)

There were 1,055 palivizumab prior authorization requests submitted for 482 unique members during fiscal year 2018. This is a decrease in both submitted petitions and number of members requesting palivizumab compared to fiscal year 2017 when there were 1,062 palivizumab prior authorization requests submitted for 521 unique members. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



The following graph shows the number of submissions and approvals for each prior authorization criteria. The graph is followed by a numbered list in which the list number corresponds to the criteria number in the graph. The most commonly requested and approved criteria selection during the 2017 to 2018 RSV season was criteria number three: infants born before 29 weeks, 0 days gestation. Infants born before 32 weeks, 0 days gestation and who had CLD of prematurity was also a commonly requested and approved criteria selection (criteria number one).

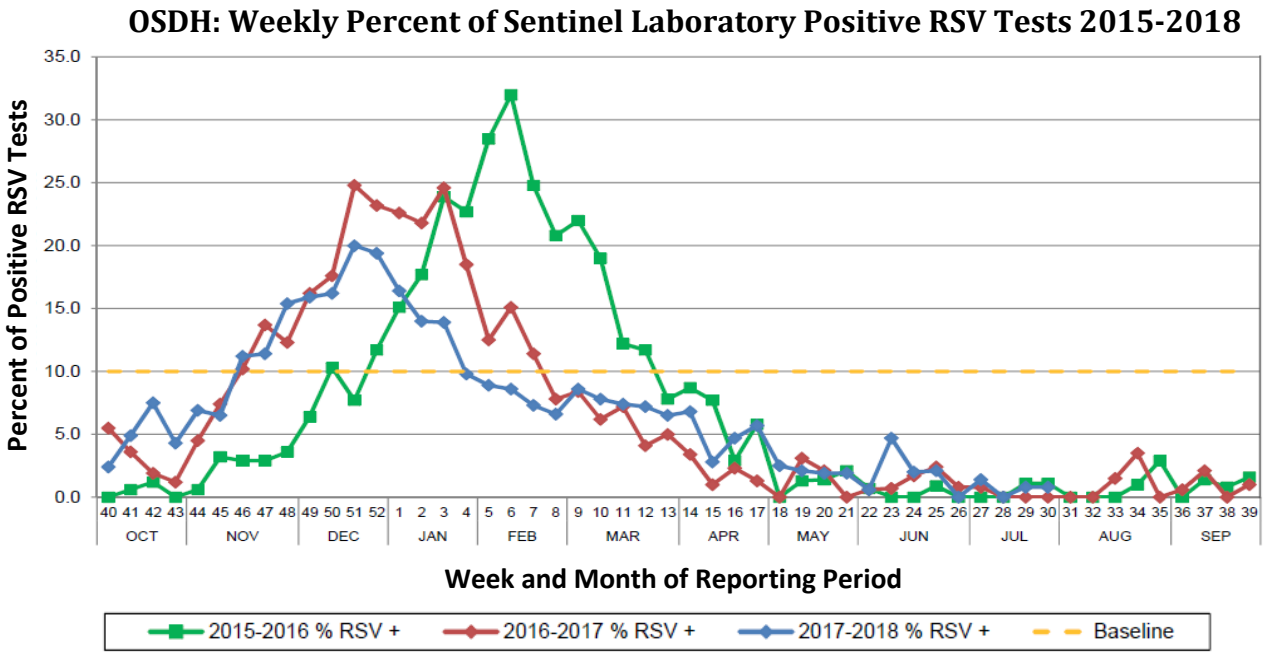


Criteria List:

1. Infants 0 to 24 months of age at the start of RSV season born before 32 weeks, 0 days gestation and have CLD of prematurity.
2. Infants who have hemodynamically significant congenital heart disease and will require surgical procedures, or have moderate-to-severe pulmonary hypertension.
3. Infants born before 29 weeks, 0 days gestation.
4. Infants with neuromuscular disease or a congenital anomaly that impairs the ability to clear secretions from the upper airway because of ineffective cough.
5. Infants who undergo cardiac transplantation during RSV season.
6. Infants who are profoundly immunocompromised during RSV season.
7. Infants with cystic fibrosis with clinical evidence of CLD and/or are nutritionally compromised.

Season Comparison[1,2,3]

The following chart contains the weekly percent of laboratory positive RSV tests in Oklahoma as reported by the Oklahoma State Department of Health (OSDH) Viral Respiratory Illness Sentinel Surveillance System. The chart is included to compare RSV seasons since 2015. RSV is determined to be in season once the percent of positive tests is >10% for two consecutive weeks. Similarly, the season is determined to be at an end when the percent of positive tests <10% for two consecutive weeks. RSV seasons appear to be similar with a peak typically in December or January and a season end by late March. Palivizumab prior authorization approvals are initiated with a start date of November 1st and continue to March 31st; this approval window corresponds to the following state monitoring graph as well as with state data reported by the Centers for Disease Control and Prevention (CDC). For the 2017 to 2018 RSV season for Oklahoma, the CDC determined the onset week by percentage of positive antigen detection tests was the week of December 2nd with a season offset the week of January 27th. There was a small resurgence of antigen positive tests in April 2018 following two months of very low percentages according to the CDC data.

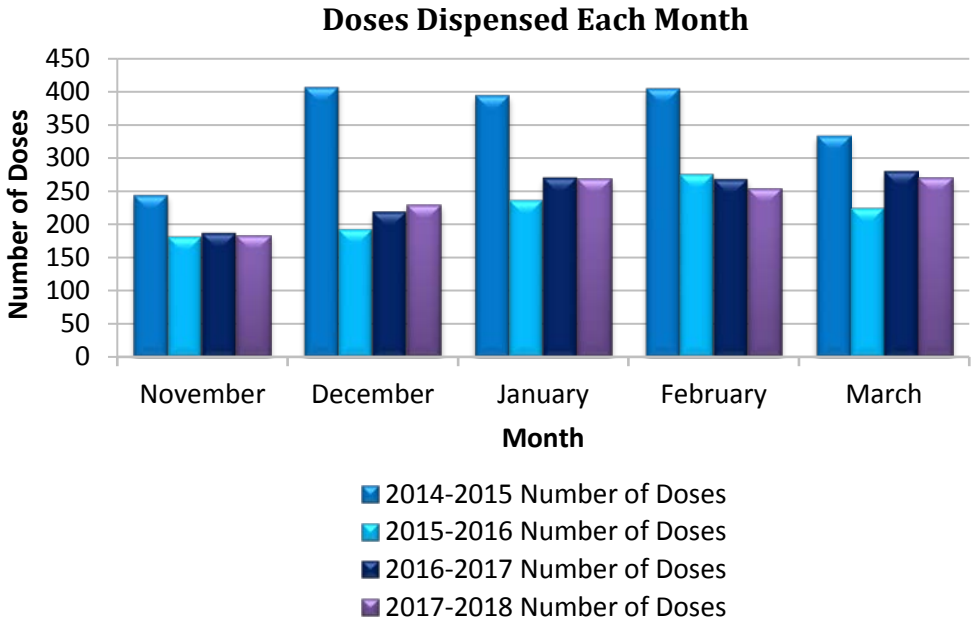


The CDC reported seasonality by using RSV polymerase chain reaction (PCR) laboratory detections. Laboratories are shifting away from antigen-based RSV testing, and since 2014 the majority of RSV detections among reporting laboratories were determined by PCR. If the Oklahoma season was based on percentage of positive PCR tests and a threshold of 10%, similar to antigen testing, season onset and offset would have occurred on the exact dates of the season as determined by positive antigen tests.

RSV season onset, when evaluated by PCR detections and a new statistical method determined by the CDC, is defined as the second of two consecutive weeks when the slope, or normalized 5-week moving average of RSV detections between subsequent weeks exceeded 10. Season offset was determined as the last week when the standardized detections exceeded the standardized detections at onset. These changes were done to reflect the adoption of a statistical method rather than a threshold or percent positive which can be influenced by volume of tests performed. For Oklahoma's region (Region 6 – Arkansas, Louisiana, New Mexico, Oklahoma, and Texas) using the CDC's statistical analysis method, the season would have had an onset the week of October 1st and an offset the week of May 6th for the 2016 to 2017 season. This is significantly longer than when determined by antigen-based RSV testing, which had an onset the week of December 3rd and an offset the week of March 11th for the 2016 to 2017 season. The CDC cautions that the statistical detection method used captures a high proportion of RSV detection for retrospectively determining seasonality but cannot be used to determine seasonal onset and offset in real time, and can only be used after the season is at an end. The CDC advises that surveillance data collected by state and local health departments might be more accurate to describe local RSV circulation trends. RSV PCR testing is not currently reported by the OSDH to evaluate local trends specific to the State of Oklahoma. The Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection released by the AAP in 2014 states the following with regard to RSV seasonality:

"During the 6 RSV seasons from July 2007 to January 2013, the median duration of the RSV season ranged from 13 to 23 weeks, with median peak activity from mid-December to early February, with the exception of Florida and Alaska. Within the 10 Health and Human Services Regions, in the few regions when the RSV season began in October, the season ended in March or early April. In regions where the RSV season began in November or December, the season ended by April or early May. Because 5 monthly doses of palivizumab at 15mg/kg per dose will provide more than 6 months of serum palivizumab concentrations above the desired serum concentration for most infants, administration of more than 5 monthly doses is not recommended within the continental United States."[3]

The following bar graph shows the number of palivizumab doses paid for by SoonerCare for each month during the last four seasons. In 2015, SoonerCare adopted the updated guidance for palivizumab prophylaxis released by the AAP. The guidance, which was released in 2014, urged more limited use than previously recommended in children born after 29 weeks gestation or those in the second year of life. Many hospitals across the state updated their protocols at that time resulting in fewer doses dispensed in the 2014 season as well as in the 2015 season when SoonerCare adopted the updated guidance.



Market News and Updates[4,5,6]

Pipeline News:

- **December 2017:** Novavax, Inc. announced it will continue the Phase 3 trial of its RSV F recombinant nanoparticle vaccine (RSV F Vaccine) intended for infants via maternal immunization at 28 to 36 weeks gestation, after an informational analysis was completed. The vaccine has been granted Fast Track designation by the U.S. Food and Drug Administration (FDA). An interim analysis is expected in mid-2018 and the primary endpoint analysis is expected in early 2019.

- **March 2018:** Bavarian Nordic announced positive results from its Phase 2 study of MVA-BN RSV, a universal RSV vaccine, in 421 adult patients. Nasal swabs demonstrated an approximately 1.5 fold increase in IgA antibodies over baseline levels. Investigators believe this observation suggests that the vaccine boosts memory responses against RSV; previous studies have shown that IgA antibodies in mucosa is associated with immune protection in subjects who do not develop RSV.
- **May 2018:** Pfizer announced it will conduct Phase 1/2 placebo-controlled trials of an RSV vaccine candidate in adult subjects. Pfizer also hopes to study the vaccine in pregnant women who would be injected during pregnancy to protect their infants.

Recent Publication(s):

- A compilation of recent palivizumab and RSV publications will be presented at the Drug Utilization Review (DUR) meeting.

Recommendations

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

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[1] Oklahoma State Department of Health. Weekly Percent of Sentinel Laboratory Positive RSV Tests, Oklahoma Viral Respiratory Illness Sentinel Surveillance System, 2015-2018: Week ending July 28, 2018. Available online at: https://www.ok.gov/health2/documents/RSV2011-12andPast2Seasons-10-06-2012.pdf. Last revised 08/03/2018. Last accessed 08/06/2018.

[2] Centers for Disease Control and Prevention (CDC). RSV State Trends. Available online at: https://www.cdc.gov/surveillance/nrevss/rsv/state.html#OK. Last accessed 08/06/2018.

[3] Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. RSV Policy Statement — Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. *Pediatrics* 2014; 134(2):415–420.

[4] Novavax, Inc. Novavax Continues Phase 3 Trial of the RSV F Vaccine for Infants via Maternal Immunization and Provides Update on Phase 1/2 Trial of the NanoFlu™ Vaccine. *Globe Newswire.* Available online at: https://ir.novavax.com/news-releases/news-release-details/novavax-continues-phase-3-trial-rsv-f-vaccine-infants-maternal. Issued 12/18/2017. Last accessed 08/06/2018.

[5] Bavarian Nordic. Bavarian Nordic Announces Additional Positive Data from a Phase 2 Study of its Universal RSV Vaccine. Available online at: http://www.bavarian-nordic.com/investor/news/news.aspx?news=5390. Issued 03/06/2018. Last accessed 08/06/2018.

[6] Sagonowsky E. Pfizer jumps on the scene in RSV, pushing vaccine candidate into human testing. *FiercePharma*. Available online at: https://www.fiercepharma.com/vaccines/pfizer-pushes-rsv-vaccine-into-human-testing. Issued 03/23/2018. Last accessed 08/06/2018.

Appendix I

Fiscal Year 2018 Annual Review of Fabry Disease Medications and 30-Day Notice to Prior Authorize Galafold™ (Migalastat)

Oklahoma Health Care Authority
September 2018

Introduction[1,2]

Fabry disease, also called Anderson-Fabry disease, is the second most prevalent lysosomal storage disorder after Gaucher disease. It is an X-linked inborn error of the glycosphingolipid metabolic pathway, caused by mutations in the galactosidase alpha (*GLA*) gene. The metabolic defect in Fabry disease causes a deficiency of alpha-galactosidase A (alpha-Gal A), which catalyzes the hydrolytic cleavage of the terminal galactose from globotriaosyl-ceramide (GL-3). This results in accumulation of GL-3 within lysosomes throughout the body, particularly cells lining blood vessels in the skin and cells in the kidneys, heart, and nervous system. This leads to variable manifestations of the disease. *GLA* gene mutations that result in an absence of alpha-Gal A activity lead to the classic, severe form of Fabry disease. Mutations that decrease but do not eliminate the enzyme's activity usually cause the milder, late-onset forms of Fabry disease that affect only the heart or kidneys. Cardiac manifestations occur in more than 80% of patients with Fabry disease, and transient ischemic attacks and strokes occur in approximately 25% of patients. Additionally, renal manifestations occur in at least 50% of male patients and about 20% of female patients.

Mutations associated with classic manifestations of Fabry disease are present in approximately 1:22,000 to 1:40,000 males, and mutations associated with atypical or late-onset presentations are present in approximately 1:1,000 to 1:3,000 males and 1:6,000 to 1:40,000 females. The prevalence of Fabry disease is probably underestimated given incomplete ascertainment due, in part, to the nonspecific manifestations of the disease.

In the setting of clearly established family history and classic phenotype, the diagnosis can usually be confirmed in males by low alpha-Gal A activity in leukocytes or plasma. Mutation analysis of the alpha-Gal A gene is required to make the diagnosis in female carriers unless the woman is an obligate heterozygote (i.e., the father is known to have Fabry), and in patients with atypical presentations or who have residual alpha-Gal A levels.

There is no cure for Fabry disease, and uniform recommendations for the use of enzyme replacement therapy (ERT) do not exist. The treatment of patients with Fabry disease primarily focuses upon replacing the missing or deficient enzyme (alpha-Gal A). All classically affected males should receive ERT (Fabrazyme®) as soon as the diagnosis is made, regardless of whether or not clinical manifestations are present. Female carriers and atypically affected males should receive ERT if clinical manifestations are present. It is recommended that patients with Fabry disease who have end-stage renal disease (ESRD) begin treatment with ERT, as this may reduce cardiovascular and neurologic complications of Fabry disease.

Current Prior Authorization Criteria

Fabrazyme® (Agalsidase Beta) Approval Criteria:

1. An FDA approved diagnosis of Fabry disease. Diagnosis must be confirmed by one of the following:
   a. Genetic testing confirming positive galactosidase alpha (*GLA*) gene mutation; or
   b. Decreased plasma levels of alpha-galactosidase A (less than 5% of normal); and
2. Fabrazyme® (agalsidase beta) will initially be approved for six months. After that time, compliance will be required for continued authorization; and
3. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Utilization of Fabrazyme® (Agalsidase Beta): Fiscal Year 2018

Fiscal Year 2018 Utilization of Fabrazyme® (Agalsidase Beta): Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Total Units
2018	3	21	$293,421.97	$13,972.47	557

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

Fabrazyme® (Agalsidase Beta) Fiscal Year Comparision: Medical Claims (J0180)

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Total Units
2017	1	12	$300,217.40	$25,018.12	1,820
2018	1	18	$287,898.80	$15,994.38	1,680
% Change	**0.00%**	**50.00%**	**-4.10%**	**-36.07%**	**-7.69%**
Change	**0**	**6**	**-$12,318.60**	**-$9,023.74**	**-140**

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

Demographics of Members Utilizing Fabrazyme® (Agalsidase Beta)

- Due to the limited number of members utilizing Fabrazyme® (agalsidase beta), detailed member demographic information cannot be provided.

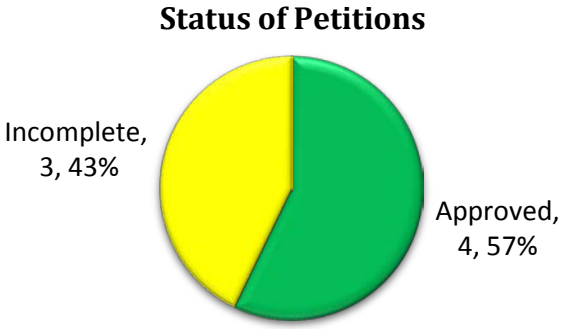
Top Prescriber Specialties of Fabrazyme® (Agalsidase Beta) by Number of Claims

- The only prescriber specialties listed on paid pharmacy claims for Fabrazyme® (agalsidase beta) during fiscal year 2018 were medical geneticist and oncologist. However, upon further review, treatment from the oncologist was started by a medical geneticist.

Prior Authorization of Fabrazyme® (Agalsidase Beta)

There were 7 prior authorization requests submitted for Fabrazyme® (agalsidase beta) during fiscal year 2018. The prior authorization of Fabrazyme® was implemented on December 15,

2017. Members that were utilizing Fabrazyme® at the time of implementation were grandfathered and given pre-emptive approvals, which are included in the submitted petition totals. The following chart shows the status of the submitted petitions for fiscal year 2018.



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

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

- **August 2018:** Amicus Therapeutics announced that the FDA granted accelerated approval of Galafold™ (migalastat) 123mg capsules. Migalastat is an oral medication for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable *GLA* gene variant based on in vitro assay data. Migalastat was approved under the Subpart H Accelerated Approval pathway based on reduction in kidney interstitial capillary cell (KIC) GL-3 substrate. As a condition of accelerated approval, Amicus Therapeutics will continue to study migalastat in a confirmatory Phase 4 program.

Guideline Updates:

- **June 2018:** The European expert consensus statement on therapeutic goals in Fabry disease was published in *Molecular Genetics and Metabolism.* Highlights of the consensus statement include the following:
  - Therapeutic goals for patients with Fabry disease should be individualized by considering the patient characteristics, disease variant, and stage.
  - The reversal of symptoms or prevention of disease progression is the goal for most parameters associated with Fabry disease.
  - Multidisciplinary input is vital at all stages of Fabry disease management and should be based on a comprehensive assessment of affected organs and regular monitoring.
  - Timing of therapy plays an important role in Fabry disease management; early initiation of disease-specific therapy can delay progression in patients with Fabry disease.
  - Optimal Fabry disease management includes both disease-specific and adjunctive treatment and should consider the balance between anticipated clinical benefits and potential therapy-related challenges.

Pipeline:

- **Apabetalone (RVX-208):** Apabetalone (RVX-208) is a medication developed by Resverlogix for the treatment of several conditions, including Fabry disease.

Apabetalone is a selective bromodomain and extra-terminal (BET) inhibitor. BET inhibition is a new approach that can regulate disease-causing genes. Due to its beneficial effects on several biochemical pathways regulating the accumulation of GL-3, apabetalone holds promise as a potential add-on therapy to accompany ERT in Fabry disease patients. In March 2017, Health Canada approved a clinical trial of apabetalone in patients with Fabry disease.

- **JR-051:** JR-051 is an alpha-Gal A liquid-formulation ERT drug, developed in Japan by JCR Pharmaceuticals Co., Ltd. as a biosimilar to agalsidase beta. A Phase 3 study in sixteen patients with Fabry disease, who were stable on agalsidase beta and switched to JR-051, demonstrated pharmacodynamic bioequivalence between the two drugs and safety of JR-051. Additionally, Amicus (developer of migalastat) and GlaxoSmithKline (GSK), in collaboration with JCR Pharmaceuticals are developing migalastat co-formulated with JR-051 as part of the Amicus and GSK expanded Fabry product collaboration.
- **Lucerastat:** Idorsia Ltd. has begun enrolling patients in MODIFY, a multicenter, double-blind, randomized, placebo-controlled, parallel-group study to determine the efficacy and safety of lucerastat for the treatment of Fabry disease. Lucerastat is being studied as a monotherapy for the treatment of adult patients with Fabry disease, irrespective of their genetic mutation type. The primary endpoint of the study is a reduction in neuropathic pain. This major symptom is reported by many patients with Fabry disease as significantly impacting their daily activities and quality of life, despite existing treatment.
- **Pegunigalsidase alfa (PRX-102):** Protalix Biotherapeutics is developing pegunigalsidase alfa for the treatment of Fabry disease. Pegunigalsidase alfa, currently in Phase 3 clinical trials, is a chemically modified version of the recombinant alpha-Gal A protein. Protein sub-units are covalently bound using PEG chains, resulting in a more active and stable molecule compared to the current available versions of the molecule (Fabrazyme®). The goals for this product are better efficacy in treating Fabry disease patients with declining renal function, and lowering the treatment burden of bi-weekly infusions by offering the option of once-monthly infusions.
- **Venglustat:** Sanofi Genzyme has developed the investigational therapy, venglustat, for the treatment of conditions caused by lysosomal dysfunction such as Fabry, Gaucher, and Parkinson's diseases. Venglustat is an oral inhibitor of the enzyme glucosylceramide synthase (GCS). When venglustat inhibits GCS, it reduces GL-3 and its accumulation in the absence of alpha-Gal A. The FDA granted venglustat Fast Track designation in 2015 for the treatment of Fabry disease.

Galafold™ (Migalastat) Product Summary[11,12]

Indication(s): Galafold™ (migalastat) is an alpha-Gal A pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable *GLA* gene variant based on in vitro assay data.

- Treatment is indicated for patients with an amenable *GLA* variant that is interpreted by a clinical genetics professional as causing Fabry disease (i.e., pathogenic, likely pathogenic) in the clinical context of the patient. Consultation with a clinical genetics

professional is strongly recommended in cases where the amenable *GLA* variant is of uncertain clinical significance or may be benign (not causing Fabry disease).

Dosing:

- Migalastat is supplied as 123mg capsules packaged in a 14-capsule wallet pack for a 4-week supply.
- The recommended dosage regimen of migalastat is 123mg orally once every other day at the same time of day.
- Migalastat should be taken on an empty stomach, with no food for at least two hours before and two hours after taking.

Mechanism of Action: Migalastat is a pharmacological chaperone that reversibly binds to the active site of alpha-Gal A protein (encoded by the *GLA* gene), which is deficient in Fabry disease. This binding stabilizes alpha-Gal A allowing its trafficking from the endoplasmic reticulum into the lysosome where it exerts its action. In the lysosome, migalastat dissociates from alpha-Gal A, allowing it to break down GL-3 and globotriaosylsphingosine (lyso-Gb3). Certain *GLA* mutations causing Fabry disease result in the production of abnormally folded and less stable forms of the alpha-Gal A protein which retain enzymatic activity. Those *GLA* variants, referred to as amenable variants, produce alpha-Gal A proteins that may be stabilized by migalastat, thereby restoring their trafficking to lysosomes and their intralysosomal activity.

Contraindication(s): None

Adverse Reactions: The most common adverse reactions reported with migalastat (≥10%) during the 6-month placebo-controlled, double-blind phase of Study 1 were headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia.

Use in Specific Populations:

- Pregnancy: There were three pregnant women with Fabry disease exposed to migalastat in clinical trials. As such, the available data are not sufficient to assess drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
- Lactation: There are no data on the presence of migalastat in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of migalastat have not been established in pediatric patients.
- Geriatric Use: Clinical trials of migalastat did not include a sufficient number of patients 65 years of age or older to determine whether they respond differently from younger patients.
- Renal Impairment: Migalastat is substantially excreted by the kidneys. Systemic exposure was significantly increased in subjects with severe renal impairment [estimated glomerular filtration rate (eGFR) <30mL/min/1.73m^2]. Migalastat has not been studied in patients with Fabry disease who have an eGFR <30mL/min/1.73m^2. Migalastat is not recommended for use in patients with severe renal impairment or ESRD requiring dialysis. No dosage adjustment is required in patients with mild-to-moderate renal impairment (eGFR ≥30mL/min/1.73m^2).

Efficacy: The efficacy of migalastat was studied in a 6-month randomized, double-blind, placebo-controlled phase (stage 1) followed by a 6-month open-label treatment phase (stage 2) and a 12-month open-label extension phase. A total of 67 patients with Fabry disease who were naïve to migalastat and ERT or were previously treated with ERT (agalsidase beta or non-U.S. approved agalsidase alfa) and had been off ERT for at least 6 months were randomized in a 1:1 ratio to receive either migalastat 123mg every other day or placebo for the first 6 months. In the second 6 months, all patients were treated with migalastat. Patients included in the study were 16 to 74 years of age, had a mutation in the *GLA* gene resulting in a mutant protein that would respond to migalastat as determined by preliminary assay, had an eGFR >30mL/min/1.73m^2, and had a urinary GL-3 level at least four times the upper limit of the normal range. Before unblinding, a new, validated assay (which was similar to the preliminary assay, but included modifications to the quality and rigor of the test) showed that 50 of the 67 participants had mutant alpha-Gal A forms suitable for targeting by migalastat. Since the assay that ultimately determined whether a mutant enzyme would respond to migalastat became available after the study had begun, the study included patients with suitable (amenable) and not suitable mutations. The primary endpoint was the percentage of patients who had a ≥50% reduction in the number of GL-3 inclusions per KIC at 6 months assessed by renal biopsy. The primary endpoint analysis, involving patients with mutant alpha-Gal A forms that were suitable or not suitable for migalastat therapy, did not show a significant treatment effect. The findings for 64 of the patients from the intention-to-treat population who had baseline biopsy samples were as follows: 13 of 32 patients (41%) who received migalastat and 9 of 32 patients (28%) who received placebo had a response at 6 months (P=0.30).

In stage 1 (6-month) post hoc analysis and stage 2 (12-month) pre-specified analysis in 45 patients with **suitable** mutant alpha-Gal A, 6 months of treatment with migalastat was associated with a significantly greater reduction in the mean number of GL-3 inclusions per KIC than placebo (−0.25±0.10 vs. 0.07±0.13; P=0.008). The reduction in KIC GL-3 at 6 months remained stable after an additional 6 months of treatment. A significant reduction in the mean number of GL-3 inclusions per KIC was observed at 12 months in patients who switched from placebo to migalastat at 6 months (−0.33±0.15, P=0.01). Patients with mutant alpha-Gal A that was not suitable for migalastat therapy according to the validated assay did not show any treatment effect in KIC GL-3.

Cost Comparison:

Medication	Cost Per Unit*	Cost Per 28 Days of Therapy
Galafold™ (migalastat) 123mg	**Unknown**	**Unknown**
Fabrazyme® (agalsidase beta) 35mg	$5,894.00	$23,576.00$^{\Delta}$

Cost does not reflect rebated price or net cost. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
*Unit = capsule or vial
$^{\Delta}$Cost per 28 days of therapy for Fabrazyme® based on 1mg/kg given every two weeks for a 70kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Galafold™ (migalastat) with the following criteria:

Galafold™ (Migalastat) Approval Criteria:

1. An FDA approved diagnosis of Fabry disease with a confirmed amenable *GLA* gene variant based on in vitro assay data; and
2. Galafold™ must be prescribed by a geneticist or an advanced care practitioner with a supervising physician who is a geneticist; and
3. Member must have an estimated glomerular filtration rate (eGFR) of at least 30mL/min/1.73m^2; and
4. Galafold™ will initially be approved for six months. After that time, compliance will be required for continued authorization; and
5. A quantity limit of 14 capsules per 28 days will apply.

Utilization Details of Fabrazyme® (Agalsidase Beta): Fiscal Year 2018

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
FABRAZYME INJ 5MG	20	3	$276,086.64	$730.39	$13,804.33	94.09%
FABRAZYME INJ 35MG	1	1	$17,335.33	$1,238.24	$17,335.33	5.91%
TOTAL	**21**	**3***	**$293,421.97**	**$748.53**	**$13,972.47**	**100.00%**

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

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[1] Mauer M, Kopp JB, Schiffmann R. Fabry disease: Clinical features and diagnosis. *UpToDate*. Available online at: http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-fabry-disease?source=search_result&search=fabry&selectedTitle=1%7E50. Last revised 07/13/2018. Last accessed 08/03/2018.

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Appendix J

30-Day Notice to Prior Authorize Qbrexza™ (Glycopyrronium)

Oklahoma Health Care Authority
September 2018

Hyperhidrosis Introduction[1,2]

Hyperhidrosis is the secretion of sweat in amounts greater than physiologically needed for thermoregulation. It is most commonly a chronic idiopathic (primary) condition; however, it can be caused by secondary medical conditions or medications (e.g., menopause, hyperthyroidism, antidepressants, hormonal agents, sulfonylureas). Idiopathic hyperhidrosis localized to certain areas of the body is called primary focal hyperhidrosis. Primary focal hyperhidrosis usually affects the axillae, palms, and soles. The condition may also affect other sites, such as the face, scalp, inguinal, and inframammary areas. Primary focal hyperhidrosis is made worse by heat or emotional stimuli, but it is not considered a psychological disorder. It may, however, have serious social, emotional, and professional consequences. Hyperhidrosis is associated with an increased incidence of other cutaneous disorders. Patients with primary focal hyperhidrosis may be more likely to suffer from dermatophytosis, pitted keratolysis, and viral warts at the sites of hyperhidrosis. In addition, atopic dermatitis and other eczematous dermatitis may be present at a greater frequency in patients with hyperhidrosis.

Hyperhidrosis prevalence estimates for children and adults in the United States range from 1 to 5% of the population. The diagnosis of primary focal hyperhidrosis is based on history, clinical findings, and, if necessary, supplementary tests aimed at determining the size of the area affected and the amount of sweat produced. There is no generally accepted lab test or other kind of measurement to confirm or rule out hyperhidrosis. The typical history in patients with hyperhidrosis includes: onset before 25 years of age; sweating that is temperature-independent, unpredictable, and cannot be consciously controlled; affects one or more sites; sweating occurs bilaterally and symmetrically; occurs more than once per week; affects everyday life; focal sweating stops during sleep; and positive family history. The American Academy of Dermatology consensus panel suggests diagnostic criteria of focal, visible, excessive sweating of at least six months duration without apparent cause and at least two of the above mentioned characteristics typical in patient history.

There are a variety of treatments available for primary hyperhidrosis. Treatment selection is based on individual patient needs and the site affected. The major therapeutic options for axillary hyperhidrosis include antiperspirants, botulinum toxin, microwave thermolysis, topical glycopyrronium, oral medications (e.g., anticholinergics), and surgery. Topical antiperspirants such as 20% aluminum chloride hexahydrate or 6.25% aluminum chloride hexahydrate are considered first-line therapy for axillary hyperhidrosis. Given the delay in onset of action of aluminum-based topical antiperspirants, it is recommended to continue treatment for several weeks; however, significant improvement may be noted within one week. Palmar and plantar hyperhidrosis are also initially treated with topical antiperspirants; however, iontophoresis may be an alternative initial treatment. Iontophoresis is the introduction of ionized substances

through intact skin by the application of direct electrical current. For hyperhidrosis, this is typically performed with tap water. The hands or feet are placed in just enough water to cover them, and the electrical current is administered directly to the treatment site where it may temporarily block sweat glands.

Qbrexza™ (Glycopyrronium) Product Summary[3,4,5,6]

U.S. Food and Drug Administration (FDA) Approval: June 2018

Indication(s): Qbrexza™ (glycopyrronium) is an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

Dosing:

- It is supplied in a carton containing 30 pouches. Each pouch contains a single-use cloth that is pre-moistened with 2.4% glycopyrronium solution.
- Glycopyrronium 2.4% cloth(es) is for topical use in the underarm area only and is not for use in other body areas.
- It is to be applied once every 24 hours to clean, dry skin in the underarm area. A single cloth should be used for both underarms.
- Hands should be washed immediately after use as glycopyrronium can cause temporary dilation and blurred vision if it comes into contact with the eyes.

Mechanism of Action: Glycopyrronium is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. In hyperhidrosis, glycopyrronium inhibits the action of acetylcholine on sweat glands, which reduces sweating.

Contraindication(s): Glycopyrronium is contraindicated in patients with medical conditions that can be exacerbated by its anticholinergic effects (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjögren's syndrome).

Adverse Reactions: The most frequent adverse reactions (incidence ≥2%) in patients with primary axillary hyperhidrosis treated with glycopyrronium 2.4% include:

- Dry mouth
- Mydriasis
- Oropharyngeal pain
- Headache
- Urinary hesitation
- Blurred vision
- Nasal dryness
- Dry throat
- Dry eye
- Dry skin
- Constipation

Additionally, the most frequently reported local skin reactions (≥8%) in patients with primary axillary hyperhidrosis treated with glycopyrronium 2.4% include:

- Erythema
- Burning/stinging
- Pruritus

Use in Specific Populations:

- Pregnancy: There are no available data on glycopyrronium use in pregnant women to inform a drug-associated risk for adverse developmental outcomes.

- Lactation: There are no data on the presence of glycopyrronium or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of glycopyrronium have not been established in pediatric patients younger than 9 years of age.
- Geriatric Use: Clinical trials of glycopyrronium did not include sufficient numbers of patients 65 years of age or older to determine whether they respond differently from younger patients.
- Renal Impairment: The elimination of glycopyrronium given intravenously is severely impaired in patients with renal failure. Pharmacokinetics of topical glycopyrronium in patients with renal impairment has not been studied.

Efficacy: Two randomized, vehicle-controlled, multicenter trials, Trial 1 and Trial 2, were conducted in patients with primary axillary hyperhidrosis. A total of 697 patients, 9 years of age or older, were enrolled in the studies. Inclusion criteria required that prior to the start of treatment, all patients produce at least 50mg of sweat in each axilla over a 5-minute period and rate the severity of their sweating daily over a week with a mean score of 4 or higher on the Axillary Sweating Daily Diary (ASDD) Item 2. The ASDD is designed to measure the severity and impact of any underarm sweating experienced by the patient within the previous 24 hours including nighttime hours. The question from Item 2 is "During the past 24 hours, how would you rate your underarm sweating at its worst?" and is scored from 0 (no sweating) to 10 (worst possible sweating). The average weekly mean score on the ASDD Item 2 at baseline was approximately 7.2 across both trials.

Patients were randomized to receive either glycopyrronium 2.4% or vehicle applied once daily to each axilla. The co-primary endpoints were the proportion of patients having at least a 4-point improvement from baseline in the weekly mean ASDD Item 2 score at week 4 and the mean absolute change from baseline in measured sweat production at week 4.

The ASDD Item 2 responder rate was significantly greater for glycopyrronium-treated (GT) patients than for vehicle-treated patients in Trial 1 and Trial 2 ($P<0.001$). After four weeks of treatment in Trial 1, scores improved 58% (4.3-point improvement) in GT patients and 35% (2.5-point improvement) in vehicle-treated patients compared with baseline. After four weeks of treatment in Trial 2, scores improved 67% (4.9-point improvement) in GT patients and 36% (2.6-point improvement) in vehicle-treated patients compared with baseline.

For Trial 1, the pre-specified sensitivity analysis identified one analysis center with extreme outlier data for gravimetric measurement of sweat, which was then excluded [14 patients (9 GT, 5 vehicle)]. Analysis of the remaining patients showed that after four weeks in Trial 1 the GT group had a greater reduction in gravimetrically measured sweat production than the vehicle group (-96.2mg/5min vs. -90.6mg/5min, respectively; $P=0.001$). In Trial 2, after four weeks, a statistically significant difference favoring glycopyrronium over vehicle for mean absolute change from baseline in sweat production was seen (-110.3mg/5min vs. -92.2mg/5min, respectively; $P<0.001$).

Cost: The cost of Qbrexza™ (glycopyrronium) is currently unavailable. Qbrexza™ (glycopyrronium) is expected to be available in October 2018; however, the manufacturer has not yet disclosed the price.

Specialist Recommendations: The College of Pharmacy received input from an Oklahoma Health Care Authority staffed physician regarding the coverage of Qbrexza™ (glycopyrronium). It was recommended that Qbrexza™ only be covered for children with hyperhidrosis where a licensed behavioral health specialist has done a paper assessment and determined the hyperhidrosis is causing social anxiety, depression, or other mental health-related issues. Additionally, it was recommended that a failed trial of Drysol™ (20% aluminum chloride) be required prior to Qbrexza™ approval consideration.

Market News and Updates[7,8,9]

Pipeline:

- **THVD-102:** In February 2017, TheraVida announced positive Phase 2 study results with its product THVD-102, an orally administered combination drug product for the treatment of primary focal hyperhidrosis. THVD-102 is a novel, proprietary formulation of oxybutynin 7.5mg plus pilocarpine 7.5mg. The study evaluated the safety and efficacy as well as the effect on dry mouth of THVD-102 versus placebo and oxybutynin alone in patients with primary focal hyperhidrosis. Significantly fewer patients receiving THVD-102 reported “moderate” or “severe" dry mouth while receiving THVD-102 compared to oxybutynin alone. There were no statistically significant differences in efficacy between THVD-102 and oxybutynin.
- **Sofpironium Bromide:** Sofpironium bromide is a topical anticholinergic developed by Brickell Biotech, Inc. that has undergone testing in a confirmatory, randomized, double-blind, vehicle-controlled Phase 2b clinical trial in patients with primary axillary hyperhidrosis. In the study, sofpironium bromide was well-tolerated and achieved statistically significant results in 227 patients with axillary hyperhidrosis. Based upon these positive Phase 2b results, a Phase 3 program will be initiated in 2018.
- **Umeclidinium:** Results of a Phase 2a randomized controlled study to evaluate the pharmacokinetic, safety, tolerability, and clinical effect of topically applied umeclidinium (UMEC) in patients with primary axillary hyperhidrosis were published in *The Journal of The European Academy of Dermatology and Venereology* in October 2017. The proof-of-concept study found that the measurable exposure, acceptable safety, and preliminary clinical activity observed suggests a potential clinical utility of topical UMEC in axillary hyperhidrosis. Developed by GlaxoSmithKline, topical UMEC 1.85% is a long-acting muscarinic antagonist (LAMA) hypothesized to block stimulation of muscarinic receptors by acetylcholine and thereby reduce the overproduction of sweat.

Recommendations

The College of Pharmacy recommends the prior authorization of Qbrexza™ (glycopyrronium) with the following criteria:

Qbrexza™ (Glycopyrronium) Approval Criteria:

1. An FDA approved diagnosis of primary axillary hyperhidrosis in pediatric patients 9 years of age to 20 years of age; and
2. Documentation of assessment by a licensed behavior specialist indicating the member's hyperhidrosis is causing social anxiety, depression, or similar mental health-related issues that impact the member's ability to function in day-to-day living must be provided; and
3. Member must have failed a trial of Drysol™ (20% aluminum chloride) at least three weeks in duration; and
4. A quantity limit of one box (30 clothes) per 30 days will apply.

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Appendix K

Fiscal Year 2018 Annual Review of Antihyperlipidemics and 30-Day Notice to Prior Authorize FloLipid® (Simvastatin Oral Suspension)

Oklahoma Health Care Authority
September 2018

Current Prior Authorization Criteria

Statin Medications and Ezetimibe Tier-2 Approval Criteria:

1. Member must have documented trials with atorvastatin and rosuvastatin, consisting of at least 8 weeks of continuous therapy each, titrated to a dose of at least 40mg atorvastatin and 20mg rosuvastatin, which did not yield adequate LDL reduction; or
2. A documented adverse effect or contraindication(s) to all available lower tiered products; or
3. Clinical exceptions for ezetimibe include the following:
    a. Documented active liver disease; or
    b. Documented unexplained, persistent elevations of serum transaminases; or
    c. Documented statin-related myopathy.

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

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

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

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

Omega-3 Fatty Acids Approval Criteria:

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

Juxtapid® (Lomitapide) and Kynamro® (Mipomersen) Approval Criteria:

1. An FDA approved diagnosis of homozygous familial hypercholesterolemia (HoFH) defined by the presence of at least one of the following criteria:
    a. A documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality via genetic testing; or
    b. An untreated total cholesterol >500mg/dL and triglycerides <300mg/dL and at least one of the following:
        i. Documentation that both parents have untreated total cholesterol >250mg/dL; or
        ii. Presence of tendinous/cutaneous xanthoma prior to age 10 years; and
2. Documented failure of high dose statin therapy (LDL reduction capability equivalent to atorvastatin 80mg or higher); and
3. Prescriber must be certified with the Juxtapid® or Kynamro® REMS program.

PCSK9 Inhibitors Approval Criteria:

1. An FDA approved diagnosis of heterozygous familial hypercholesterolemia (HeFH) defined by the presence of one of the following criteria:
    a. Documented functional mutation(s) in the LDL receptor (LDLR) gene or other HeFH-related genes via genetic testing; or
    b. Definite HeFH using either the Simon Broome Register criteria or the Dutch Lipid Network criteria; or
2. An FDA approved diagnosis of homozygous familial hypercholesterolemia (HoFH) defined by the presence of at least one of the following:
    a. Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality via genetic testing; or
    b. An untreated total cholesterol >500mg/dL and at least one of the following:
        i. Documented evidence of definite HeFH in both parents; or
        ii. Presence of tendinous/cutaneous xanthoma prior to age 10 years; or
3. An FDA approved diagnosis of clinical atherosclerotic cardiovascular disease defined by the presence of one of the following criteria:
    a. High cardiovascular risk confirmed by Framingham risk score; and
        i. Supporting diagnoses/conditions signifying this risk level; or
    b. Documented history of Coronary Heart Disease (CHD); and
        i. Supporting diagnoses/conditions and dates of occurrence signifying history of CHD; and
4. Member must be 13 years of age or older for the diagnosis of HoFH or must be 18 years of age or older for all other FDA-approved diagnoses or indications; and
5. Member must be on high dose statin therapy (LDL reduction capability equivalent to rosuvastatin 40mg) or on maximally tolerated statin therapy; and
    a. Statin trials must be at least 12 weeks in duration (dosing, dates, duration of treatment, and reason for discontinuation must be provided); and
    b. LDL-cholesterol (LDL-C) levels should be included following at least 12 weeks of treatment with each statin medication; and

c. For statin intolerance due to myalgia, creatine kinase (CK) labs verifying rhabdomyolysis must be provided; and
d. Tier structure rules still apply; and

6. Member requires additional lowering of LDL-C (baseline, current, and goal LDL-C levels must be provided); and
7. Prescriber must verify that member has been counseled on appropriate use, storage of the medication, and administration technique; and
8. A quantity limit of two syringes or pens per 28 days will apply for Praluent®. A quantity limit of two syringes or autoinjectors per 28 days will apply for Repatha® 140mg and a quantity limit of one autoinjector per 28 days for Repatha® 420mg. Patients requesting Repatha® 420mg strength will not be approved for multiple 140mg syringes but instead should use one 420mg autoinjector.
9. Initial approvals will be for the duration of three months. Continued authorization at that time will require the prescriber to provide recent LDL-C levels to demonstrate the effectiveness of this medication, and compliance will be checked at that time and every six months thereafter for continued approval.

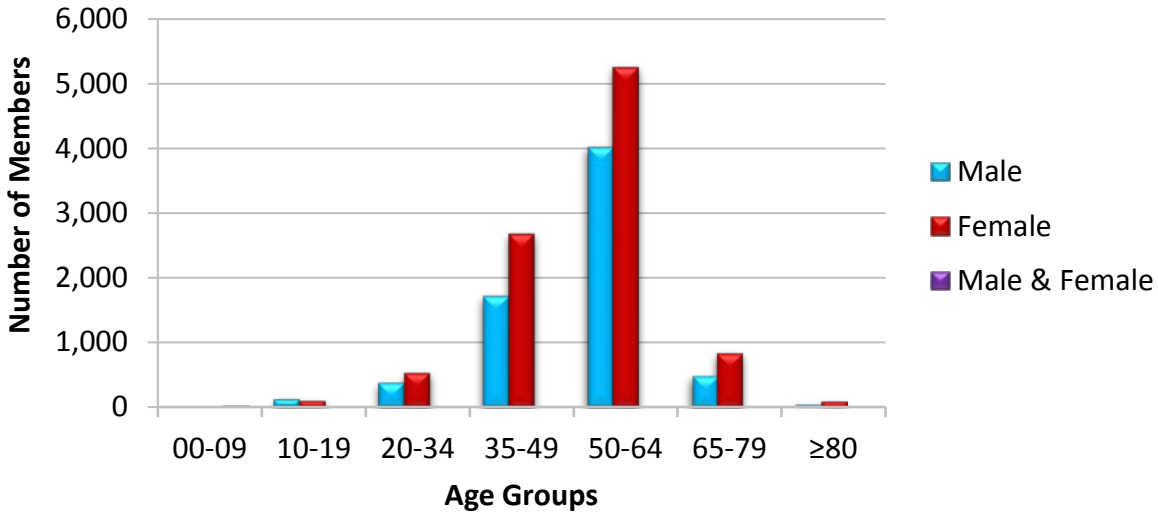
Utilization of Antihyperlipidemics: Fiscal Year 2018

Comparison of Fiscal Years: Antihyperlipidemics

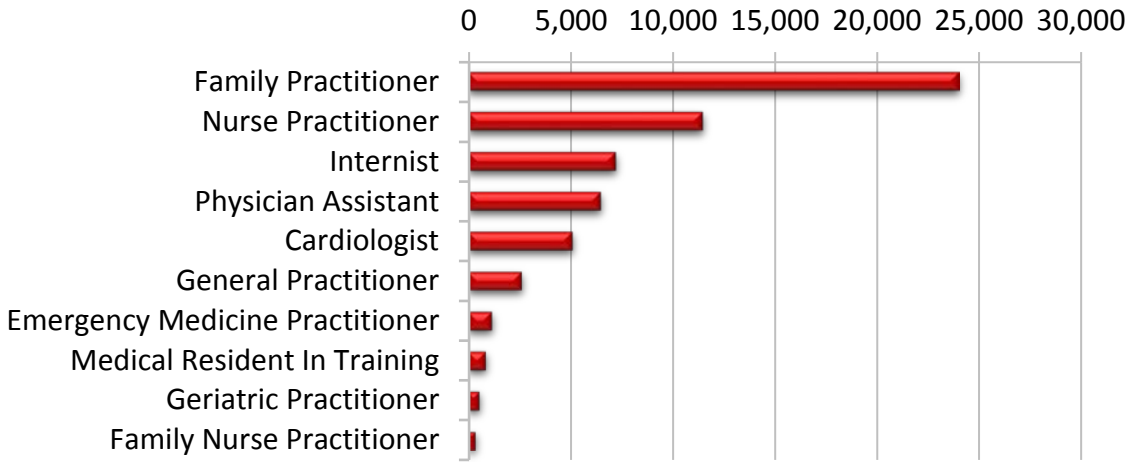
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	15,600	61,414	$1,029,252.54	$16.76	$0.35	2,961,277	2,925,429
2018	16,299	62,369	$894,205.07	$14.34	$0.29	3,151,604	3,118,668
% Change	**4.50%**	**1.60%**	**-13.10%**	**-14.40%**	**-17.10%**	**6.40%**	**6.60%**
Change	**699**	**955**	**-$135,047.47**	**-$2.42**	**-$0.06**	**190,327**	**193,239**

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

Demographics of Members Utilizing Antihyperlipidemics



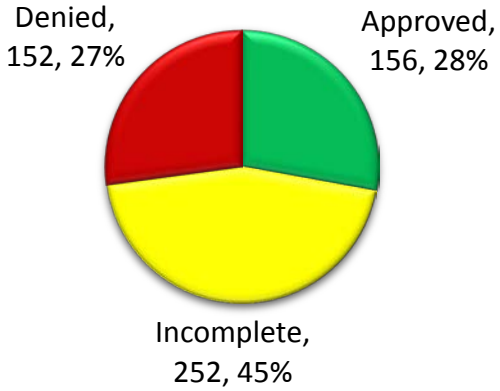
Top Prescriber Specialties of Antihyperlipidemics by Number of Claims



Prior Authorization of Antihyperlipidemics

There were 560 prior authorization requests submitted for antihyperlipidemics during fiscal year 2018. Computer edits are in place to detect lower tiered statin medications in a member's recent claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Kynamro® (mipomersen injection): January 2027
- Juxtapid® (lomitapide capsules): August 2027
- FloLipid® (simvastatin oral suspension): February 2030
- Vascepa® (icosapent ethyl capsules): April 2030
- Zypitamag™ (pitavastatin magnesium tablets): January 2031
- Epanova® (omega-3-carboxylic acids capsules): January 2033

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

- **FloLipid® (simvastatin oral suspension):** In April 2016, the FDA approved FloLipid® (simvastatin oral suspension), the first liquid formulation of simvastatin available in the United States. FloLipid® is available as a 20mg/5mL and 40mg/5mL strawberry-flavored oral suspension. Each bottle of oral suspension contains 150mL and should be used within one month of opening. FloLipid® is bioequivalent to Zocor® (simvastatin tablets). FloLipid® recently became available on the market, and the wholesale acquisition cost (WAC) of FloLipid® 40mg/5mL is $1.66 per milliliter, resulting in a monthly cost of $249.00 at a dose of 40mg per day. In comparison, the National Average Drug Acquisition Cost (NADAC) of generic simvastatin 40mg tablets is $0.04 per tablet, resulting in a monthly cost of $1.20 at a dose of 40mg per day.
- **Repatha® (evolocumab):** In December 2017, the FDA approved Repatha® (evolocumab) for the prevention of heart attacks, strokes, and coronary revascularization in adults with established cardiovascular (CV) disease. In the Repatha® CV outcomes study (FOURIER), Repatha® reduced the risk of heart attack by 27%, the risk of stroke by 21%, and the risk of coronary revascularization by 22%. The FDA also approved Repatha® to be used as an adjunct to diet, alone or in combination with other lipid-lowering therapies, such as statins, for the treatment of adults with primary hyperlipidemia to reduce low density lipoprotein cholesterol (LDL-C). Repatha® was first FDA approved in 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic CV disease, who require additional lowering of LDL-C, and as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients 13 years of age or older with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
    - **Institute for Clinical and Economic Review (ICER):** In September 2017, ICER released a new evidence update for evolocumab, based on the results and clinical evidence from the FOURIER trial. ICER is an independent, non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Replacing earlier assumptions about treatment outcomes with actual clinical results, the updated analyses found evolocumab to be less cost-effective leading to a lower calculated range for a value-based price that would align with the added benefit for patients. The FOURIER trial provided additional clarity on the longer-term outcomes for evolocumab for patients with atherosclerotic CV disease (ASCVD) whose LDL-C levels had not met an appropriate target of 70mg/dL or lower with statin therapy alone. ICER concludes that evolocumab combined with statin therapy is effective in reducing the incidence of CV events such as heart attack and stroke, but that evidence has failed to demonstrate a statistically-significant reduction in CV mortality. Based on these findings, ICER updated the value-based price range ($1,725 to $2,242 per year) for the use of evolocumab in patients with ASCVD whose LDL-C has not met an appropriate target. Conclusions for other populations, including those with familial

hypercholesterolemia, remain unchanged, as significant data on these populations has not yet emerged.

News:

- **October 2017:** Statin use was linked to a heightened risk of developing type 2 diabetes mellitus (T2DM) in susceptible individuals, according to findings in the Diabetes Prevention Program Outcomes Study (DPPOS). DPPOS is a long-term follow up study to a randomized clinical trial [Diabetes Prevention Program (DPP)] which looked at whether modest weight loss through lifestyle changes or treatment with metformin could reduce or delay development of T2DM in individuals at high risk. The DPP trial participants were given standard advice on healthy eating and exercise and were randomly assigned to either an intensive lifestyle intervention, metformin, or placebo. At the end of the main trial, all participants were offered a group-administered version of the lifestyle intervention and were invited to enroll in the DPPOS. During the DPPOS, all participants were offered quarterly lifestyle sessions, the former metformin group received open-label metformin, and the former intensive lifestyle group was offered two additional lifestyle programs per year. In the DPP and DPPOS, statin use was recorded along with other concomitant medications based on self-report. This information was collected at baseline and at each semiannual follow-up visit. Statin use was infrequent at DPP baseline (~4%), but increased progressively over the duration of the study. At 10 years of follow-up, the cumulative incidence of reported statin use prior to T2DM diagnosis was similar among the treatment groups, with 35%, 37%, and 33% in the placebo, metformin, and lifestyle groups, respectively (P=0.36). The prevalence of statin use increased over time and was substantially higher following the diagnosis of T2DM. In this analysis, statin use was associated with a clear increase in T2DM risk in the cohort as a whole, with point estimates of hazard ratios suggesting this risk is increased by close to 30%. The analysis concludes that for individual patients, a potential modest increase in diabetes risk clearly needs to be balanced against the consistent and highly significant reductions in myocardial infarction, stroke, and CV death associated with statin treatment, and glucose status should be monitored and healthy lifestyle behaviors reinforced in high-risk patients who are prescribed statins for CV disease (CVD) prophylaxis.
- **January 2018:** Statins were associated with lower amputation and death risk in patients with peripheral artery disease (PAD), according to an observational cohort study that included 155,647 patients with incident PAD. More than one quarter (28%) of patients with PAD included in the study were not on statins, and use of high-intensity statins was lowest in patients with PAD only (6.4%) in comparison with comorbid coronary/carotid disease (18.4%). Incident amputation and mortality risk declined significantly with any statin use in comparison with no statin use (antiplatelet therapy only). Low- to moderate-intensity statins had significant reductions in the risk of amputation and mortality in comparison with antiplatelet therapy only (no statins), but the effect size was significantly weaker than the high-intensity statins. The association of high-intensity statins with lower amputation and death risk remained significant and robust in propensity score-matched sensitivity and subgroup analyses. The study concludes

that statins, especially high-intensity formulations, are underused in patients with PAD. This is the first population-based study to show that high-intensity statin use at the time of PAD diagnosis is associated with a significant reduction in limb loss and mortality in comparison with low- to moderate-intensity statin users, as well as in comparison with patients treated only with antiplatelet medications.

- **March 2018:** In the ODYSSEY Outcomes trial, Praluent® (alirocumab) reduced the risk of major cardiac events by 15% among patients who had suffered heart attacks and other coronary events. Alirocumab met the primary endpoint by reducing the overall risk of major adverse CV events (MACE) in patients who had suffered a recent acute coronary syndrome (ACS) event. The MACE composite endpoint includes patients who experienced a heart attack, ischemic stroke, death from coronary heart disease (CHD), or unstable angina requiring hospitalization. Alirocumab was also associated with lower all-cause mortality and there were numerically fewer CHD deaths. Patients with baseline LDL-C ≥100mg/dL experienced a more pronounced effect from alirocumab, reducing their risk of MACE by 24%. Regeneron and Sanofi, the makers of Praluent®, announced that they will "offer payers that agree to reduce burdensome access barriers for high-risk patients a further reduced net price for Praluent®." The drugmakers did not announce a specific price but said it would be "in alignment with" ICER's new projection of cost-effectiveness at an annual price point of $4,500 to $8,000 in higher-risk patients with LDL-C ≥100mg/dL despite intensive statin therapy.
    - **ICER:** In March 2018, ICER released a preliminary new evidence update for alirocumab, based on the results from the ODYSSEY Outcomes trial. ICER updated the estimates of the long-term cost-effectiveness of alirocumab based on data from the ODYSSEY Outcomes trial. Results from the trial suggest greater benefit with alirocumab for patients with an LDL-C ≥100mg/dL despite intensive statin therapy. ICER calculated a value-based price range ($4,500 to $8,000 per year), net of rebates and discounts, for this group using two different assumptions about mortality benefits. A lower value-based price range ($2,300 to $3,400 per year), net of rebates and discounts, would apply if the drug were used to treat all patients with an acute coronary event in the past year and an LDL-C ≥70mg/dL.
- **August 2018:** Early evidence has shown a preventative effect of statins for some cancers, but their effect on the risk of Non-Hodgkin lymphomas (NHL) was unclear. Statins exert their anti-tumor effects (including pro-apoptotic, anti-proliferative, anti-inflammatory, and anti-angiogenic effects) through cholesterol-mediated and cholesterol-independent pathways. Previous laboratory and animal studies demonstrated that statins could reduce the risk of certain NHL subtypes via these mechanisms. A population-based, nested, case-control study was conducted involving 5,541 NHL cases and 27,315 controls matched for gender, age, place of residence, and length of period of available prescription drug data. The study assessed the use of statins prior to NHL diagnosis (excluding the 12 months prior to the index date). More than one quarter of cases (26.7%) and controls (27.2%) were prescribed statins. Ever-use of any statin was associated with lower risk of total NHL and of certain subtypes including diffuse large B-cell lymphomas (DLBCL), plasma cell neoplasms (PCN), and other B-cell NHL. Analysis of statin type suggested that the association was limited to high-potency statin and

lipophilic statin users. No clear duration or dose-response relationships were observed. These findings provide evidence that statin use can reduce the risk of DLBCL and PCN, but not other NHL types, and the study concludes that further studies are warranted to verify these associations and to examine the biological mechanisms.

- **August 2018:** A secondary analysis of data from the ACCORD trial was performed to assess whether metformin was associated with reduced statin muscle pain. An ACCORD sub-study assessed patients for muscle cramps and/or leg pain while walking, typically non-severe statin muscle pain symptoms. The study compared muscle pain between patients using a statin (n=445) or both a statin and metformin (n=869) at baseline. Overall patient characteristics were balanced between groups. Unadjusted analysis showed fewer reports of muscle cramps (35%) and leg pain while walking (40%) with statins and metformin compared to statins only (muscle cramps: 42% and leg/calve pain while walking: 47%). Multivariable regression demonstrated a 22% odds reduction for muscle cramps and a 29% odds reduction for leg pain while walking. The study concludes that metformin appears to reduce the risk of non-severe statin muscle pain, and additional research is needed to confirm the findings and assess metformin's impact on statin adherence and related CV outcomes.

Pipeline:

- **MGL-3196:** Madrigal Pharmaceuticals is currently developing MGL-3196, a first-in-class, orally administered, small-molecule, liver-directed, thyroid hormone receptor-β (THR-β)-selective agonist. Preclinical, toxicology, and Phase 1 clinical data suggest MGL-3196 as a potential treatment for non-alcoholic steatohepatitis (NASH) and dyslipidemias. THR β-selectivity also enhances the safety profile of MGL-3196, compared to non-selective agents. MGL-3196 is currently in Phase 2 clinical trials for biopsy-confirmed NASH and for HeFH, with a protocol for a Phase 2 clinical trial in HoFH also in development. Madrigal Pharmaceuticals has another product, MGL-3745, also a THR-β-selective agonist in preclinical development that could be a follow-on compound to MGL-3196.
- **Bempedoic Acid:** Esperion is currently developing bempedoic acid, a first-in-class, non-statin, targeted therapy that works in the liver to block cholesterol biosynthesis. Bempedoic acid is a complementary, once-daily, oral LDL-C lowering medication that significantly reduces elevated LDL-C levels in patients with hypercholesterolemia, including patients inadequately treated with current lipid-modifying therapies. In the liver, bempedoic acid is converted to a coenzyme A (CoA) derivative, or ETC-1002-CoA, which directly inhibits ATP citrate lyase (ACL), a key enzyme that supplies substrates for cholesterol and fatty acid synthesis in the liver. Inhibition of ACL by ETC-1002-CoA results in reduced cholesterol synthesis and upregulation of LDL receptor activity in the liver; this promotes the removal of LDL-C from the blood. Esperion is currently evaluating bempedoic acid in four, fully-enrolled global pivotal Phase 3 LDL-C lowering efficacy and safety studies consisting of approximately 3,600 patients, a Phase 3 open-label extension study, and the CLEAR Outcomes global CV outcomes trial (CVOT). Esperion plans to submit a New Drug Application (NDA) to the FDA by the first quarter of 2019 for an LDL-C lowering indication for bempedoic acid based on the successful

completion of the company's ongoing and fully-enrolled global pivotal Phase 3 program. The proposed product label would include specific language for use of bempedoic acid as an adjunct to maximally tolerated statin therapy in patients with hypercholesterolemia, specifically those at high CVD risk with ASCVD and/or HeFH who require additional LDL-C lowering.

- **Inclisiran:** The Medicines Company and Alnylam Pharmaceuticals are currently developing inclisiran, a long-acting, subcutaneous (sub-Q), N-acetylgalactosamine (GalNAc)-conjugated synthetic small interfering RNA (siRNA) molecule, which inhibits the synthesis of PCSK9 in the liver, thereby reducing liver cell LDL receptor turnover and lowering plasma LDL-C levels. In contrast to anti-PCSK9 monoclonal antibodies (e.g., alirocumab, evolocumab) that bind to PCSK9 in the blood, inclisiran is a first-in-class investigational medication that acts by turning off PCSK9 synthesis in the liver. Inclisiran is currently in Phase 3 clinical trials, with results expected in the second half of 2019.
- **Evinacumab:** Regeneron is currently developing evinacumab, an investigational monoclonal antibody to angiopoietin-like protein 3 (ANGPTL3). ANGPTL3 acts as an inhibitor of lipoprotein lipase and endothelial lipase, and appears to play a role in lipoprotein metabolism. Evinacumab received Breakthrough Therapy designation from the FDA for the treatment of HoFH in April 2017 and is currently in Phase 3 clinical trials.
- **Cholesteryl Ester Transfer Protein (CETP) Inhibitors:** For the past few years, a class of drugs known as CETP inhibitors have been under investigation for their potential to increase HDL-C levels and, in effect, reduce CV risk. CETP is a glycoprotein that aids in the transfer of cholesteryl ester and triglycerides from HDL-C to apolipoprotein B-containing lipoprotein, very-low-density lipoprotein, and LDL-C. With the inhibition of CETP, HDL-C levels are likely to increase while LDL-C levels decrease. Since the discovery of CETP inhibitors, clinical studies have been conducted to evaluate their safety and efficacy. Evacetrapib, torcetrapib, and dalcetrapib are all CETP inhibitors that once sought approval from the FDA for patients at risk for CV events and low HDL-C, but their development was halted after clinical research showed an increased mortality risk, a CV event risk equivalence to placebo, and/or a lack of clinically meaningful results. Despite the failure of earlier CETP inhibitors to come to market, the development of anacetrapib was initially more promising. Anacetrapib was well tolerated overall, and early research showed significant increases in HDL-C levels and decreases in LDL-C levels. However, the initial studies were not designed to assess the impact of anacetrapib on patient-oriented CV events. The REVEAL trial, which enrolled over 30,000 patients, found that, in addition to significantly increasing HDL-C and decreasing LDL-C, anacetrapib reduced the risk for a first major coronary event by 9% and reduced the risk for coronary death or myocardial infarction by 11% compared with placebo. Despite positive results, the pharmaceutical company ultimately halted its pursuit of approval by the FDA for anacetrapib. While statistically significant, the CV risk reduction reported in the REVEAL trial is modest at best and likely explained by the reduction in LDL-C rather than an increase in HDL-C. While CETP inhibitors have produced extremely large increases in HDL-C levels, this has not resulted in clinically meaningful outcomes thus far. Additionally, some research suggests that extremely high HDL-C levels are associated with an increased risk for mortality. Currently, two CETP inhibitors remain under

investigation. Dalcetrapid is currently in a Phase 3 trial of patients with a specific genotype that showed a positive association in previous studies between this genotype and reduced CV events. CKD-519, another CETP inhibitor, is under early development.

Recommendations

The College of Pharmacy recommends the following changes to the Statin Medications and Ezetimibe Product Based Prior Authorization (PBPA) category (changes noted in red):

1. Placement of FloLipid® (simvastatin oral suspension) into the Special Prior Authorization (PA) Tier:
   a. Use of FloLipid® will require a patient-specific, clinically significant reason why the member cannot use simvastatin oral tablets, even when the tablets are crushed.
2. Moving ezetimibe to Tier-1 based on generic availability and low net cost.

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

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

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

1. Use of any Special PA medication will require a patient-specific, clinically significant reason why lower tiered medications with similar or higher LDL reduction cannot be used; and
2. Use of FloLipid® (simvastatin oral suspension) will require a patient specific, clinically significant reason why the member cannot use simvastatin oral tablets, even when the tablets are crushed.

Additionally, the College of Pharmacy recommends removing the prior authorization for omega-3-acid ethyl esters (generic Lovaza®), based on low net cost (changes noted in red):

Omega-3 Fatty Acids Approval Criteria:

1. Laboratory documentation of severe hypertriglyceridemia (fasting triglycerides ≥500mg/dL), and controlled diabetes (fasting glucose <150mg/dL at the time of triglycerides measurement and HgA1c <7.5%); and
2. Previous failure with both nicotinic acid and fibric acid medications; and
3. Use of Vascepa® or Epanova® requires a previous failure of or a patient-specific, clinically significant reason why the member cannot use omega-3-acid ethyl esters (generic Lovaza®), which is available without prior authorization; and

4. Use of Vascepa® 0.5 gram requires a patient-specific, clinically significant reason why the member cannot use Vascepa® 1 gram.

Furthermore, the College of Pharmacy recommends the following updates to the current Juxtapid® and Kynamro® Approval Criteria, based on net costs (changes noted in red):

Juxtapid® (Lomitapide) and Kynamro® (Mipomersen) Approval Criteria:

1. An FDA approved diagnosis of homozygous familial hypercholesterolemia (HoFH) defined by the presence of at least one of the following criteria:
    a. A documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality via genetic testing; or
    b. An untreated total cholesterol >500mg/dL and triglycerides <300mg/dL and at least one of the following:
        i. Documentation that both parents have untreated total cholesterol >250mg/dL; or
        ii. Presence of tendinous/cutaneous xanthoma prior to age 10 years; and
2. Documented ~~failure~~ trial of high dose statin therapy (LDL reduction capability equivalent to ~~atorvastatin 80mg or higher~~ rosuvastatin 40mg) or maximally tolerated statin therapy at least 12 weeks in duration; and
3. Documented trial of Repatha® (evolocumab) at least 12 weeks in duration; and
4. Member requires additional lowering of LDL-C (baseline, current, and goal LDL-C levels must be provided); and
5. Prescriber must be certified with Juxtapid® or Kynamro® REMS program.

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

PCSK9 Inhibitors Approval Criteria:

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

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

Utilization Details of Antihyperlipidemics: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
STATIN MEDICATIONS AND EZETIMIBE						
TIER-1 MEDICATIONS						
ATORVASTATIN TAB 40MG	14,136	4,237	$195,691.77	$13.84	3.34	21.88%
ATORVASTATIN TAB 20MG	10,184	3,100	$129,655.47	$12.73	3.29	14.50%
ATORVASTATIN TAB 10MG	6,534	1,756	$77,256.99	$11.82	3.72	8.64%
SIMVASTATIN TAB 20MG	5,294	1,475	$50,775.87	$9.59	3.59	5.68%
ATORVASTATIN TAB 80MG	4,733	1,473	$72,978.25	$15.42	3.21	8.16%
PRAVASTATIN TAB 40MG	4,628	1,239	$76,963.44	$16.63	3.74	8.61%
SIMVASTATIN TAB 40MG	3,922	1,094	$39,486.04	$10.07	3.59	4.42%
PRAVASTATIN TAB 20MG	2,956	847	$42,280.07	$14.30	3.49	4.73%
LOVASTATIN TAB 20MG	1,993	667	$17,551.49	$8.81	2.99	1.96%
SIMVASTATIN TAB 10MG	1,766	488	$17,681.90	$10.01	3.62	1.98%
LOVASTATIN TAB 40MG	1,145	314	$13,455.88	$11.75	3.65	1.50%
ROSUVASTATIN TAB 20MG	866	285	$13,107.61	$15.14	3.04	1.47%
PRAVASTATIN TAB 80MG	863	222	$19,283.31	$22.34	3.89	2.16%
PRAVASTATIN TAB 10MG	766	227	$12,216.76	$15.95	3.37	1.37%
ROSUVASTATIN TAB 40MG	719	217	$11,598.31	$16.13	3.31	1.30%
ROSUVASTATIN TAB 10MG	464	162	$6,579.32	$14.18	2.86	0.74%
SIMVASTATIN TAB 80MG	320	93	$3,866.18	$12.08	3.44	0.43%
ROSUVASTATIN TAB 5MG	167	69	$2,292.16	$13.73	2.42	0.26%
SIMVASTATIN TAB 5MG	80	22	$894.67	$11.18	3.64	0.10%
TIER-1 SUBTOTAL	**61,536**	**17,987**	**$803,615.49**	**$13.06**	**3.42**	**89.87%**
TIER-2 MEDICATIONS						
EZETIMIBE TAB 10MG	529	130	$14,686.00	$27.76	4.07	1.64%
ZETIA TAB 10MG	33	23	$14,534.43	$440.44	1.43	1.63%
TIER-2 SUBTOTAL	**562**	**153**	**$29,220.43**	**$51.99**	**3.67**	**3.27%**
SPECIAL PRIOR AUTHORIZATION (PA) MEDICATIONS						
LIVALO TAB 4MG	33	6	$14,884.35	$451.04	5.50	1.66%
EZETIM/SIMVA TAB 10-40MG	28	8	$5,675.43	$202.69	3.50	0.63%
LIVALO TAB 2MG	24	4	$8,948.35	$372.85	6.00	1.00%
VYTORIN TAB 10-40MG	5	2	$4,089.12	$817.82	2.50	0.46%
VYTORIN TAB 10-80MG	4	1	$3,774.98	$943.75	4.00	0.42%
VYTORIN TAB 10-20MG	3	1	$2,799.59	$933.20	3.00	0.31%
EZETIM/SIMVA TAB 10-80MG	2	1	$363.38	$181.69	2.00	0.04%
SPECIAL PA SUBTOTAL	**99**	**23**	**$40,535.20**	**$409.45**	**4.30**	4.53%
STATINS AND EZETIMIBE TOTAL	**62,197**	**16,290***	**$873,371.12**	**$14.04**	**3.82**	**97.67%**
OMEGA-3 FATTY ACIDS						
OMEGA-3-ACID CAP 1GM	153	21	$7,518.58	$49.14	7.29	0.84%
VASCEPA CAP 1GM	9	2	$2,308.73	$256.53	4.50	0.26%
OMEGA-3 FATTY ACIDS TOTAL	**162**	**23***	**$9,827.31**	**$60.66**	**7.04**	**1.10%**
PCSK9 INHIBITORS						

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
PRALUENT INJ 150MG/ML	7	2	$7,635.51	$1,090.79	3.50	0.85%
REPATHA INJ 140MG/ML	3	1	$3,371.13	$1,123.71	3.00	0.38%
PCSK9 INHIBITORS TOTAL	**10**	**3***	**$11,006.64**	**$1,100.66**	**3.33**	**1.23%**
TOTAL	**62,369**	**16,299***	**$894,205.07**	**$14.34**	**3.83**	**100.00%**

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

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Appendix L

Fiscal Year 2018 Annual Review of Parathyroid Medications

Oklahoma Health Care Authority
September 2018

Current Prior Authorization Criteria

Natpara® (Parathyroid Hormone) Approval Criteria:

1. An FDA approved indication for use as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism; and
    a. Natpara® is not FDA approved for hypoparathyroidism caused by calcium-sensing receptor mutations; and
    b. Natpara® is not FDA approved for hypoparathyroidism due to acute post-surgery; and
2. Magnesium deficiency must be ruled out; and
3. Member must have pretreatment serum calcium level >7.5mg/dL before starting Natpara®; and
4. Prescriber must verify the member has sufficient 25-hydroxyvitamin D level per standard of care; and
5. Member must be unable to be adequately well-controlled on calcium supplements and active forms of vitamin D alone; and
6. Health care provider and dispensing pharmacy must be certified through the Natpara® REMS Program; and
7. A quantity limit of two cartridges (each package contains two 14-day cartridges) per 28 days will apply. The maximum covered dose will be 100mcg per day.

Rayaldee® [Calcifediol Extended-Release (ER) Capsules] Approval Criteria:

1. An FDA approved indication for the treatment of secondary hyperparathyroidism (SHPT) in adults with chronic kidney disease (CKD) stage 3 or 4; and
2. Member must not have CKD stage 5 or end-stage renal disease on dialysis; and
3. Member should have a serum total 25-hydroxyvitamin D level <30ng/mL before starting treatment; and
4. Member should have a serum calcium level <9.8mg/dL before initiating treatment; and
5. Rayaldee® must be prescribed by a nephrologist, endocrinologist, or provider who specializes in the treatment of SHPT; and
6. Member must have a documented failure or clinically significant reason why the member cannot use available generic vitamin D analogs including calcitriol; and
7. Initial approval will be for 30mcg daily for three months; and
    a. After three months, approval for 60mcg daily for 12 months can be considered if intact parathyroid hormone (iPTH) is above the treatment goal and serum calcium <9.8mg/dL, phosphorus <5.5mg/dL, and 25-hydroxyvitamin D <100ng/mL.

    b. Additional approvals will not be granted if iPTH is persistently abnormally low, serum calcium is consistently above the normal range, or serum 25-hydroxyvitamin D is consistently >100ng/mL.
8. A quantity limit of 60 capsules per 30 days will apply.

Parsabiv™ (Etelcalcetide Injection) Approval Criteria:

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

Zemplar® (Paricalcitol Capsules) Approval Criteria:

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

Hectorol® (Doxercalciferol Capsules) Approval Criteria:

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

Utilization of Parathyroid Medications: Fiscal Year 2018

Comparison of Fiscal Years: Natpara® (Parathyroid Hormone Injection)

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	1	12	$105,073.65	$8,756.14	$312.72	24	336
2018	5	39	$360,036.85	$9,231.71	$329.70	78	1,092
% Change	**400.00%**	**225.00%**	**242.70%**	**5.40%**	**5.40%**	**225.00%**	**225.00%**
Change	**4**	**27**	**$254,963.20**	**$475.57**	**$16.98**	**54**	**756**

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

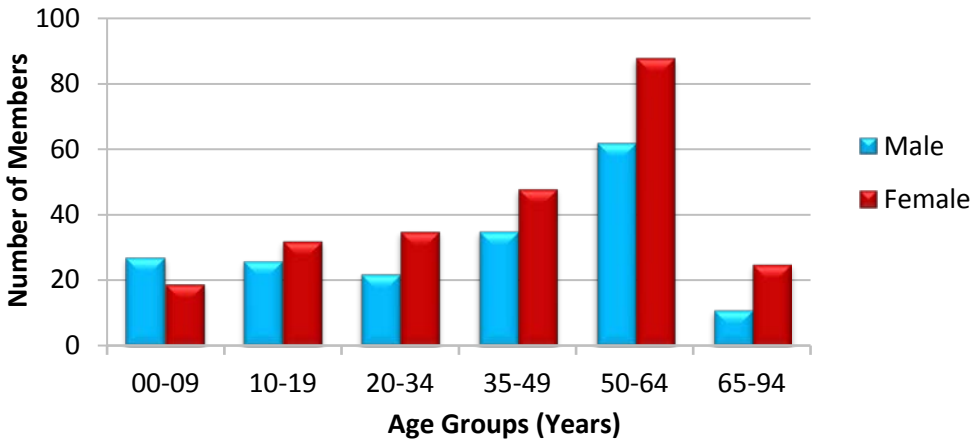
Comparison of Fiscal Years: Calcimimetics and Vitamin D Analogs

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	430	1,929	$971,038.80	$503.39	$12.70	85,284	76,475
2018	428	1,952	$995,180.58	$509.83	$13.25	81,256	75,086
% Change	**-0.50%**	**1.20%**	**2.50%**	**1.30%**	**4.30%**	**-4.70%**	**-1.80%**
Change	**-2**	**23**	**$24,141.78**	**$6.44**	**$0.55**	**-4,028**	**-1,389**

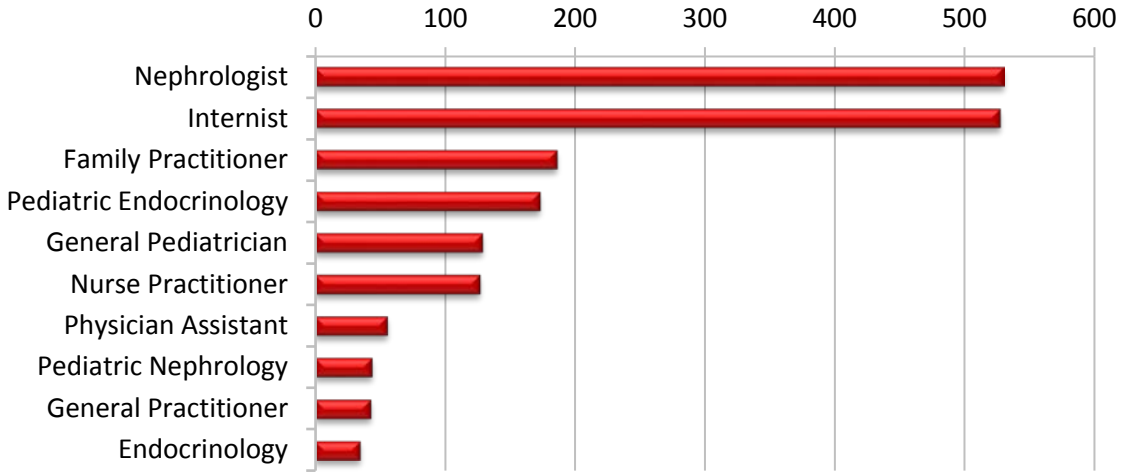
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- The prior authorization criteria for Rayaldee®, Parsabiv™, Zemplar®, and Hectorol® was voted on by the Drug Utilization Review (DUR) Board in September of 2017 and went into effect November 20, 2017. Members utilizing Rayaldee®, Parsabiv™, Zemplar®, and Hectorol® were "grandfathered" for members who were using the products at the time the prior authorization went into effect.

Demographics of Members Utilizing Parathyroid Medications



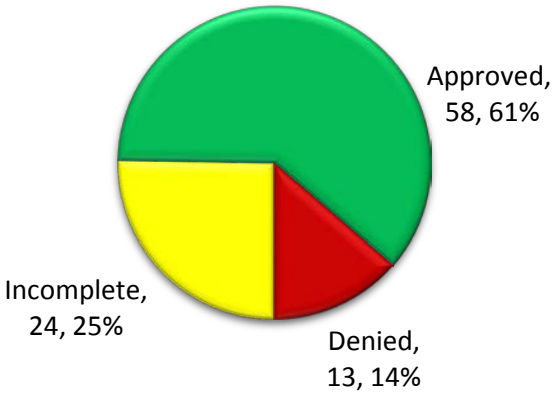
Top Prescriber Specialties of Parathyroid Medications by Number of Claims



Prior Authorization of Parathyroid Medications

There were 95 prior authorization requests submitted for parathyroid medications during fiscal year 2018. Of those, there were 21 prior authorization requests submitted for Natpara® for 6 unique members. The prior authorization of Rayaldee®, Parsabiv™, Zemplar®, and Hectorol® was implemented November 20, 2017. Members that were utilizing Rayaldee®, Parsabiv™, Zemplar®, and Hectorol® at the time of implementation were grandfathered and given pre-emptive approvals, which are included in the submitted petition totals. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Sensipar® (cinacalcet tablets): September 2026
- Rayaldee® (calcifediol extended-release [ER] capsules): August 2028
- Parsabiv™ (etelcalcetide injection): June 2034

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

- **March 2018:** The FDA approved the first generic version of Sensipar® (cinacalcet tablets) on March 8, 2018. In February 2018, Amgen was denied a six month extension of market exclusivity for Sensipar® by the District of Columbia's District Court after the company appealed for pediatric exclusivity. The generic formulation is not currently available as Amgen remains in litigation regarding the patent for Sensipar®.

Pipeline:

- **June 2018:** Amgen is currently recruiting for an open-label, single-dose study for use of Parsabiv™ (etelcalcetide) in pediatric patients 2 to 18 years of age with secondary hyperparathyroidism (SHPT) who are receiving dialysis; the study is designed to evaluate the safety and pharmacokinetics in this population. The study completion date is estimated to be the end of November 2018.
- **August 2018:** Amgen is currently recruiting for a head-to-head study of etelcalcetide and cinacalcet in Asian hemodialysis patients with SHPT. The purpose of the study is to demonstrate that treatment with etelcalcetide is non-inferior to treatment with cinacalcet for lowering serum intact parathyroid hormone (PTH) levels by >30% from baseline among subjects with chronic kidney disease (CKD) and SHPT who require management with hemodialysis. The head-to-head study has an estimated completion date of July 2019. Amgen previously published a head-to-head study of etelcalcetide and cinacalcet in *The Journal of the American Medical Association (JAMA)* in 2017 which included participants from 22 countries, but did not include participants from Asian countries. In the 2017 randomized clinical trial of 683 adults receiving hemodialysis with PTH levels >500pg/mL, 68.2% of patients randomized to receive etelcalcetide versus 57.7% randomized to receive cinacalcet experienced >30% reduction in mean PTH concentrations over 27 weeks. The use of etelcalcetide was non-inferior to cinacalcet in reducing serum PTH concentrations over 26 weeks; it also met superiority criteria.

Guideline Update(s):

- **July 2017:** The updated Kidney Disease: Improving Global Outcomes (KDIGO) practice guideline on the management of chronic kidney disease-mineral and bone disorder (CKD-MBD) was released in July 2017. This is the first update since the 2009 KDIGO CKD-MBD guidelines were published. The 2017 guidance no longer recommends routine use of calcitriol or its analogs in CKD stages 3A to 5 in adult patients not on dialysis. The recommendations state it is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKD stages 4 to 5 with severe and progressive hyperparathyroidism. In children, calcitriol and vitamin D analogs may be considered to maintain serum calcium levels in the age-appropriate normal range. In patients with CKD stage 5D, the updated guidance recommends requiring parathyroid hormone (PTH)-lowering therapy, and the guidelines suggest calcimimetics, calcitriol, or vitamin D analogs, or a combination of calcimimetics with calcitriol or vitamin D analogs (2B grade recommendation).

Recommendations

The College of Pharmacy does not recommend any changes to the current parathyroid medications prior authorization criteria at this time.

Utilization Details of Calcimimetics and Vitamin D Analogs: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
CALCIMIMETIC PRODUCTS						
CINACALCET PRODUCTS						
SENSIPAR TAB 30MG	338	89	$364,871.39	$28.72	$1,079.50	39.36%
SENSIPAR TAB 60MG	158	35	$334,851.38	$64.74	$2,119.31	36.12%
SENSIPAR TAB 90MG	69	21	$227,244.62	$87.07	$3,293.40	24.51%
SUBTOTAL	**565**	**114**	**$926,967.39**	**$45.25**	**$1,640.65**	**93.14%**
VITAMIN-D ANALOG PRODUCTS						
CALCITRIOL PRODUCTS						
CALCITRIOL CAP 0.25MCG	822	209	$15,622.93	$0.47	$19.01	22.90%
CALCITRIOL CAP 0.5MCG	303	87	$11,880.61	$1.05	$39.21	17.42%
CALCITRIOL SOL 1MCG/ML	112	32	$14,440.22	$2.95	$128.93	21.17%
SUBTOTAL	**1,237**	**328**	**$41,943.76**	**$0.85**	**$33.91**	**4.21%**
PARICALCITOL PRODUCTS						
PARICALCITOL CAP 1MCG	94	23	$7,479.62	$2.33	$79.57	10.97%
PARICALCITOL CAP 2MCG	38	8	$7,235.26	$6.35	$190.40	10.61%
PARICALCITOL CAP 4MCG	7	2	$3,087.85	$8.58	$441.12	4.53%
SUBTOTAL	**139**	**33**	**$17,802.73**	**$3.78**	**$128.08**	**1.79%**
DOXERCALCIFEROL PRODUCTS						
DOXERCALCIFEROL CAP 1MCG	6	2	$5,882.87	$33.81	$980.48	8.62%
DOXERCALCIFEROL CAP 2.5MCG	5	1	$2,583.83	$17.23	$516.77	3.79%
SUBTOTAL	**11**	**3**	**$8,466.70**	**$26.13**	**$769.70**	**0.85%**
TOTAL	**1,952**	**428***	**$995,180.58**	**$13.25**	**$509.83**	**100%**

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

Utilization Details of Natpara® (Parathyroid Hormone Injection): Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
PARATHYOID HORMONE PRODUCTS						
NATPARA INJ 100MCG	19	2	$175,046.95	$329.04	$9,213.00	48.62%
NATPARA INJ 75MCG	10	4	$93,299.83	$333.21	$9,329.98	25.91%
NATPARA INJ 50MCG	10	4	$91,690.07	$327.46	$9,169.01	25.47%
TOTAL	**39**	**5***	**$360,036.85**	**$329.70**	**$9,231.71**	**100%**

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

[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 06/2018. Last accessed 08/06/2018.
[2] Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl* 2017; 7:1-59.
[3] Amgen®. A Single-dose Study in Pediatric Subjects Ages 2 to Less than 18 Years With (sHPT) Receiving Hemodialysis. ClinicalTrials.gov. Available online at: https://clinicaltrials.gov/ct2/show/NCT02833857?term=etelcalcetide&rank=17. Last updated 06/2018. Last accessed 08/10/2018.
[4] Amgen®. Head-to-Head Study of Etelcalcetide and Cinacalcet in Asian HD Subjects with SHPT. ClinicalTrials.gov. Available online at: https://clinicaltrials.gov/ct2/show/NCT03299244?term=etelcalcetide&rank=6. Last updated 08/2018. Last accessed 08/10/2018.
[5] Block GA, Bushinsky DA, Cheng S, et al. Effect of Etelcalcetide vs Cinacalcet on Serum Parathyroid Hormone in Patients Receiving Hemodialysis with Secondary Hyperparathyroidism A Randomized Clinical Trial. *JAMA* 2017; 317(2):156-164. doi:10.1001/jama.2016.19468.
[6] Sagonowsky E. Amgen sued FDA for a 6-month reprieve from Sensipar® generics—and lost. *Fierce Pharma*. Available online at: https://www.fiercepharma.com/legal/amgen-comes-up-short-lawsuit-against-fda-sensipar-pediatric-exclusivity-as-generics-inch. Issued 02/21/2018. Last accessed 08/14/2018.
[7] FDA approves generic version of Amgen's Sensipar®. *Healio Nephrology News and Issues.* Available online at: https://www.healio.com/nephrology/kidney-care-community/news/online/%7Bd96ae362-3338-472c-9062-e563481947c9%7D/fda-approves-generic-version-of-amgens-sensipar. Issued 03/14/2018. Last accessed 08/14/2018.

Appendix M

Fiscal Year 2018 Annual Review of Growth Hormone

Oklahoma Health Care Authority
September 2018

Current Prior Authorization Criteria

Growth Hormone Products	
Tier-1*	**Tier-2**
Genotropin® (Pfizer) - Cartridge, MiniQuick	**Humatrope®** (Eli Lilly) - Vials, Cartridge Kits
	Norditropin® (NovoNordisk) - FlexPro® Pens
	Nutropin® and Nutropin AQ® (Genentech) - Vials, Pen Cartridge, NuSpin®
	Omnitrope® (Sandoz) - Vials, Cartridge
	Saizen® (EMD Serono) - Vials, click.easy®
	Serostim® (EMD Serono) - Vials
	Zomacton™ and Zoma-Jet™ (Ferring) - Vials, Injection Device
	Zorbtive® (EMD Serono) - Vials

*Supplementally rebated product(s); tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Cost (NADAC), or Wholesale Acquisition Cost (WAC) if NADAC unavailable.
[All products contain the identical 191 amino acid sequence found in pituitary-derived human growth hormone (hGH)].

Growth Hormone Covered Indications *(prior to epiphyseal closure)*:

1. Classic human growth hormone (hGH) deficiency as determined by childhood hGH stimulation tests
2. Panhypopituitarism with history of pituitary or hypothalamic injury due to tumor, trauma, surgery, whole brain radiation, irradiation, hemorrhage or infarction, or a congenital anomaly, and one of the following:
    a. Deficiency of three or more pituitary hormones and insulin-like growth factor (IGF)-1 ≥2.5 standard deviations (SD) below the mean for the member's age and gender; or
    b. No deficiency or deficiency in less than three pituitary hormones and IGF-1 <50th percentile and failure of a growth hormone stimulation test; or
    c. Member is 12 months post trauma or surgery and does not have evidence of tumor recurrence and member's growth has not restarted; the member must still meet all the other criteria, however authorization does not require height to be ≥2.25 SD below the mean for age in these circumstances
3. Panhypopituitarism in children with height ≤2.25 SD below the mean for age and gender and magnetic resonance imaging (MRI) evidence of pituitary stalk agenesis, empty sella, or ectopic posterior pituitary "bright spot"
4. Short stature associated with Prader-Willi Syndrome
5. Short stature associated with Noonan Syndrome
6. Short stature associated with chronic renal insufficiency (pre-transplantation)
7. History of intrauterine growth restriction who have not reached a normal height (≥2.25 SD below the mean for age and gender) by age two years

8. Idiopathic short stature (ISS) who are ≥2.25 SD below the mean for height (based on age and gender) and are unlikely to catch up in height
9. Turner syndrome or 45X, 46XY mosaicism
10. Hypoglycemia with evidence for hGH deficiency
11. Short-stature homeobox-containing gene (SHOX) deficiency with genetic evidence for SHOX deficiency
12. Other evidence for hGH deficiency submitted for panel review and decision

Growth Hormone Tier-2 Approval Criteria:

1. Documented allergic reaction to non-active components of all available Tier-1 medications; or
2. A clinical exception applies to members with a diagnosis of acquired immunodeficiency syndrome (AIDS) wasting syndrome, in which case Serostim® can be used, regardless of its current Tier status.

Discontinuation of Therapy or Transition to Adult Therapy Criteria:

1. Failure to show improvement in height percentile on growth chart after one year of treatment; or
2. Growth velocity <2.5cm/year unless associated with another growth-limiting and treatable medical condition (i.e., hypothyroidism); or
3. Epiphyseal closure; or
4. Covered height has been reached:
    a. 152.4cm (60 inches) for girls; or
    b. 165.1cm (65 inches) for boys; or
5. Inadequate compliance; or
6. Significant adverse effects.

Insulin-Like Growth Factor-1 (IGF-1) Analog Medications: Increlex® and Iplex™ [Mecasermin (rDNA Origin) Injection] Approval Criteria:

1. Therapy initiated by an endocrinologist; and
2. Diagnosis of Primary IGF-1 deficiency with all of the following:
    a. Height >3 standard deviations (SD) below the mean; and
    b. Basal IGF-1 >3 SD below the mean; and
    c. Normal or elevated growth hormone (GH); and
3. Documentation of mutation in GH receptor (GHR) or mutation in post-GHR signaling pathway or IGF-1 gene defects (Laron Syndrome); and
4. IGF-1 analog medications will not be approved for use in secondary IGF-1 deficiencies related to GH deficiency, malnutrition, hypothyroidism, or chronic steroid therapy.

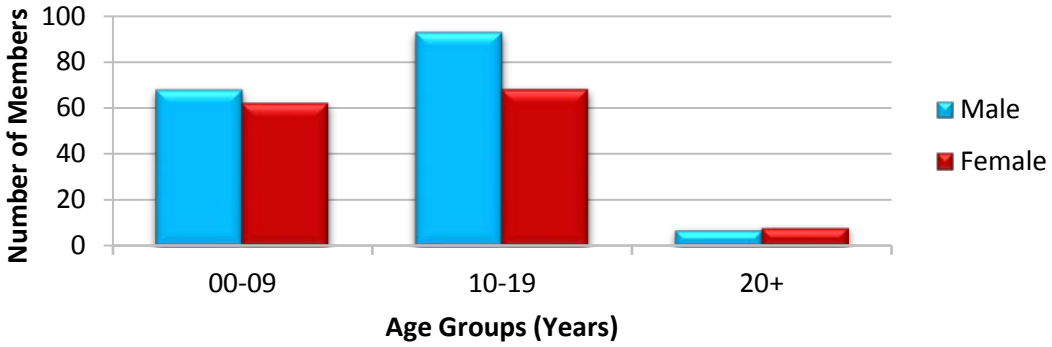
Utilization of Growth Hormone: Fiscal Year 2018

Comparison of Fiscal Years

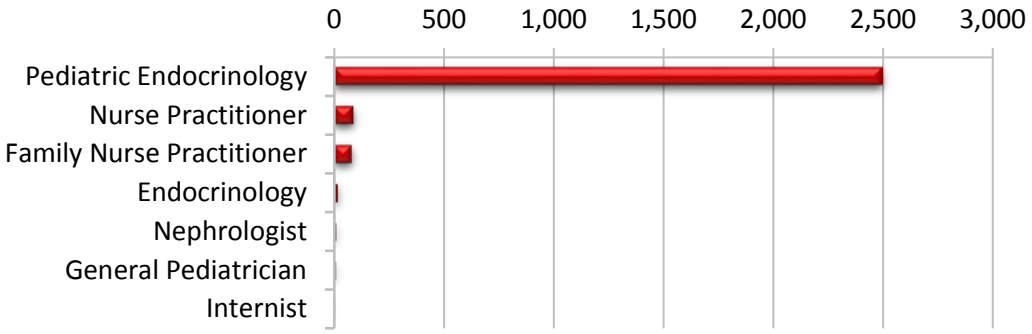
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	301	2,505	$8,303,001.35	$3,314.57	$116.64	34,753	71,182
2018	306	2,697	$8,860,134.27	$3,285.18	$116.40	38,603	76,120
% Change	**1.70%**	**7.70%**	**6.70%**	**-0.90%**	**-0.20%**	**11.10%**	**6.90%**
Change	**5**	**192**	**$557,132.92**	**-$29.39**	**-$0.24**	**3,850**	**4,938**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs. Growth hormone medication category is heavily influenced by supplemental rebate participation.
There was no utilization of insulin-like growth factor-1 (IGF-1) analog medications during fiscal year 2017 or 2018.

Demographics of Members Utilizing Growth Hormone



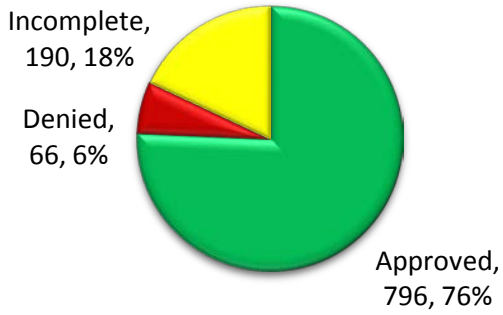
Top Prescriber Specialties of Growth Hormone by Number of Claims



Prior Authorization of Growth Hormone

There were 1,052 prior authorization requests submitted for 329 unique members for growth hormone during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Norditropin® FlexPro® [somatropin (rDNA origin) for injection]: September 2027

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

- **December 2017:** Aeterna Zentaris, Inc. announced FDA approval of Macrilen™ (macimorelin), an orally available ghrelin agonist, used in the diagnosis of patients with adult growth hormone (GH) deficiency. Macrilen™ stimulates the release of GH from the pituitary gland; stimulated GH levels are then measured in four blood samples over 90 minutes. Macrilen™ solution must be used within 30 minutes after preparation. Since Macrilen™ is diagnostic it will be covered under the medical benefit.
- **February 2018:** Ferring Pharmaceuticals announced that the FDA approved Zomacton® [somatropin (rDNA origin)] for the replacement of GH in adults with GH deficiency. Zomacton® was previously approved for pediatric patients who have growth failure due to inadequate secretion of endogenous GH.

Pipeline:

- **October 2017:** Novo Nordisk published results of a Phase 1 trial of somapacitan, a once-weekly, reversible, albumin-binding GH derivative. The trial was a 1-week, randomized, open-label, active control study comparing the pharmacokinetic and adverse event profiles of somapacitan to once daily GH in 32 prepubertal children with GH deficiency. Investigators concluded that a single-dose of once-weekly somapacitan was well tolerated with insulin-like growth factor-1 (IGF-1) levels supporting weekly dosing.
- **November 2017:** Ascendis Pharma published an article on the rationale and design of TransCon GH, a long-acting, once weekly GH therapy in Phase 3 development for adults and pediatric patients with GH deficiency. TransCon GH is formulated with an inert polyethylene glycol (PEG)-containing carrier molecule designed to extend the half-life and reduce dosing from daily to once-weekly. TransCon is also being developed in an autoinjector formulation that can be stored at room temperature. Phase 3 clinical trial data is expected the first quarter of 2019.

Recommendations

The College of Pharmacy does not recommend any changes to the current growth hormone prior authorization criteria at this time.

Utilization Details of Growth Hormone: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ DAY	COST/ CLAIM
TIER-1 PRODUCTS						
GENOTROPIN PRODUCTS						
GENOTROPIN INJ 5MG	1,068	117	$3,032,119.21	9.13	$100.31	$2,839.06
GENOTROPIN INJ 12MG	347	48	$1,962,630.19	7.23	$194.82	$5,655.99
GENOTROPIN INJ 1MG	207	30	$746,544.49	6.9	$126.75	$3,606.50
GENOTROPIN INJ 0.4MG	192	31	$257,973.46	6.19	$48.05	$1,343.61
GENOTROPIN INJ 0.8MG	151	25	$415,883.72	6.04	$99.28	$2,754.20
GENOTROPIN INJ 0.6MG	149	27	$293,622.56	5.52	$69.91	$1,970.62
GENOTROPIN INJ 0.2MG	114	22	$77,998.92	5.18	$24.10	$684.20
GENOTROPIN INJ 1.4MG	87	12	$411,903.15	7.25	$169.09	$4,734.52
GENOTROPIN INJ 2MG	86	14	$637,948.14	6.14	$268.27	$7,418.00
GENOTROPIN INJ 1.2MG	73	13	$316,073.27	5.62	$154.63	$4,329.77
GENOTROPIN INJ 1.8MG	56	12	$357,219.84	4.67	$227.82	$6,378.93
GENOTROPIN INJ 1.6MG	27	7	$154,170.53	3.86	$203.93	$5,710.02
TIER-1 SUBTOTAL	**2,557**	**284**	**$8,664,087.48**	**9**	**$119.72**	**$3,388.38**
TIER-2 PRODUCTS[+]						
NORDITROPIN PRODUCTS						
NORDITROPIN INJ 5/1.5ML	62	8	$40,163.76	7.75	$25.91	$647.80
NORDITROPIN INJ 10/1.5ML	30	6	$45,178.06	5	$57.99	$1,505.94
NORDITROPIN INJ 15/1.5ML	29	5	$91,525.74	5.8	$108.83	$3,156.06
SUBTOTAL	**121**	**16**	**$176,867.56**	**7.56**	**$55.79**	**$1,461.72**
OMNITROPE PRODUCTS						
OMNITROPE INJ 10/1.5ML	5	2	$10,578.13	2.5	$61.86	$2,115.63
OMNITROPE INJ 5.8MG/VIAL	4	1	$4,606.43	4	$38.39	$1,151.61
OMNITROPE INJ 5/1.5ML	1	1	$155.74	1	$5.56	$155.74
SUBTOTAL	**10**	**4**	**$15,340.30**	**2.5**	**$48.09**	**$1,534.03**
HUMATROPE PRODUCTS						
HUMATROPE INJ 12MG	5	1	$2,338.95	5	$15.91	$467.79
HUMATROPE INJ 24MG	3	1	$1,030.04	3	$12.12	$343.35
HUMATROPE INJ 6MG	1	1	$469.94	1	$15.66	$469.94
SUBTOTAL	**9**	**3**	**$3,838.93**	**3**	**$14.65**	**$426.55**
TIER-2 SUBTOTAL	**140**	**22**	**$196,046.79**	**6.36**	**$52.27**	**$1,400.33**
TOTAL	**2,697**	**306***	**$8,860,134.27**	**8.81**	**$116.40**	**$3,285.18**

*Total number of unduplicated members.

Costs do not reflect rebated prices or net costs.

[+]Claims for Tier-2 products largely consist of claims for which SoonerCare is not the primary payer and therefore the reimbursed amount is not a true reflection of the cost of the medication.

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Appendix N

Industry News and Updates

Oklahoma Health Care Authority
September 2018

Introduction

The following report is an overview of recent issues, important literature, and select guideline updates impacting pharmacy and health care. Information that is expected to have a particular impact in the SoonerCare population has been included for review.

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

News:

- **Alzheimer's Disease:** A study published in the journal *Neuron* in June 2018 found that viruses interact with genes linked to Alzheimer's disease and may play a role in how the disease develops and progresses. The authors emphasized that they did not find that these viruses cause Alzheimer's, but the research suggests that the viruses may initiate an immune response that could increase the accumulation of amyloid, a protein that forms the plaques of Alzheimer's. The study analyzed samples from approximately 950 human brains in four different brain banks and found links to the molecular, genetic, and clinical symptoms of Alzheimer's disease. The virus theory is not accepted by most experts in Alzheimer's; however, the new findings will be strengthened by another upcoming study in *Neuron*, led by neuroscientists who have broken ground on the virus idea for years. Their new experiments, which were performed in mice and three-dimensional brain cells in a dish, found that the same herpes species caused a protective reaction in amyloid, causing it to ensnare the virus in fibrous nets that form plaques. Dr. Tanzi, one of the neuroscientists involved in the research, said that viruses and microbes are the "prequel" to the prevailing theory that Alzheimer's is caused by amyloid accumulation the brain cannot clear out.
- **Medicaid:** The Centers for Medicare and Medicaid Services (CMS) sent a letter to states in June 2018 clarifying guidance that medications approved by the U.S. Food and Drug Administration (FDA) under its accelerated approval pathway must by covered by state Medicaid programs if they are defined as a "covered outpatient drug." Medications approved under the FDA's accelerated approval program are meant to address unmet medical needs and often show some previously unseen benefit or target a disease for which there are limited, if any, treatment options. The program allows the drugs to go to market without first going through the more rigorous late-stage testing in order to get the treatments to patients faster. However, post-market safety and efficacy trials are still required and can either support or muddy a drug's profile. For example, last year Roche's Tecentriq® (atezolizumab) failed a Phase 3 trial for locally advanced or metastatic urothelial cancer, calling into question whether it deserved accelerated approval for that indication.

- **Drug Labels:** The FDA released draft guidance for industry in July 2018 regarding updates to prescription drug labels. The new guidance is expected to give prescribers more precise yet also more understandable information on the conditions and patient populations for which the drug is indicated. One example of the changes includes "if a study evaluating a drug in adults enrolled patients of a certain age range…the indication should be worded to reflect the broader age group (i.e., 'in adults') rather than the exact ages studied," as long as there is no reason to believe that use of the medication outside that range is unsafe. The guidance also includes what information should be omitted from the labels, mainly information that is obvious and simply clutters the label. For example, the document said, "if an indication is clearly worded as being approved for use in combination with another drug, there is no need for a limitation of use stating that the subject drug should be used only in combination and not as monotherapy." The FDA will accept comments on the draft guidance for 60 days, after which the agency will issue a final version.
- **Prenatal Depression:** Results of a study published in *JAMA Network Open* show that depression among pregnant women may be more common now than in prior generations. In the longitudinal analysis, 25% of the current generation mothers in the study, whose pregnancies occurred between 2012 to 2016, experienced higher levels of depressive symptoms compared to 17% in the generation of their mothers, whose pregnancies occurred between 1990 to 1992 [relative risk (RR) 1.51; 95% confidence interval (CI) 1.15-1.97]. The current generation of mothers were more likely to have higher depression symptom scores than their mothers' generation were (RR 1.77, 95% CI 1.27-2.46), even after adjustment for several variables including age, education, body-mass index, and smoking status. Additionally, daughters of mothers who had prenatal depression were much more likely to have prenatal depression themselves (RR 3.33, 95% CI 1.65-6.67). The researchers suggested that possible explanations for these findings include changes in society and lifestyle habits that vary from generation to generation. According to the authors, "this generation of young women has also experienced rapid change in technology, internet, and social media use, which has been associated with increased feelings of depression and social isolation and changes to social relationships." Other factors that may be contributing to this increase in maternal depression include poor eating habits, sedentary lifestyle, sleep deprivation, increase in chronic stress, and a faster pace of modern life compared to previous generations.
- **Nonprescription Drugs:** In July 2018, the FDA announced a new effort to increase access to a broader selection of nonprescription drug products for consumers. The FDA stated that while they do not have a direct role in the cost of medicines, they are mindful of the financial cost to patients and the health care system to fill a prescription medication. The FDA hopes that this new framework will contribute to lower costs for the health care system overall and provide greater efficiency for consumers by providing access to certain products that would otherwise only be available by prescription. The FDA stated that although not all prescription drugs can or should be available directly to consumers, there are select types of drugs that are appropriate for nonprescription use if the resources are available to help patients determine if the medicine is right for them. This approach includes applying innovative tools, such as digital health technologies, that

would support consumers in safely and appropriately selecting and using certain drugs. The FDA will continue to confirm that products considered under this framework receive a robust scientific review to ensure consumers can use them safely.

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Appendix O

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

FDA NEWS RELEASE

For Immediate Release: July 30th, 2018
FDA approves first treatment for rare adrenal tumors

The FDA approved Azedra® (iobenguane I 131) injection for intravenous (IV) use for the treatment of adults and adolescents age 12 years and older with rare tumors of the adrenal gland (pheochromocytoma or paraganglioma) that cannot be surgically removed (unresectable), have spread beyond the original tumor site, and require systemic anticancer therapy. This is the first FDA-approved drug for this use.
Pheochromocytomas are rare tumors of the adrenal glands. These glands are located right above the kidneys and make hormones including stress hormones called epinephrines and norepinephrines. Pheochromocytomas increase the production of these hormones, leading to hypertension and symptoms such as headaches, irritability, sweating, rapid heart rate, nausea, vomiting, weight loss, weakness, chest pain, or anxiety. When this type of tumor occurs outside the adrenal gland, it is called a paraganglioma.
The efficacy of Azedra® was shown in a single-arm, open-label, clinical trial in 68 patients that measured the number of patients who experienced a ≥50% reduction of all antihypertensive medications lasting for at least six months. This endpoint was supported by the secondary endpoint, overall tumor response measured by traditional imaging criteria. The study met the primary endpoint, with 17 (25%) of the 68 evaluable patients experiencing a ≥50% reduction of all antihypertensive medication for at least six months. Overall tumor response was achieved in 15 (22%) of the patients studied.
The most common severe side effects reported by patients receiving Azedra® in clinical trials included low levels of white blood cells (lymphopenia), abnormally low count of a type of white blood cells (neutropenia), low blood platelet count (thrombocytopenia), fatigue, anemia, increased international normalized ratio (a laboratory test which measures blood clotting), nausea, dizziness, hypertension, and vomiting.
As it is a radioactive therapeutic agent, Azedra® includes a warning about radiation exposure to patients and family members, which should be minimized while the patient is receiving Azedra®. The risk of radiation exposure is greater in pediatric patients. Other warnings and precautions include a risk of lower levels of blood cells (myelosuppression), underactive thyroid, elevations in blood pressure, renal failure or kidney injury, and inflammation of lung tissue (pneumonitis). Myelodysplastic syndrome and acute leukemias, which are cancers of the blood and bone marrow, were observed in patients who received Azedra®, and the magnitude of this risk will continue to be studied. Azedra® can cause harm to a developing fetus; women should be advised of the potential risk to the fetus and to use effective contraception after receiving Azedra®. Radiation exposure associated with Azedra® may cause infertility in males and females.
The FDA granted this application Fast Track, Breakthrough Therapy, and Priority Review designations. Azedra® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted the approval of Azedra® to Progenics Pharmaceuticals, Inc.

FDA NEWS RELEASE

For Immediate Release: August 8th, 2018
FDA approves treatment for two rare types of non-Hodgkin lymphoma

The FDA approved Poteligeo® (mogamulizumab-kpkc) injection for IV use for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy. This approval provides a new treatment option for patients with MF and is the first FDA approval of a drug specifically for SS.
Non-Hodgkin lymphoma is a cancer that starts in white blood cells called lymphocytes. MF and SS are types of non-Hodgkin lymphoma in which lymphocytes become cancerous and affect the skin. MF accounts for about half of all lymphomas arising from the skin. It causes itchy red rashes and skin lesions and can spread to other parts of the body. SS is a rare form of skin lymphoma that affects the blood and lymph nodes.
Poteligeo® is a monoclonal antibody that binds to a protein (called CC chemokine receptor type 4 or CCR4) found on some cancer cells.

The approval was based on a clinical trial of 372 patients with relapsed MF or SS who received either Poteligeo® or a type of chemotherapy called vorinostat. Progression-free survival (the amount of time a patient stays alive without the cancer growing) was longer for patients taking Poteligeo® (median 7.6 months) compared to patients taking vorinostat (median 3.1 months).
The most common side effects of treatment with Poteligeo® included rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection.
Serious warnings of treatment with Poteligeo® include the risk of dermatologic toxicity, infusion reactions, infections, autoimmune problems (a condition where the immune cells in the body attack other cells or organs in the body), and complications of stem cell transplantation that uses donor stem cells (allogeneic) after treatment with the drug.
The FDA granted this application Priority Review and Breakthrough Therapy designation. Poteligeo® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted this approval to Kyowa Kirin, Inc.

FDA NEWS RELEASE

For Immediate Release: August 10th, 2018
FDA approves first-of-its kind targeted RNA-based therapy to treat a rare disease

The FDA approved Onpattro™ (patisiran) infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients. This is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating, and often fatal genetic disease characterized by the buildup of abnormal amyloid protein in peripheral nerves, the heart and other organs. It is also the first FDA approval of a new class of drugs called small interfering ribonucleic acid (siRNA) treatment.
RNA acts as a messenger within the body's cells, carrying instructions from DNA for controlling the synthesis of proteins. RNA interference is a process that occurs naturally within our cells to block how certain genes are expressed. Since its discovery in 1998, scientists have used RNA interference as a tool to investigate gene function and its involvement in health and disease. Researchers at the National Institutes of Health, for example, have used robotic technologies to introduce siRNAs into human cells to individually turn off nearly 22,000 genes.
This new class of drugs, called siRNAs, work by silencing a portion of RNA involved in causing the disease. More specifically, Onpattro™ encases the siRNA into a lipid nanoparticle to deliver the drug directly into the liver, in an infusion treatment, to alter or halt the production of disease-causing proteins.
Affecting about 50,000 people worldwide, hATTR is a rare condition. It is characterized by the buildup of abnormal deposits of protein fibers called amyloid in the body's organs and tissues, interfering with their normal functioning. These protein deposits most frequently occur in the peripheral nervous system, which can result in a loss of sensation, pain, or immobility in the arms, legs, hands, and feet. Amyloid deposits can also affect the functioning of the heart, kidneys, eyes, and gastrointestinal tract. Treatment options have generally focused on symptom management.
Onpattro™ is designed to interfere with RNA production of an abnormal form of the protein transthyretin (TTR). By preventing the production of TTR, the drug can help reduce the accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients better manage the condition.
The efficacy of Onpattro™ was shown in a clinical trial involving 225 patients, 148 of whom were randomly assigned to receive an Onpattro™ infusion once every three weeks for 18 months, and 77 of whom were randomly assigned to receive a placebo infusion at the same frequency. The patients who received Onpattro™ had better outcomes on measures of polyneuropathy including muscle strength, sensation (pain, temperature, numbness), reflexes, and autonomic symptoms (blood pressure, heart rate, digestion) compared to those receiving the placebo infusions. Onpattro™-treated patients also scored better on assessments of walking, nutritional status, and the ability to perform activities of daily living.
The most common adverse reactions reported by patients treated with Onpattro™ are infusion-related reactions including flushing, back pain, nausea, abdominal pain, dyspnea, and headache. All patients who participated in the clinical trials received premedication with a corticosteroid, acetaminophen, and antihistamines (H_1 and H_2 blockers) to reduce the occurrence of infusion-related reactions. Patients may also experience vision problems including dry eyes, blurred vision, and eye floaters (vitreous floaters). Onpattro™

leads to a decrease in serum vitamin A levels, so patients should take a daily Vitamin A supplement at the recommended daily allowance.
The FDA granted this application Fast Track, Priority Review, and Breakthrough Therapy designations. Onpattro™ also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
Approval of Onpattro™ was granted to Alnylam Pharmaceuticals, Inc.

FDA NEWS RELEASE

For Immediate Release: August 16th, 2018
FDA approves first generic version of EpiPen®

The FDA approved the first generic version of EpiPen® and EpiPen® Jr (epinephrine) auto-injector for the emergency treatment of allergic reactions, including those that are life-threatening (anaphylaxis), in adults and pediatric patients who weigh more than 33 pounds. Teva Pharmaceuticals USA gained approval to market its generic epinephrine auto-injector in 0.3mg and 0.15mg strengths.
Life-threatening allergies can include reactions to insect bites or stings, foods, medications, latex, or other causes. Anaphylaxis is a medical emergency that affects the whole body and, in some cases, leads to death. Anaphylaxis occurs in approximately 1 in 50 Americans. People who have had an anaphylaxis episode always face the risk of another one. Because of this risk, they must carry an emergency dose of epinephrine at all times. Many must keep more than one dose at hand.
The EpiPen® is intended to automatically inject a dose of epinephrine into a person's thigh to stop an allergic reaction. The FDA has approved several epinephrine auto-injector products under new drug applications to treat anaphylaxis, including EpiPen®, Adrenaclick®, and Auvi-Q®. In addition, "authorized generic" versions of EpiPen® and Adrenaclick® are marketed without the brand names. An authorized generic is made under the brand name's existing new drug application using the same formulation, process, and manufacturing facilities that are used by the brand name manufacturer. The labeling or packaging is, however, changed to remove the brand name or other trade dress. In some cases, a company may choose to sell an authorized generic at a lower cost than the brand-name drug product.
Epinephrine auto-injector products are known as "combination products" because they consist of a drug (epinephrine) and a device (the auto-injector). The development of generic combination products can be more challenging than typical drug products, and the FDA regularly takes steps to help guide industry through the process. The agency works with individual companies to support their development of such complex products, and creates publicly available guidance describing the steps the FDA recommends companies take to submit complete, approvable applications for various types of medical products. In this case, the FDA has published three draft or final guidances since 2009 related to the development of generic epinephrine auto-injectors. In addition, as with brand-name drugs, the FDA inspects manufacturing and packaging facilities for generic drugs to ensure that they are capable of consistently producing quality products.
This epinephrine injection (auto-injector) is intended for immediate administration to patients. When given intramuscularly or subcutaneously, it has a rapid onset and short duration of action. Epinephrine works by reducing swelling in the airway and increasing blood flow in the veins.
The most common side effects associated with epinephrine injection are anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties. Rare cases of serious skin and soft tissue infections have been reported following use of the drug. In patients with heart disease, use of epinephrine injection may cause chest pain (angina pectoris) or abnormal heart beats (ventricular arrhythmias). Following use of epinephrine injection, patients should seek immediate medical or hospital care. Epinephrine should not be injected into the vein, buttock, fingers, hands, or feet. To minimize risk of injection-site injury, movement of the leg should be limited during injection.
The agency requires appropriate data and information to demonstrate that complex drug-device combination products meet the FDA's rigorous approval standards to ensure quality drug products that are safe and effective are available to patients.

FDA NEWS RELEASE

For Immediate Release: August 22nd, 2018
FDA approves first drug for neurotrophic keratitis, a rare eye disease

The FDA approved the first drug, Oxervate™ (cenegermin), for the treatment of neurotrophic keratitis, a rare disease affecting the cornea.
Neurotrophic keratitis is a degenerative disease resulting from a loss of corneal sensation. The loss of corneal sensation impairs corneal health causing progressive damage to the top layer of the cornea, including corneal thinning, ulceration, and perforation in severe cases. The prevalence of neurotrophic keratitis has been estimated to be less than five in 10,000 individuals.
The safety and efficacy of Oxervate™, a topical eye drop containing cenegermin, was studied in a total of 151 patients with neurotrophic keratitis in two, eight-week, randomized, controlled, multi-center, double-masked studies. In the first study, patients were randomized into three different groups. One group received Oxervate™, a second group received an eye drop with a different concentration of cenegermin, and the third group received an eye drop without cenegermin. In the second study, patients were randomized into two groups. One group was treated with Oxervate™ eye drops and the other group was treated with an eye drop without cenegermin. All eye drops in both studies were given six times daily in the affected eye(s) for eight weeks. In the first study, only patients with the disease in one eye were enrolled, while in the second study, patients with the disease in both eyes were treated in both eyes. Across both studies, complete corneal healing in eight weeks was demonstrated in 70% of patients treated with Oxervate™ compared to 28% of patients treated without cenegermin.
The most common adverse reactions in patients taking Oxervate™ are eye pain, ocular hyperemia (enlarged blood vessels in the white of the eyes), eye inflammation, and increased lacrimation (watery eyes).
Oxervate™ was granted Priority Review designation, under which the FDA's goal is to take action on an application within six months of application filing where the agency determines that the drug, if approved, would provide a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious condition. Oxervate™ also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted approval of Oxervate™ to Dompé farmaceutici SpA.

Safety Announcements

FDA warns about increased risk of cancer relapse with long-term use of azithromycin (Zithromax®, Zmax®) antibiotic after donor stem cell transplant

[08/30/2018] The FDA is warning that the antibiotic azithromycin (Zithromax®, Zmax®) should not be given long-term to prevent a certain inflammatory lung condition in patients with cancers of the blood or lymph nodes who undergo a donor stem cell transplant. Results of a clinical trial found an increased rate of relapse in cancers affecting the blood and lymph nodes, including death, in these patients. The FDA is reviewing additional data and will communicate their conclusions and recommendations when their review is complete.
The serious lung condition for which long-term azithromycin was being studied called bronchiolitis obliterans syndrome is caused by inflammation and scarring in the airways of the lungs, resulting in severe shortness of breath and dry cough. Cancer patients who undergo stem cell transplants from donors are at risk for bronchiolitis obliterans syndrome. The manufacturer of brand name azithromycin is providing a Dear Healthcare Provider letter on this safety issue to health care professionals who care for patients undergoing donor stem cell transplants.
Azithromycin is not approved for preventing bronchiolitis obliterans syndrome. It is an FDA-approved antibiotic used to treat many types of infections affecting the lungs, sinuses, skin, and other parts of the body. The drug has been used for more than 26 years. It is sold under the brand names Zithromax® and Zmax® and as generics by many different drug companies. It works by stopping the growth of bacteria that can cause infections.
There are no known effective antibiotic treatments for prophylaxis of bronchiolitis obliterans syndrome.
Health care professionals should not prescribe long-term azithromycin for prophylaxis of bronchiolitis obliterans syndrome to patients who undergo donor stem cell transplants because of the increased potential for cancer relapse and death.
Patients who have had a stem cell transplant should not stop taking azithromycin without first consulting with their health care professional. Doing so could be harmful without their health care professional's direct supervision. Patients should talk with their health care provider if they have any questions or concerns about taking this medicine.
Researchers in France identified this increased risk of cancer relapse and death while conducting a clinical trial investigating the effectiveness of long-term azithromycin to prevent bronchiolitis obliterans syndrome in

patients who undergo donor, or allogenic, stem cell transplants for cancers of the blood and lymph nodes. The researchers concluded that the risks of long-term azithromycin exposure after donor stem cell transplantation may exceed the benefits. The trial could not determine why the rates of cancer relapse and death were higher with azithromycin.
The researchers stopped the ALLOZITHRO trial approximately 13 months after the study completed enrollment of 480 patients because an unexpected increase in the rate of both cancer relapses and death was observed in patients taking azithromycin. Cancer relapse was observed in 77 patients (32.9%) with azithromycin treatment compared to 48 patients (20.8%) with placebo. A total of 95 patients died in the azithromycin treatment group versus 66 patients in the placebo group; thus, the 2-year survival rate was 56.6% in azithromycin-treated patients compared to 70.1% in those receiving a placebo. In the first few months of the trial, the death rate was about equal between those receiving azithromycin and placebo. However, an imbalance occurred subsequently and continued until the 2-year time point when the study was stopped.
To help the FDA track safety issues with medicines, the FDA urges health care professionals and patients to report side effects involving azithromycin and other drugs to the FDA MedWatch program.

Safety Announcements

FDA warns about rare occurrences of a serious infection of the genital area with SGLT2 inhibitors for diabetes

[08/29/2018] The FDA is warning that cases of a rare but serious infection of the genitals and area around the genitals have been reported with the class of type 2 diabetes medicines called sodium-glucose cotransporter-2 (SGLT2) inhibitors. This serious rare infection, called necrotizing fasciitis of the perineum, is also referred to as Fournier's gangrene. The FDA is requiring a new warning about this risk to be added to the prescribing information of all SGLT2 inhibitors and to the patient Medication Guide.
SGLT2 inhibitors are FDA-approved for use with diet and exercise to lower blood sugar in adults with type 2 diabetes. SGLT2 inhibitors lower blood sugar by causing the kidneys to remove sugar from the body through the urine. First approved in 2013, medicines in the SGLT2 inhibitor class include canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. In addition, empagliflozin is approved to lower the risk of death from heart attack and stroke in adults with type 2 diabetes and heart disease. Untreated, type 2 diabetes can lead to serious problems, including blindness, nerve and kidney damage, and heart disease.
Patients should **seek medical attention immediately** if they experience any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4° F or a general feeling of being unwell. These symptoms can worsen quickly, so it is important to seek treatment right away.
Health care professionals should assess patients for Fournier's gangrene if they present with the symptoms described above. If suspected, treatment should be started immediately with broad-spectrum antibiotics and surgical debridement if necessary. The SGLT2 inhibitor should be discontinued, blood glucose levels should be closely monitored, and appropriate alternative therapy for glycemic control should be provided.
Fournier's gangrene is an extremely rare but life-threatening bacterial infection of the tissue under the skin that surrounds muscles, nerves, fat, and blood vessels of the perineum. The bacteria usually get into the body through a cut or break in the skin, where they quickly spread and destroy the tissue they infect. Having diabetes is a risk factor for developing Fournier's gangrene; however, this condition is still rare among diabetic patients. Overall published literature about the occurrence of Fournier's gangrene for men and women is very limited. Publications report that Fournier's gangrene occurs in 1.6 out of 100,000 males annually in the United States, and most frequently occurs in males 50 to 79 years of age (3.3 out of 100,000). In the FDA's case series, however, they observed events in both women and men.
In the five years from March 2013 to May 2018, the FDA identified 12 cases of Fournier's gangrene in patients taking an SGLT2 inhibitor. This number includes only reports submitted to FDA and found in the medical literature, so there may be additional cases about which the FDA is unaware. In 2017, an estimated 1.7 million patients received a dispensed prescription for an SGLT2 inhibitor from outpatient retail pharmacies. Although most cases of Fournier's gangrene have previously been reported in men, the FDA's 12 cases included 7 men and 5 women. Fournier's gangrene developed within several months of the patients starting an SGLT2 inhibitor and the drug was stopped in most cases. All 12 patients were hospitalized and required surgery. Some patients required multiple disfiguring surgeries, some developed complications, and one patient died. In comparison, only six cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years.

To help FDA track safety issues with medicines, the FDA urges patients and health care professionals to report side effects involving SGLT2 inhibitors or other medicines to the FDA MedWatch program.

Current Drug Shortages Index (as of August 30th, 2018):

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

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

Folic Acid Injection	Currently in Shortage
Gemifloxacin Mesylate (Factive) Tablets	Currently in Shortage
Guanfacine Hydrochloride Tablets	Currently in Shortage
Heparin Sodium and Sodium Chloride 0.9% Injection	Currently in Shortage
Hydromorphone Hydrochloride Injection, USP	Currently in Shortage
Imipenem and Cilastatin for Injection, USP	Currently in Shortage
Isocarboxazid Tablets	Currently in Shortage
Ketamine Injection	Currently in Shortage
Ketoprofen Capsules	Currently in Shortage
Ketorolac Tromethamine Injection	Currently in Shortage
L-Cysteine Hydrochloride Injection	Currently in Shortage
Labetalol Hydrochloride Injection	Currently in Shortage
Leucovorin Calcium Lyophilized Powder for Injection	Currently in Shortage
Leuprolide Acetate Injection	Currently in Shortage
Lidocaine Hydrochloride (Xylocaine) and Dextrose Injection Solution-Premix Bags	Currently in Shortage
Lidocaine Hydrochloride (Xylocaine) Injection	Currently in Shortage
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	Currently in Shortage
Liotrix (Thyrolar) Tablets	Currently in Shortage
Lorazepam Injection, USP	Currently in Shortage
Magnesium Sulfate Injection	Currently in Shortage
Methadone Hydrochloride Injection	Currently in Shortage
Methocarbamol Tablets	Currently in Shortage
Methotrexate Sodium Injection	Currently in Shortage
Methyldopa Tablets	Currently in Shortage
Methylphenidate Hydrochloride (QUILLICHEW ER) Extended-Release Chewable Tab	Currently in Shortage
Methylphenidate Hydrochloride (QUILLIVANT XR) for Extended-Release Oral Susp	Currently in Shortage
Metoclopramide Injection, USP	Currently in Shortage
Metronidazole Injection, USP	Currently in Shortage
Molindone Hydrochloride Tablets	Currently in Shortage
Morphine Sulfate Injection, USP	Currently in Shortage
Multi-Vitamin Infusion (Adult and Pediatric)	Currently in Shortage
Mupirocin Calcium Nasal Ointment	Currently in Shortage
Ondansetron Hydrochloride Injection	Currently in Shortage
Pantoprazole (Protonix) Powder for Injection	Currently in Shortage
Penicillamine (Depen) Titratable Tablets	Currently in Shortage
Penicillin G Benzathine and Penicillin G Procaine (Bicillin C-R) Injection	Currently in Shortage
Penicillin G Procaine Injection	Currently in Shortage
Peritoneal Dialysis Solutions	Currently in Shortage
Phenytoin Sodium Injection, USP	Currently in Shortage
Phosphate Injection Products	Currently in Shortage
Piperacillin and Tazobactam (Zosyn) Injection	Currently in Shortage
Potassium Chloride Injection	Currently in Shortage
Potassium Phosphate Injection	Currently in Shortage
Procainamide Hydrochloride Injection, USP	Currently in Shortage
Progesterone Injection, USP	Currently in Shortage
Promethazine (Phenergan) Injection	Currently in Shortage
Ranitidine Injection, USP	Currently in Shortage

Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	Currently in Shortage
Rocuronium Bromide 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
Valsartan Tablets	Currently in Shortage
Zolpidem Tartrate (Edluar) Sublingual Tablets	Currently in Shortage