Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
May 10, 2017
4 p.m.

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 Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – May 10, 2017

DATE: May 1, 2017

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

Enclosed are the following items related to the May 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/Spring Pipeline Update – Appendix B

Action Item – Vote to Prior Authorize Fosamax® (Alendronate 40mg Tablets) – Appendix C

Action Item – Vote to Prior Authorize Byvalson™ (Nebivolol/Valsartan) and Qbrelis™ (Lisinopril Oral Solution) – Appendix D

Action Item – Vote to Prior Authorize Giazo® (Balsalazide Disodium Tablets) – Appendix E

Action Item – Vote to Prior Authorize Invokamet® XR (Canagliflozin/Metformin Extended-Release), Jentadueto® XR (Linagliptin/Metformin Extended-Release), Adlyxin® (Lixisenatide), Xultophy® 100/3.6 (Insulin Degludec/Liraglutide), Soliqua™ 100/33 (Insulin Glargine/Lixisenatide), Synjardy® XR (Empagliflozin/Metformin Extended-Release), and Qtern® (Dapagliflozin/Saxagliptin) – Appendix F

Annual Review of Lung Cancer Medications and 30-Day Notice to Prior Authorize Tarceva® (Erlotinib), Gilotrif® (Afatinib), Tagrisso™ (Osimertinib), Xalkori® (Crizotinib), Zykadia® (Ceritinib), Alecensa® (Alectinib), Cyramza® (Ramucirumab), Tecentriq® (Atezolizumab), and Alunbrig™ (Brigatinib) – Appendix G

30-Day Notice to Prior Authorize Kuvan® (Sapropterin) – Appendix H

30-Day Notice to Prior Authorize Lumizyme® (Alglucosidase Alfa Injection) – Appendix I

30-Day Notice to Prior Authorize Alpha$_1$-Proteinase Inhibitors: Aralast NP™, Glassia™, Prolastin®-C, and Zemaira® – Appendix J

Annual Review of Antiparasitic Medications and 30-Day Notice to Prior Authorize Impavido® (Miltefosine) – Appendix K

Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize ColPrep™ Kit (Sodium Sulfate/Potassium Sulfate/Magnesium Sulfate) – Appendix L

30-Day Notice to Prior Authorize Elaprase® (Idursulfase) – Appendix M

Annual Review of Botulinum Toxins – Appendix N

Annual Review of Gaucher Disease Medications – Appendix O

Annual Review of Gonadotropin-Releasing Hormone (GnRH) Medications – Appendix P

FDA and DEA Updates – Appendix Q

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – May 10, 2017 @ 4:00 p.m.

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. Acknowledgement 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. April 12, 2017 DUR Minutes – Vote
B. April 12, 2017 DUR Recommendations Memorandum

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

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

A. Medication Coverage Activity for April 2017
B. Pharmacy Help Desk Activity for April 2017
C. 2017 Spring Pipeline Update

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

5. Action Item – Vote to Prior Authorize Fosamax® (Alendronate 40mg Tablets) – See Appendix C

A. Introduction
B. College of Pharmacy Recommendations

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

6. Action Item – Vote to Prior Authorize Byvalson™ (Nebivolol/Valsartan) and Qbrelis™ (Lisinopril Oral Solution) – See Appendix D

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Giazo® (Balsalazide Disodium Tablets) – See Appendix E

A. Introduction
B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Invokamet® XR (Canagliflozin/Metformin Extended-Release), Jentadueto® XR (Linagliptin/Metformin Extended-Release), Adlyxin® (Lixisenatide), Xultophy® 100/3.6 (Insulin Degludec/Liraglutide), Soliqua™ 100/33 (Insulin Glargine/Lixisenatide), Synjardy® XR (Empagliflozin/Metformin Extended-Release), and Qtern® (Dapagliflozin/ Saxagliptin) – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

9. Annual Review of Lung Cancer Medications and 30-Day Notice to Prior Authorize Tarceva® (Erlotinib), Gilotrif® (Afatinib), Tagrisso™ (Osimertinib), Xalkori® (Crizotinib), Zykadia® (Ceritinib), Alecensa® (Alectinib), Cyramza® (Ramucirumab), Tecentriq® (Atezolizumab), and Alunbrig™ (Brigatinib) – See Appendix G

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

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

10. 30-Day Notice to Prior Authorize Kuvan® (Sapropterin) – See Appendix H

A. Phenylketonuria
B. Utilization of Kuvan® (Sapropterin)
C. Market News and Updates
D. Kuvan® (Sapropterin) Product Summary
E. College of Pharmacy Recommendations

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

11. 30-Day Notice to Prior Authorize Lumizyme® (Alglucosidase Alfa Injection) – See Appendix I

A. Pompe Disease (Acid Alpha-Glucosidase Deficiency)
B. Utilization of Lumizyme® (Alglucosidase Alfa)
C. Market News and Updates
D. Lumizyme® (Alglucosidase Alfa) Product Summary
E. College of Pharmacy Recommendations

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

12. 30-Day Notice to Prior Authorize Alpha$_1$-Proteinase Inhibitors: Aralast NP™, Glassia™, Prolastin®-C, and Zemaira® – See Appendix J

A. Alpha$_1$ Antitrypsin Deficiency
B. Utilization of Alpha$_1$-Proteinase Inhibitors
C. Market News and Updates
D. Alpha$_1$-Proteinase Inhibitors Class Summary
E. College of Pharmacy Recommendations
F. Utilization Details of Alpha$_1$-Proteinase Inhibitors

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

13. Annual Review of Antiparasitic Medications and 30-Day Notice to Prior Authorize Impavido® (Miltefosine) – See Appendix K

A. Current Prior Authorization Criteria
B. Utilization of Antiparasitic Medications
C. Prior Authorization of Antiparasitic Medications
D. Leishmaniasis Background Information
E. Impavido® (Miltefosine) Product Summary
F. College of Pharmacy Recommendations
G. Utilization Details of Antiparasitic Medications

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

14. Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize ColPrep™ Kit (Sodium Sulfate/Potassium Sulfate/Magnesium Sulfate) – See Appendix L

A. Current Prior Authorization Criteria
B. Utilization of Bowel Preparation Medications
C. Market News and Updates
D. Prior Authorization of Bowel Preparation Medications
E. ColPrep™ Kit (Sodium Sulfate/Potassium Sulfate/Magnesium Sulfate) Product Summary

F. College of Pharmacy Recommendations
G. Utilization Details of Bowel Preparation Medications

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

15. 30-Day Notice to Prior Authorize Elaprase® (Idursulfase) – See Appendix M

A. Introduction
B. Utilization of Elaprase® (Idursulfase)
C. Elaprase® (Idursulfase) Product Summary
D. College of Pharmacy Recommendations

Non-presentation; Questions Only:

16. Annual Review of Botulinum Toxins – See Appendix N

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

Non-presentation; Questions Only:

17. Annual Review of Gaucher Disease Medications – See Appendix O

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

Non-presentation; Questions Only:

18. Annual Review of Gonadotropin-Releasing Hormone (GnRH) Medications – See Appendix P

A. Introduction
B. FDA Approved GnRH Options for Treatment of Central Precocious Puberty or Endometriosis
C. Current Prior Authorization Criteria
D. Utilization of GnRH Medications
E. Prior Authorization of GnRH Medications
F. Market News and Updates
G. College of Pharmacy Recommendations
H. Utilization Details of GnRH Medications

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

19. FDA and DEA Updates – See Appendix Q

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

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

A. Various Special Formulations
B. ADHD and Narcolepsy Medications
C. Atypical Antipsychotic Medications
D. Prostate Cancer Medications
E. H.P. Acthar® Gel (Respository Corticotropin Injection)
F. Ingrezza™ (Valbenazine)
G. Inhaled Cystic Fibrosis Medications
H. Austedo™ (Deutetrabenazine)
I. Tazorac® (Tazarotene)

**Future business subject to change.*

21. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF APRIL 12, 2017

BOARD MEMBERS:	PRESENT	ABSENT
Theresa Garton, M.D.	x	
Carla Hardzog-Britt, M.D.		x
Anetta Harrell, Pharm.D.	x	
Ashley Huddleston, Pharm.D., BCOP	x	
John Muchmore, M.D., Ph.D.; Chairman	x	
Lee Munoz, Pharm.D.	x	
James Osborne, Pharm.D.	x	
Paul Louis Preslar, D.O., MBA; Vice Chairman	x	
Bruna Varalli-Claypool, MHS, PA-C		x
Eric Winegardner, D.Ph.	x	

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Melissa Abbott, Pharm.D.; Clinical Pharmacist	x	
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Wendi Chandler, Pharm.D.; Clinical Pharmacist	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Erin Ford, 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	
Stephanie Nichols, 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
Corby Thompson, Pharm.D.	x	
Visiting Pharmacy Student(s): Not applicable		

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	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	
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist	x	
Garth Splinter, M.D.; M.B.A.; Deputy Chief Executive Officer	x	
Joseph Young, Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Danielle Walters, Sanofi	Brandon Ross, Merck	Aaron Shaw, BI
David Truong, Intern SWOSU	Paul Gomez, Family Member	Jim Dunlap, PhRMA
Walkidia Gomez, Family Member	Heather Yost, Family Member	David Large, Supernus
Eileen O'Connor, Biogen	Christy Barker, Family Member	Gay Thomas, BMS
Jim Chapman, AbbVie	Bennie Barker, Family Member	Kari Suttee, Novartis
Nima Nabavi, Novo Nordisck	Greg Giraud, Alexion	Nicole Wilkerson, Novartis
Matt Forney, Merck	Tyler Craddock, The Medicines Co.	Mai Duong, Novartis
Torey Batts, Teva	Marc Parker, Sunovion	Eric Gardner, Vertex
Andrew Thompson, Celgene	Marla Weiderman, NNI	Jignsh Patel, Novo Nordisk
Terry McCurren, Otsuka America	Davondra Owens, Family Member	Ron Schnare, Shire
Jason Schwier, Amgen	Josh Diesselhorst, Novo Nordisk	Kimi Vesta, Sanofi
Shawn Hansen, Novo Nordisk	Jennifer Norman, M.D., Integris	

PRESENT FOR PUBLIC COMMENT:	
Kimi Vesta	Sanofi
Brandon Ross	Merck
Eileen O'Connor	Biogen
Shawn Hansen	Novo Nordisk
Paul Gomez	Family Member
Torey Batts	Teva
Jennifer Norman, M.D.	Integris/MDA Center

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 NO. 6 SPEAKER: EILEEN O'CONNOR
2B: AGENDA NO. 6 SPEAKER: PAUL GOMEZ
2C: AGENDA NO. 6 SPEAKER: JENNIFER NORMAN
2D: AGENDA NO. 8 SPEAKER: BRANDON ROSS
2E: AGENDA NO. 12 SPEAKER: KIMI VESTA
2F: AGENDA NO. 12 SPEAKER: SHAWN HANSEN
2G: AGENDA NO. 16 SPEAKER: TOREY BATTS

ACTION: NONE REQUIRED

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

3A: MARCH 8, 2017 DUR MINUTES – VOTE
3B: MARCH 8, 2017 DUR RECOMMENDATIONS MEMORANDUM
3C: CORRESPONDENCE

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **STATE FISCAL YEAR (SFY) 2018 APPROPRIATION SCENARIOS AND ACCESS TO CARE**

Materials included in agenda packet; presented by Carrie Evans, Tywanda Cox

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) SAFETY MAILING UPDATE**

5A: MEDICATION COVERAGE ACTIVITY FOR MARCH 2017

5B: PHARMACY HELP DESK ACTIVITY FOR MARCH 2017
5C: NONSTEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) SAFETY MAILING UPDATE
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE SPINRAZA™ (NUSINERSEN)
6A: INTRODUCTION
6B: MOTOR FUNCTION TESTS USED IN NUSINERSEN CLINICAL TRIALS
6C: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
Dr. Harrell moved to approve; seconded by Dr. Winegardner
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE ZINBRYTA™ (DACLIZUMAB)
7A: INTRODUCTION
7B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Abbott
Dr. Harrell moved to approve; seconded by Dr. Munoz
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE ZINPLAVA™ (BEZLOTOXUMAB)
8A: INTRODUCTION
8B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Garton moved to approve; seconded by Dr. Preslar
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE HYDROXYPROGESTERONE CAPROATE INJECTION (GENERIC DELALUTIN®)
9A: INTRODUCTION
9B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Adams
Dr. Winegardner moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: VOTE TO UPDATE ADEMPAS® (RIOCIGUAT) APPROVAL CRITERIA
10A: INTRODUCTION
10B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nawaz
Dr. Munoz moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: FISCAL YEAR 2016 ANNUAL REVIEW OF SOONERCARE PHARMACY BENEFIT
11A: SUMMARY
11B: MEDICAID DRUG REBATE PROGRAM
11C: ORPHAN DRUGS
11D: TRADITIONAL VERSUS SPECIALTY PHARMACY PRODUCTS
11E: TOP 10 THERAPEUTIC CLASSES BY REIMBURSEMENT
11F: TOP 10 MEDICATIONS BY REIMBURSEMENT
11G: COST PER CLAIM
11H: CONCLUSION
11I: TOP 100 REIMBURSED DRUGS BY FISCAL YEAR
11J: TOP 50 MEDICATIONS BY TOTAL NUMBER OF CLAIMS
11K: TOP TRADITIONAL THERAPEUTIC CLASSES BY FISCAL YEAR

11L: TOP SPECIALTY THERAPEUTIC CLASSES BY FISCAL YEAR
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

<u>AGENDA ITEM NO. 12:</u> ANNUAL REVIEW OF DIABETES MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE INVOKAMET® XR (CANAGLIFLOZIN/METFORMIN EXTENDED-RELEASE), JENTADUETO® XR (LINAGLIPTIN/METFORMIN EXTENDED-RELEASE), ADLYXIN® (LIXISENATIDE), XULTOPHY® 100/3.6 (INSULIN DEGLUDEC/LIRAGLUTIDE), SOLIQUA™ 100/33 (INSULIN GLARGINE/LIXISENATIDE), SYNJARDY® XR (EMPAGLIFLOZIN/METFORMIN EXTENDED-RELEASE), AND QTERN® (DAPAGLIFLOZIN/SAXAGLIPTIN)
12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF DIABETES MEDICATIONS
12C: PRIOR AUTHORIZATION OF DIABETES MEDICATIONS
12D: MARKET NEWS AND UPDATES
12E: PRODUCT SUMMARIES
12F: COLLEGE OF PHARMACY RECOMMENDATIONS
12G: UTILIZATION DETAILS OF NON-INSULIN DIABETES MEDICATIONS
12H: UTILIZATION DETAILS OF INSULIN MEDICATIONS
Materials included in agenda packet; presented by Dr. Nawaz
ACTION: NONE REQUIRED

<u>AGENDA ITEM NO. 13:</u> ANNUAL REVIEW OF ULCERATIVE COLITIS (UC) MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE GIAZO® (BALSALAZIDE DISODIUM TABLETS)
13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF UC MEDICATIONS
13C: PRIOR AUTHORIZATION OF UC MEDICATIONS
13D: MARKET NEWS AND UPDATES
13E: GIAZO® (BALSALAZIDE) PRODUCT SUMMARY
13F: COLLEGE OF PHARMACY RECOMMENDATIONS
13G: UTILIZATION DETAILS OF UC MEDICATIONS
Materials included in agenda packet; presented by Dr. Nawaz
ACTION: NONE REQUIRED

<u>AGENDA ITEM NO. 14:</u> ANNUAL REVIEW OF ANTIHYPERTENSIVE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE BYVALSON™ (NEBIVOLOL/VALSARTAN) AND QBRELIS™ (LISINOPRIL ORAL SOLUTION)
14A: CURRENT PRIOR AUTHORIZATION CRITERIA
14B: UTILIZATION OF ANTIHYPERTENSIVE MEDICATIONS
14C: PRIOR AUTHORIZATION OF ANTIHYPERTENSIVE MEDICATIONS
14D: MARKET NEWS AND UPDATES
14E: BYVALSON™ (NEBIVOLOL/VALSARTAN) PRODUCT SUMMARY
14F: QBRELIS™ (LISINOPRIL ORAL SOLUTION) PRODUCT SUMMARY
14G: COLLEGE OF PHARMACY RECOMMENDATIONS
14H: UTILIZATION DETAILS OF ANTIHYPERTENSIVE MEDICATIONS
Materials included in agenda packet; presented by Dr. Abbott
ACTION: NONE REQUIRED

<u>AGENDA ITEM NO. 15:</u> ANNUAL REVIEW OF OSTEOPOROSIS MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE FOSAMAX® (ALENDRONATE 40MG TABLETS)
15A: CURRENT PRIOR AUTHORIZATION CRITERIA
15B: UTILIZATION OF OSTEOPOROSIS MEDICATIONS
15C: PRIOR AUTHORIZATION OF OSTEOPOROSIS MEDICATIONS
15D: MARKET NEWS AND UPDATES
15E: COST COMPARISON

15F: COLLEGE OF PHARMACY RECOMMENDATIONS
15G: UTILIZATION DETAILS OF OSTEOPOROSIS MEDICATIONS
Materials included in agenda packet; presented by Dr. Chandler
ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: ANNUAL REVIEW OF GRANULOCYTE COLONY-STIMULATING FACTORS (G-CSFS)
16A: CURRENT PRIOR AUTHORIZATION CRITERIA
16B: UTILIZATION OF G-CSFS
16C: PRIOR AUTHORIZATION OF G-CSFS
16D: MARKET NEWS AND UPDATES
16E: COLLEGE OF PHARMACY RECOMMENDATIONS
16F: UTILIZATION DETAILS OF G-CSFS
Materials included in agenda packet; presented by Dr. Adams
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: ANNUAL REVIEW OF IDIOPATHIC PULMONARY FIBROSIS (IPF) MEDICATIONS
17A: INTRODUCTION
17B: CURRENT PRIOR AUTHORIZATION CRITERIA
17C: UTILIZATION OF IPF MEDICATIONS
17D: PRIOR AUTHORIZATION OF IPF MEDICATIONS
17E: MARKET NEWS AND UPDATES
17F: COLLEGE OF PHARMACY RECOMMENDATIONS
17G: UTILIZATION DETAILS OF IPF MEDICATIONS
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: ANNUAL REVIEW OF STRENSIQ® (ASFOTASE ALFA)
18A: INTRODUCTION
18B: CURRENT PRIOR AUTHORIZATION CRITERIA
18C: UTILIZATION OF STRENSIQ® (ASFOTASE ALFA)
18D: PRIOR AUTHORIZATION OF STRENSIQ® (ASFOTASE ALFA)
18E: MARKET NEWS AND UPDATES
18F: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: FDA AND DEA UPDATES
Materials included in agenda packet; presented by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 20: FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)
20A: BOWEL PREPARATION MEDICATIONS
20B: LUNG CANCER MEDICATIONS
20C: GAUCHER DISEASE MEDICATIONS
20D: ALPHA$_1$ PROTEINASE INHIBITORS
20E: BOTULINUM TOXINS
20F: GONADOTROPIN RELEASING HORMONE MEDICATIONS
20G: ELAPRASE® (IDURSULFASE)
20H: ANTIPARASITIC MEDICATIONS
20I: LUMIZYME® (ALGLUCOSIDASE ALFA)
Future business subject to change.

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

AGENDA ITEM NO. 21: ADJOURNMENT
The meeting was adjourned at 5:40 pm.

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

Memorandum

Date: April 13, 2017

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

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

Subject: DUR Board Recommendations from Meeting of April 12, 2017

Recommendation 1: Nonsteroidal Anti-Inflammatory Drug (NSAID) Safety Mailing Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Spinraza™ (Nusinersen)

MOTION CARRIED. Approval was not unanimous.

The College of Pharmacy recommends the prior authorization of Spinraza™ (nusinersen) with the following criteria, with the addition of #3 based on the recommendation from the Drug Utilization Review (DUR) Board at the March 2017 DUR meeting:

Spinraza™ (Nusinersen) Approval Criteria:

1. A diagnosis of spinal muscular atrophy (SMA):
    a. Type I; or
    b. Type II; or
    c. Type III with symptoms; and
2. Molecular genetic testing to confirm biallelic pathogenic variants in the survival motor neuron gene 1 (*SMN1*); and

3. Member is not currently dependent on permanent ventilation; and
4. Spinraza™ must be prescribed by a neurologist or specialist with expertise in treatment of SMA (or be an advanced care practitioner with a supervising physician who is a neurologist or specialist with expertise in treatment of SMA); and
5. Platelet count, coagulation laboratory testing, and quantitative spot urine protein testing at baseline and prior to each dose and verification that levels are acceptable to the prescriber; and
6. Spinraza™ must be administered in a healthcare facility by a specialist experienced in performing lumbar punctures; and
7. A baseline assessment must be provided using at least one of the following exams as functionally appropriate:
    a. Hammersmith Infant Neurological Exam (HINE); or
    b. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); or
    c. Upper Limb Module (ULM) Test; or
    d. Hammersmith Functional Motor Scale Expanded (HFMSE); and
8. Initial authorizations will be for the duration of six months, at which time the prescriber must verify the member is responding to the medication as demonstrated by clinically-significant improvement or maintenance of function from pretreatment baseline status using the same exam as performed at baseline assessment:
    a. Hammersmith Infant Neurological Exam (HINE); or
    b. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND); or
    c. Upper Limb Module (ULM) Test; or
    d. Hammersmith Functional Motor Scale Expanded (HFMSE); and
9. Approval quantity will be based on Spinraza™ prescribing information and FDA approved dosing regimen.

Recommendation 3: Vote to Prior Authorize Zinbryta™ (Daclizumab)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Zinbryta™ (daclizumab) with the following criteria:

Zinbryta™ (Daclizumab) Approval Criteria:

1. An FDA approved diagnosis of relapsing forms of Multiple Sclerosis (MS); and
2. Member must have had an inadequate response to two or more medications indicated for the treatment of MS; and
3. The prescriber must agree to monitor serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and total bilirubin levels prior to starting treatment, monthly, and for at least six months after treatment; and
4. Member must not have pre-existing hepatic disease (including hepatitis B or C) or hepatic impairment including ALT or AST at least two times the upper limit of normal; and
5. Member, prescriber, and pharmacy must all enroll in the Zinbryta™ REMS Program and maintain enrollment throughout therapy.

Additionally, the College of Pharmacy recommends updating the existing prior authorization criteria for Gilenya® (fingolimod) and Tecfidera® (dimethyl fumarate) with the changes noted in red:

Gilenya® (Fingolimod) Approval Criteria:

1. An FDA approved diagnosis of relapsing forms of Multiple Sclerosis (MS) with at least one relapse in the previous 12 months, or transitioning from existing MS therapy; and
2. Approvals will not be granted for concurrent use with other disease-modifying therapies; and
3. The first dose should be observed in the doctor's office for signs and symptoms of bradycardia for six hours after first dose; and
4. Verification from the prescriber that member has no active infection(s); and
5. Complete blood counts (CBC) and verification that levels are acceptable to the prescriber; and
6. Liver function tests and verification that levels are acceptable to the prescriber; and
7. Compliance will be checked for continued approval every six months.

Tecfidera® (Dimethyl Fumarate) Approval Criteria:

1. An FDA approved diagnosis of relapsing forms of Multiple Sclerosis (MS); and
2. Approvals will not be granted for concurrent use with other disease-modifying therapies; and
3. Verification from the prescriber that member has no active infection(s); and
4. Complete blood counts (CBC) and verification that levels are acceptable to the prescriber; and
5. Serum aminotransferase, alkaline phosphatase, and total bilirubin levels and verification that levels are acceptable to the prescriber; and
6. Compliance will be checked for continued approval every six months; and
7. A quantity limit of 60 tablets per 30 days will apply.

Recommendation 4: Vote to Prior Authorize Zinplava™ (Bezlotoxumab)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Zinplava™ (bezlotoxumab) with the following criteria:

Zinplava™ (Bezlotoxumab) Approval Criteria:

1. An FDA approved diagnosis of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment of CDI and are at a high risk for CDI recurrence; and
    a. Prescriber must document the member has one or more of the following risk factors for high risk of CDI recurrence:
        i. Age of 65 years or older; or
        ii. One or more episodes of CDI within the six months prior to the episode under treatment; or
        iii. Need for ongoing therapy with concomitant antibiotics during treatment for CDI; or

iv. Severe underlying medical disorders; or
v. Immunocompromised; or
vi. Clinically severe CDI (Zar score ≥ 2); and

2. Current or planned antibacterial drug for CDI must be provided on the prior authorization request to ensure medication is within standard of care; and
3. Prescriber must document that Zinplava™ (bezlotoxumab) will be administered while the member is receiving antibacterial drug treatment of CDI; and
4. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Recommendation 5: Vote to Prior Authorize Hydroxyprogesterone Caproate Injection (Generic Delalutin®)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of hydroxyprogesterone caproate 250mg/mL injection with the following criteria:

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

1. An FDA approved indication of one of the following in non-pregnant women:
    a. For the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV); or
    b. For the management of amenorrhea (primary and secondary) or abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer; or
    c. As a test for endogenous estrogen production or for the production of secretory endometrium and desquamation; and
2. The quantity approved will be patient-specific depending on patient diagnosis, maximum recommended dosage, and manufacturer packaging.
3. Requests for the prevention of preterm birth in pregnant women with a history of previous singleton spontaneous preterm delivery (SPTD) prior to 37 weeks gestation will not be approved for generic Delalutin® and should be resubmitted for authorization of Makena® (hydroxyprogesterone caproate).

Recommendation 6: Vote to Update Adempas® (Riociguat) Approval Criteria

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes noted in red to the Adempas® (riociguat) approval criteria:

Adempas® (Riociguat) Approval Criteria:

1. An FDA approved diagnosis of pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH); and
    a. Members with a diagnosis of PAH must have previous failed trials of at least one of each of the following categories:

i. Revatio® (sildenafil) or Adcirca® (tadalafil); and
ii. Letairis® (ambrisentan) or Tracleer® (bosentan); and

b. Members with a diagnosis of CTEPH must currently be on anticoagulation therapy; and

2. Medical supervision by a pulmonary specialist or cardiologist; and
3. Member must not be on any concurrent phosphodiesterase (PDE) inhibitor therapy; and
4. Member must not have a diagnosis of pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP); and
5. Female members and all healthcare professionals (prescribers and dispensing pharmacies) must be enrolled in the Adempas® REMS program.
6. A quantity limit of 90 tablets per 30 days will apply.

Recommendation 7: Fiscal Year 2016 Annual Review of SoonerCare Pharmacy Benefit

NO ACTION REQUIRED.

Recommendation 8: Annual Review of Diabetes Medications and 30-Day Notice to Prior Authorize Invokamet® XR (Canagliflozin/Metformin Extended-Release), Jentadueto® XR (Linagliptin/Metformin Extended-Release), Adlyxin® (Lixisenatide), Xultophy® 100/3.6 (Insulin Degludec/Liraglutide), Soliqua™ 100/33 (Insulin Glargine/Lixisenatide), Synjardy® XR (Empagliflozin/Metformin Extended-Release), and Qtern® (Dapagliflozin/Saxagliptin)

NO ACTION REQUIRED.

Recommendation 9: Annual Review of Ulcerative Colitis (UC) Medications and 30-Day Notice to Prior Authorize Giazo® (Balsalazide Disodium Tablets)

NO ACTION REQUIRED.

Recommendation 10: Annual Review of Antihypertensive Medications and 30-Day Notice to Prior Authorize Byvalson™ (Nebivolol/Valsartan) and Qbrelis™ (Lisinopril Oral Solution)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Osteoporosis Medications and 30-Day Notice to Prior Authorize Fosamax® (Alendronate 40mg Tablets)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Granulocyte Colony-Stimulating Factors (G-CSFs)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Idiopathic Pulmonary Fibrosis (IPF) Medications

NO ACTION REQUIRED.

Esbriet® (Pirfenidone) Approval Criteria:

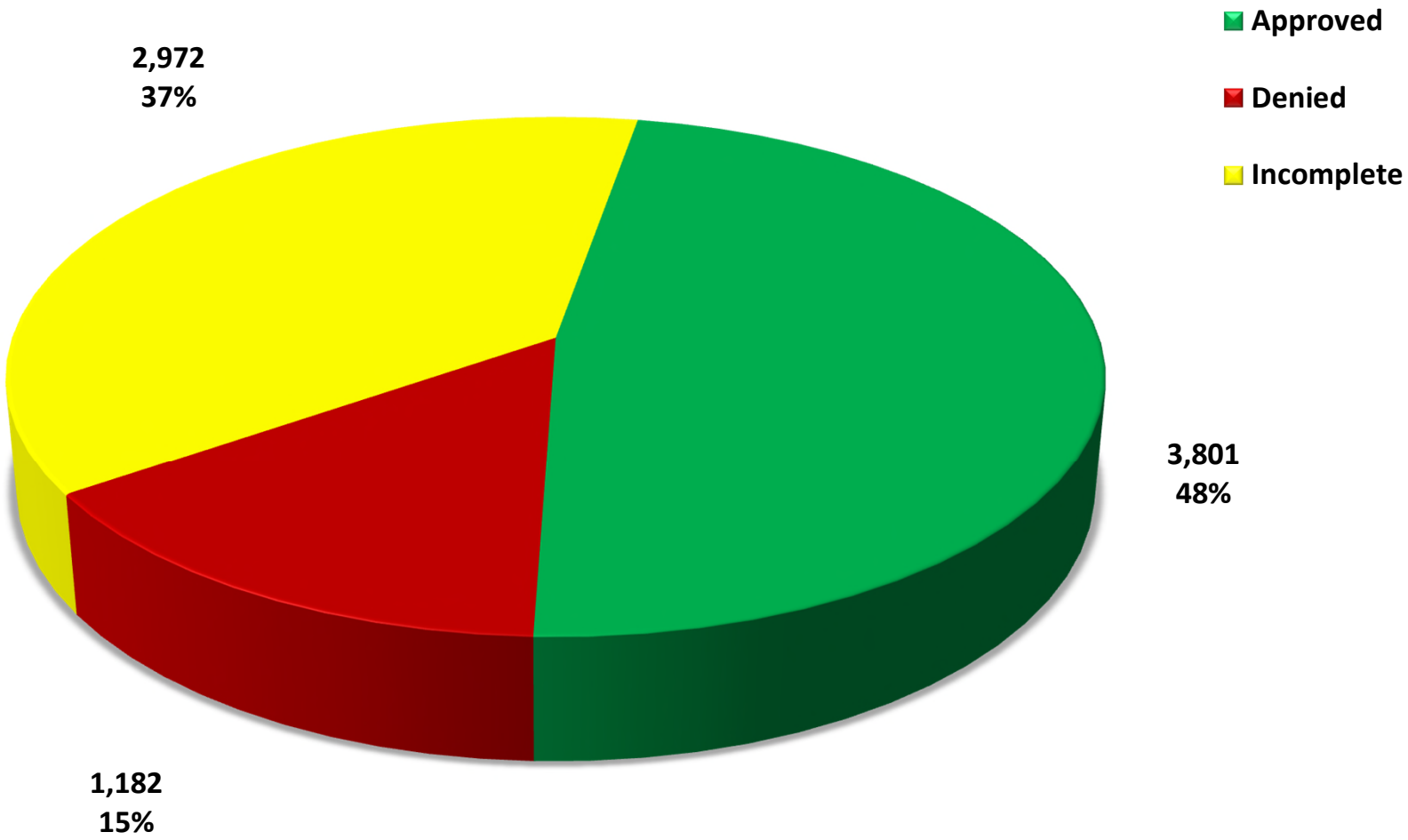
1. An FDA approved diagnosis of idiopathic pulmonary fibrosis (IPF); and
2. Member must be 18 years of age or older; and
3. Medication must be prescribed by a pulmonologist or pulmonary specialist; and
4. A quantity limit of 270 capsules or tablets per 30 days will apply for the 267mg strength capsules and tablets, and a quantity limit of 90 tablets per 30 days will apply for the 801mg strength tablets.

Recommendation 14: Annual Review of Strensiq® (Asfotase Alfa)

NO ACTION REQUIRED.

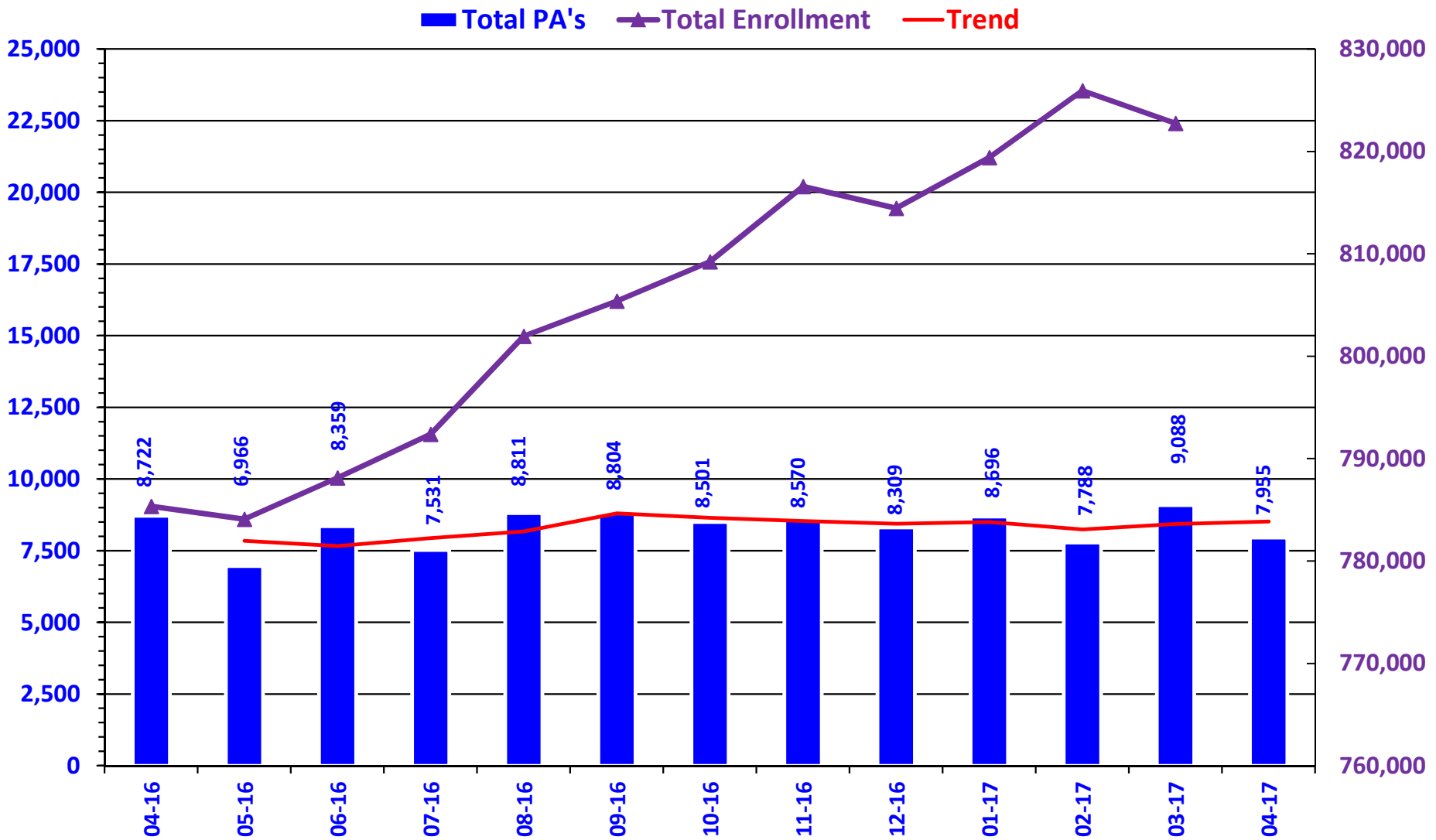
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: APRIL 2017



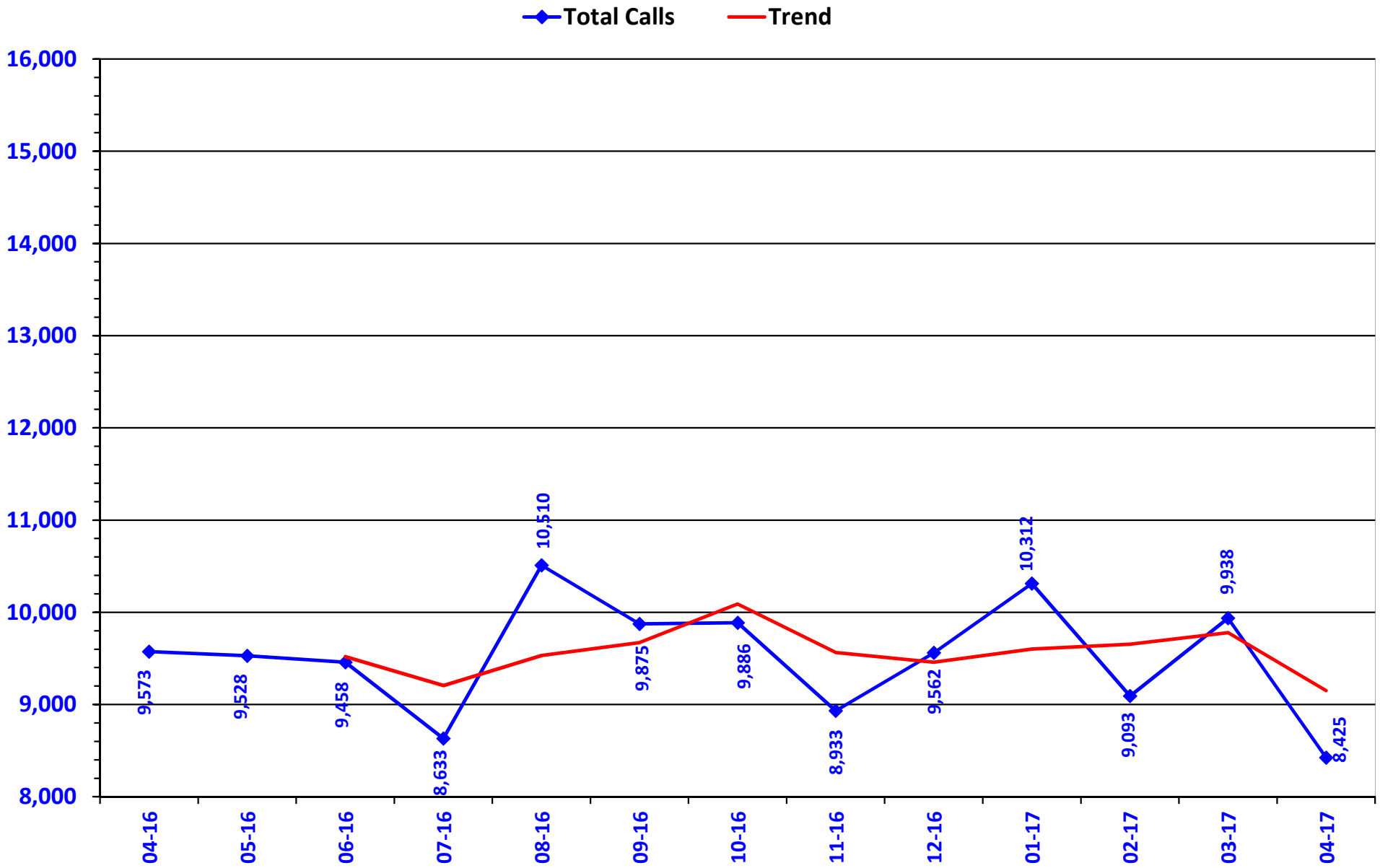
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: APRIL 2016 – APRIL 2017



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
APRIL 2016 – APRIL 2017



Prior Authorization Activity

4/1/2017 Through 4/30/2017

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	126	17	23	86	325
Analgesic - NonNarcotic	19	0	3	16	0
Analgesic - Narcotic	439	222	50	167	161
Angiotensin Receptor Antagonist	19	6	4	9	335
Antiasthma	48	6	17	25	358
Antibiotic	21	6	4	11	262
Anticonvulsant	91	32	20	39	337
Antidepressant	76	11	20	45	345
Antidiabetic	197	82	35	80	357
Antihistamine	260	218	6	36	346
Antimigraine	31	2	11	18	8
Antineoplastic	56	42	3	11	164
Antiulcers	151	32	40	79	196
Antiviral	79	38	10	31	8
Anxiolytic	66	32	10	24	246
Atypical Antipsychotics	227	123	11	93	317
Biologics	111	63	12	36	308
Bladder Control	48	15	9	24	339
Blood Thinners	249	135	21	93	324
Botox	43	34	2	7	348
Buprenorphine Medications	273	204	9	60	69
Cardiovascular	102	47	15	40	285
Cephalosporins	13	6	1	6	7
Chronic Obstructive Pulmonary Disease	196	24	53	119	335
Constipation/Diarrhea Medications	151	25	63	63	121
Contraceptive	25	20	0	5	337
Dermatological	103	17	48	38	163
Diabetic Supplies	533	293	19	221	205
Endocrine & Metabolic Drugs	79	63	2	14	131
Erythropoietin Stimulating Agents	27	16	3	8	105
Fibromyalgia	179	28	93	58	330
Fish Oils	14	1	6	7	360
Gastrointestinal Agents	145	23	52	70	178
Genitourinary Agents	15	4	7	4	153
Glaucoma	14	4	5	5	175
Growth Hormones	90	67	9	14	149
Hepatitis C	90	34	17	39	7
HFA Rescue Inhalers	78	17	20	41	357
Insomnia	39	1	13	25	20
Insulin	82	21	18	43	330
Miscellaneous Antibiotics	30	5	5	20	81
Multiple Sclerosis	64	21	9	34	177
Muscle Relaxant	42	8	17	17	65
Nasal Allergy	93	18	29	46	255
Neurological Agents	44	21	8	15	341
NSAIDs	167	26	48	93	240
Ocular Allergy	39	2	12	25	223
Osteoporosis	4	1	1	2	355
Other*	292	75	61	156	278
Otic Antibiotic	33	6	3	24	7

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Respiratory Agents	18	14	0	4	151
Statins	56	18	12	26	313
Stimulant	762	400	86	276	303
Testosterone	42	11	16	15	324
Topical Antifungal	33	6	7	20	74
Topical Corticosteroids	130	6	32	92	165
Vitamin	75	22	26	27	255
Pharmacotherapy	63	58	0	5	286
Emergency PAs	0	0	0	0	
Total	**6,592**	**2,749**	**1,136**	**2,707**	
Overrides					
Brand	37	26	2	9	269
Diabetic Supplies	4	1	0	3	360
Dosage Change	303	281	0	22	13
High Dose	6	5	0	1	253
Ingredient Duplication	24	16	0	8	9
Lost/Broken Rx	106	95	3	8	12
NDC vs Age	205	144	8	53	259
Nursing Home Issue	53	49	0	4	12
Opioid Quantity	28	23	2	3	150
Other*	28	27	0	1	12
Quantity vs. Days Supply	545	375	25	145	243
STBS/STBSM	10	5	1	4	37
Stolen	16	12	2	2	18
Temporary Unlock	1	1	0	0	27
Third Brand Request	29	16	5	8	13
Overrides Total	**1,363**	**1,052**	**46**	**265**	
Total Regular PAs + Overrides	**7,955**	**3,801**	**1,182**	**2,972**	

Denial Reasons	
Unable to verify required trials.	2,280
Does not meet established criteria.	1,206
Lack required information to process request.	667

Other PA Activity	
Duplicate Requests	614
Letters	7,209
No Process	4
Changes to existing PAs	560
Helpdesk Initiated Prior Authorization	642
PAs Missing Information	42

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

2017 Spring Pipeline Update

Oklahoma Health Care Authority
May 2017

Introduction

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

Xeglyze™ (Abametapir)[1,2]

Anticipated Indication(s): Metalloproteinase inhibitor with ovicidal and lousicidal activity (one-time, topical lice treatment)

Clinical Trials: Abametapir was evaluated in two double-blind, randomized, vehicle-controlled Phase 3 studies enrolling 704 subjects six months and older in the United States. Compared to vehicle-lotion, a single, ten minute application of abametapir resulted in a statistically significant increase in the proportion of subjects cleared of lice. A total 81.5% of patients who received abametapir without nit-combing remained lice free at all follow up visits through day 14. No serious adverse events related to abametapir treatment were reported.

Place in Therapy: Abametapir differs from other head lice treatments by having both ovicidal and lousicidal activity and therefore requiring only one treatment and no nit combing. Additionally, abametapir has a different mechanism of action with no known resistance. Resistance to some of the currently available head lice treatments has created a need for novel head lice treatment options.

Projected FDA Decision: 09/14/2016 (currently pending)

SoonerCare Impact: During fiscal year 2016, a total of 18,946 members utilized pediculicide medications, accounting for $2,356,362.36 in drug spending and an average cost per claim of $90.05.

Glecaprevir/Pibrentasvir[1,3,4,5]

Anticipated Indication(s): Once daily combination of glecaprevir, a NS3/4A protease inhibitor, and pibrentasvir, a NS5A inhibitor, for pan-genotypic treatment (genotypes 1 through 6) of chronic hepatitis C virus (HCV) and in patients with treatment challenges such as those with previous treatment failure or those with severe chronic kidney disease (CKD)

Clinical Trials: Eight weeks of glecaprevir/pibrentasvir treatment in noncirrhotic, treatment-naïve patients with chronic HCV (genotypes 1 through 6) demonstrated 97.5% (n = 693/711) of patients achieved sustained virologic response (SVR). Patients with severe CKD were also evaluated and twelve weeks of treatment resulted in a SVR of 98% (n = 102/104). The most common adverse events reported during clinical studies were pruritus, fatigue, headache, and nausea. Glecaprevir/pibrentasvir has been studied in more than 2,300 patients across all six major HCV genotypes and in special populations including patients with severe CKD, treatment-experienced patients, and cirrhotic patients.

Place in Therapy: Currently there is only one pan-genotypic product available for the treatment of HCV, Epclusa® [sofosbuvir/velpatasvir], which is taken for twelve weeks with or without ribavirin depending on decompensated cirrhosis status. Glecaprevir/pibrentasvir would offer another pan-genotypic treatment option for chronic HCV with a possibly shorter treatment duration of eight weeks. Shorter regimens are particularly needed in difficult to treat populations such as those with CKD or those with prior treatment experience.

Projected FDA Decision: 08/19/2017

SoonerCare Impact: During fiscal year 2016, a total of 371 members utilized hepatitis C medications, accounting for $32,105,818.63 in drug spending and an average cost per claim of $23,694.33. Hepatitis C treated SoonerCare members have an average treatment length of 12.8 weeks and approximately 18.3% of members were treatment-experienced.

Sofosbuvir/Velpatasvir/Voxilaprevir[1,3,4,6,7]

Anticipated Indication(s): Once daily, single-tablet combination of sofosbuvir, a NS5B polymerase inhibitor, velpatasvir, a pan-genotypic NS5A inhibitor, and voxilaprevir, a pangenotypic NS3/4A protease inhibitor, for the pan-genotypic (genotypes 1 through 6) treatment of chronic HCV in direct-acting antiviral (DAA) treatment-experienced patients with or without compensated cirrhosis

Clinical Trials: Phase 3 studies of sofosbuvir/velpatasvir/voxilaprevir have been performed in both DAA-experienced patients and DAA-naïve patients. Two Phase 3 studies evaluated twelve weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-experienced patients with HCV genotypes 1 through 6. Results revealed 97% (n = 430/445) of patients achieved SVR. Additional studies have been conducted in 611 DAA-naïve HCV-infected patients who received eight weeks of sofosbuvir/velpatasvir/voxilaprevir, all of which had an SVR of 95% or greater. During clinical trials, the most common adverse events reported were headache, fatigue, diarrhea, and nausea.

Place in Therapy: Currently there is only one pan-genotypic product available for the treatment of HCV, Epclusa® [sofosbuvir/velpatasvir], which is taken for twelve weeks with or without ribavirin depending on decompensated cirrhosis status. Sofosbuvir/velpatasvir/voxilaprevir would offer another pan-genotypic treatment option for chronic HCV with a possibly shorter treatment duration of eight weeks. Additionally, sofosbuvir/velpatasvir/voxilaprevir would offer a high cure rate option for those who have failed prior treatment with DAAs.

Projected FDA Decision: 08/08/2017

SoonerCare Impact: During fiscal year 2016, a total of 371 members utilized hepatitis C medications, accounting for $32,105,818.63 in drug spending and an average cost per claim of $23,694.33. Hepatitis C treated SoonerCare members have an average treatment length of 12.8 weeks and approximately 18.3% of members were treatment-experienced.

Solosec™ (Secnidazole)[1,8,9,10]

Anticipated Indication(s): Oral, single-dose 5-nitroimidazole antibiotic for bacterial vaginosis (BV)

Clinical Trials: The efficacy of secnidazole was evaluated in a Phase 3 randomized, double-blind, placebo-controlled study of 189 women with BV. Patients were randomized 2:1 to a single oral dose of 2g secnidazole or placebo. The primary endpoint was clinical response (CR), defined as a normal vaginal discharge, negative whiff test, and clue cells <20%, between days 21 and 30 (EOS). CR for secnidazole was superior to placebo at EOS (53% vs. 19%, $p<0.001$). Additionally, microbiological cure for secnidazole was superior to placebo at EOS (44% vs. 5.3%, $p<0.001$). The most common adverse effects reported during clinical studies included vulvovaginal mycotic infection, vulvovaginal candidiasis, nausea, diarrhea, and headache.

Place in Therapy: Secnidazole would be the first single-dose, oral therapy approved for BV. Twice daily oral administration of metronidazole 500mg for seven days or once daily vaginal administration of metronidazole vaginal gel 0.75% for five days is recommended by the Centers for Disease Control and Prevention (CDC) for the treatment of BV. A one-time oral dose may improve adherence and reduce bacterial resistance associated with non-adherence.

Projected FDA Decision: 09/17/2017

SoonerCare Impact: During fiscal year 2016, a total of 7,870 members had a submitted diagnosis of acute vaginitis in their diagnosis claims history and a total of 1,109 members utilized metronidazole vaginal gel. It is estimated that more than 50% of women treated for BV have a recurrence within 12 months.

Translarna™ (Ataluren)[1,4,11]

Anticipated Indication(s): Oral protein restoration therapy for genetic disorders due to a nonsense mutation (e.g., Duchenne muscular dystrophy caused by a nonsense mutation [nmDMD] and cystic fibrosis caused by a nonsense mutation [nmCF])

Clinical Trials:

- Ataluren was evaluated in a Phase 3, double-blind, placebo-controlled, 48-week trial for the treatment of nmDMD. The primary efficacy endpoint was change from baseline in the 6-minute walk test (6MWT); ataluren demonstrated a 15 meter benefit ($p=0.213$), which was not statistically significant. The pre-specified patient population of 300 to 400 at baseline as measured by the 6MWT demonstrated a benefit of 47 meters ($p=0.007$); no patients in this group lost ambulation (0/47) vs. four patients in the placebo group

(4/52). Ataluren showed a benefit over placebo across secondary and tertiary endpoints, including timed function tests (10 meter Run/Walk, 4 Stair Climb, 4 Stair Descend) and the North Star Ambulatory Assessment test.

- Ataluren was evaluated in a Phase 3 double-blind, placebo-controlled, 48-week clinical trial comparing ataluren to placebo in nmCF patients six years of age or older not receiving chronic inhaled aminoglycosides. A total of 279 patients were randomized to receive either ataluren or placebo. The primary endpoint of lung function as measured by absolute change in percent-predicted forced expiratory volume in one second (FEV_1), over 48 weeks from baseline, showed a 0.6% difference in favor of ataluren vs. placebo (-1.4% change on ataluren vs. -2.0% change on placebo; p=0.534). For the secondary endpoint of rate of pulmonary exacerbations, there was a trend in favor of ataluren, with the rate in the ataluren group being 14% lower than the placebo group (p=0.401). The results were not statistically significant. PTC Therapeutics plans to discontinue current development of ataluren for CF.

Place in Therapy: Currently there are only two FDA approved therapies for the treatment of DMD, Exondys 51™ (eteplirsen) and Emflaza™ (deflazacort). Exondys 51™ (eteplirsen) is an antisense oligonucleotide for use in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping, and Emflaza™ (deflazacort) is a corticosteroid used in the treatment of DMD. The limited number of treatment options for DMD and the high cost of these therapies generates an opportunity for new drug products.

Projected FDA Decision: 10/24/2017

SoonerCare Impact: No SoonerCare members have utilized Exondys 51™ (eteplirsen) or Emflaza™ (deflazacort) since their FDA approvals. DMD affects approximately 1 in every 3,500 live births.[12] During fiscal year 2016, a total of 283 male members had a submitted diagnosis of muscular dystrophy in their diagnosis claims history (diagnosis claims specific to DMD were not available).

Pipeline Table*[1,3,4,13]

Medication Name	Manufacturer	Therapeutic Use	Route of Administration	Approval Status	Anticipated FDA Response
Xeglyze™ (abametapir)	Hatchtech	Lice	Topical	Filed NDA	Pending
Brineura™ (cerliponase alfa)	Biomarin	CLN2 disease	IV	Filed NDA	Pending
Kevzara™ (sarilumab)	Regeneron/Sanofi	RA	SC	Filed BLA	Pending
nonacog beta pegol	Novo Nordisk	Hemophilia B	IV	Filed BLA	05/16/2017
Aristada® (aripiprazole lauroxil)	Alkermes	Schizophrenia (2-month dosing)	IM	Filed sNDA	06/05/2017
epinephrine	Adamis	Anaphylaxis	Injectable	Filed NDA	06/15/2017
Radicava™ (edaravone)	Mitsubishi Tanabe	Amyotrophic lateral sclerosis	IV	Filed NDA	06/16/2017
Baxdela™ (delafloxacin)	Melinta Therapeutics	ABSSI	IV, Oral	Filed NDA	06/19/2017

Medication Name	Manufacturer	Therapeutic Use	Route of Administration	Approval Status	Anticipated FDA Response
dextoamphetamine/ amphetamine	Shire	ADHD	Oral	Filed NDA	06/20/2017
Cotempla XR-ODT™ (methlphenidate ER)	Neos Therapeutics	ADHD	ODT	Filed NDA	06/20/2017
betrixaban	Portola	VTE prevention	Oral	Filed NDA	06/24/2017
ozenoxacin	Medimetriks/ Ferrer	Impetigo	Topical	Filed NDA	06/27/2017
abaloparatide-SC	Radius Health	Osteoporosis	SC	Filed NDA	06/30/2017
Soliris® (eculizumab)	Alexion	Myasthenia gravis	IV	Filed NDA	07/09/2017
Evenity™ (romosozumab)	Amgen/UCB	Postmenopausal osteoporosis	SC	Filed BLA	07/19/2017
Dextenza™ (dexamethasone insert)	Ocular Therapeutix	Ocular pain following surgery	Ophthalmic	Filed NDA	07/19/2017
methylphenidate ER	Highland/Ironshore	ADHD	Oral	Filed NDA	07/20/2017
Benlysta® (belimumab)	GlaxoSmithKline	SLE	SC	Filed BLA	07/23/2017
CCP-08	Vernalis/Tris Pharma	Cough/cold	Oral	Filed NDA	08/04/2017
sofosbuvir/velpatasvir/ voxilaprevir	Gilead	Hepatitis C	Oral	Filed NDA	08/08/2017
glecaprevir/pibrentasvir	AbbVie	Hepatitis C	Oral	Filed NDA	08/19/2017
amantadine ER	Adamas	Dyskinesia	Oral	Filed NDA	08/24/2017
Vesneo® (latanoprostene)	Bausch + Lomb/ Nicox	Glaucoma/ocular hypertension	Ophthalmic	Filed NDA	08/24/2017
Victoza® (liraglutide)	Novo Nordisk	CV risk reduction	SC	Filed sNDA	08/25/2017
Austedo™ (deutetrabenazine)	Teva (Auspex)	Tardive dyskinesia	Oral	Filed sNDA	08/30/2017
Duzallo™ (lesinurad/allopurinol)	AstraZeneca	Gout	Oral	Filed NDA	09/2017
OPN-375 (fluticasone)	OptiNose	Nasal polyposis	Intranasal	Filed NDA	09/2017
Solosec™ (secnidazole)	Symbiomix Therapeutics	Bacterial vaginosis	Oral	Filed NDA	09/17/2017
amphetamine ER suspension	Neos Therapeutics	ADHD	Oral	Filed NDA	09/17/2017
exenatide SC pump	Intarcia	Diabetes	SC	Filed NDA	09/21/2017
fluticasone furoate/ umeclidinium/vilanterol	GlaxoSmithKline/ Innoviva	COPD	Inhalation	Filed NDA	09/21/2017
sirukumab	GlaxoSmithKline/ Janssen	RA	SC	Filed BLA	09/23/2017
Rexista™ (oxycodone CR)	Intellipharmaceutics	Pain (abuse-deterrent)	Oral	Filed NDA	09/25/2017
Zilretta™ (triamcinolone ER)	Flexion Therapeutics	Osteoarthritis of knee	Intra-articular	Filed NDA	10/12/2017
sufentanil	AcelRx	Moderate-to-severe acute pain	SL	Filed NDA	10/13/2017
QuickShot® testosterone	Antares	Hypogonadism	SC	Filed NDA	10/20/2017
Translarna™ (ataluren)	PTC Therapeutics	DMD	Oral	Filed NDA	10/24/2017
eptacog beta	Revo Biologics	Hemophilia A or B	IV	Filed BLA	11/2017

Medication Name	Manufacturer	Therapeutic Use	Route of Administration	Approval Status	Anticipated FDA Response
guselkumab	Janssen	Psoriasis	SC	Filed BLA	11/17/2017
ertugliflozin ertugliflozin/metformin ertugliflozin/sitagliptin	Merck/Pfizer	Diabetes	Oral	Filed NDA	12/2017
semaglutide	Novo Nordisk	Diabetes	SC	Filed NDA	12/05/2017
fostamatinib	Rigel	ITP	Oral	Filed NDA	Unknown
Scenesse® (afamelanotide)	Clinuvel	Erythropoietic protoporphyria	SC implant	Filed NDA	Unknown
Human plasminogen	Prometic Life Sciences	Plasminogen deficiency	IV	Filed BLA	Unknown
Cinvanti™ (aprepitant)	Heron Therapeutics	CINV	IV	Filed NDA	Unknown

NDA = New Drug Application; BLA = Biologic License Application; CLN2 = classic late infantile neuronal ceroid lipofuscinosis; IV = intravenous; RA = rheumatoid arthritis; SC = subcutaneous; IM = intramuscular; ABSSI = acute bacterial skin and skin structure infections; ADHD = attention deficit hyperactivity disorder; ER = extended-release; ODT = orally disintigrating tablet; VTE = venous thromboembolism; SLE = systemic lupus erythematosus; CV = cardiovascular; sNDA = supplemental New Drug Application; CR = controlled-release; DMD= Duchenne muscular dystrophy; COPD = chronic obstructive pulmonary disease; SL = sublingual; ITP = immune thrombocytopenia purpura; CINV = chemotherapy-induced nausea and vomiting
*Biosimilars and oncology medications excluded from table. Medications known to have received a Complete Response Letter from the FDA that have not resubmitted were excluded.

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[3] OptumRx. RxOutlook®: 1st Quarter 2017. Available online at: https://professionals.optumrx.com/publications/rx-outlook.html. Issued 02/15/2017. Last accessed 04/24/2017.
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[13] US Specialty Care. Pipeline Report: Specialty Drugs. Available online at: https://www.usspecialtycare.com/Forms/Pipeline%20Report_Specialty_July2016_USSC.pdf. Issued 07/2016. Last accessed 04/25/2017.

Appendix C

Vote to Prior Authorize Fosamax® (Alendronate 40mg Tablets)

Oklahoma Health Care Authority
May 2017

Introduction[1]

There are several strengths of alendronate available for the treatment and prevention of osteoporosis. Alendronate 40mg differs from other strengths in that it is only indicated for the treatment of Paget's disease. Additionally, the cost of alendronate 40mg differs greatly from the cost of other strengths of alendronate. The wholesale acquisition cost (WAC) of alendronate 40mg is $5.78 per tablet. This results in a 30-day supply costing $173.40. As shown below, a 30-day supply of the other available strengths of alendronate is less than $5.00.

Cost Comparison:

Medication	Cost Per Tablet	Cost for 30 Days of Therapy*
Fosamax® 40mg (alendronate tablet)	**$5.78[+]**	**$173.40[+]**
Fosamax® 70mg (alendronate tablet)	$0.36[Δ]	$1.44[Δ]
Fosamax® 35mg (alendronate tablet)	$0.53[Δ]	$2.12[Δ]
Fosamax® 10mg (alendronate tablet)	$0.16[Δ]	$4.80[Δ]
Fosamax® 5mg (alendronate tablet)	$0.15[Δ]	$4.50[Δ]

*30 days of therapy based on usual dose of medication
[+]WAC = Wholesale Acquisition Cost
[Δ]NADAC = National Average Drug Acquisition Cost

Recommendations

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

1. The placement of Fosamax® (alendronate) 40mg tablets into the Special Prior Authorization (PA) Tier of the Osteoporosis Medications PBPA category due to the WAC in comparison to other alendronate strengths. The following criteria shown in red would apply:
    a. **Atelvia® (Risedronate Delayed-Release Tablets), Binosto® (Alendronate Effervescent Tablets), Actonel® (Risedronate 30mg Tablets), and Fosamax® (Alendronate 40mg Tablets):**
        i. A patient specific, clinically significant reason why the member cannot use all other available Tier-1 and Tier-2 products.
        ii. Members with a diagnosis in history of Paget's disease will not require prior authorization.
2. Placement of Reclast® (zoledronic acid) into Tier-2 of the Osteoporosis Medications PBPA category due to WAC. Current Tier-2 criteria will apply.

Osteoporosis Medications Tier-2 Approval Criteria:

1. A trial of at least one Tier-1 medication, compliantly used for at least six months concomitantly with calcium + vitamin D, that failed to prevent fracture, or improve bone mineral density (BMD) scores; or
2. Hypersensitivity to or intolerable adverse effects with all Tier-1 medications.
3. Quantity limits apply based on FDA approved maximum doses.

Osteoporosis Medications		
Tier-1	**Tier-2**	**Special PA**
alendronate (Fosamax®)	alendronate + D (Fosamax® +D)	alendronate effervescent tablets (Binosto®)
calcium + vitamin D*	ibandronate (Boniva®)	alendronate solution (Fosamax®)
	risedronate (Actonel®)	**alendronate 40mg tablet (Fosamax®)**
	zoledronic acid (Reclast®)	denosumab (Prolia®)
		ibandronate (Boniva® IV)
		risedronate 30mg tablet (Actonel®)
		risedronate delayed-release tablets (Atelvia®)
		teriparatide (Forteo®)

*Must be used in combination with a bisphosphonate to count as a Tier-1 trial.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

[1] Lexicomp® Lexi-Drugs: Monograph: Alendronate. Available online at: http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6298. Last revised 04/17/2017. Last accessed 04/13/2017.

Appendix D

Vote to Prior Authorize Byvalson™ (Nebivolol/Valsartan) and Qbrelis™ (Lisinopril Oral Solution)

Oklahoma Health Care Authority
May 2017

Introduction[1,2]

- **Byvalson™ (nebivolol/valsartan)** is a combination of a beta adrenergic blocker and an angiotensin receptor blocker (ARB) indicated for the treatment of hypertension. Byvalson™ is available as an oral tablet containing 5mg of nebivolol and 80mg of valsartan per tablet. As initial therapy and in patients not adequately controlled on valsartan 80mg or nebivolol up to and including 10mg, the recommended dose is 5mg/80mg orally once daily. The maximum antihypertensive effects are attained within 2 to 4 weeks. Increasing the dose does not result in any meaningful further blood pressure reduction.
- **Qbrelis™ (lisinopril oral solution)** is an angiotensin converting enzyme (ACE) inhibitor indicated for the treatment of hypertension in adults and pediatric patients 6 years of age and older, adjunct therapy for heart failure, and treatment of acute myocardial infarction in adults. The recommended starting dose for pediatric patients 6 years of age and older with a glomerular filtration rate greater than 30mL/min/1.73m^2 is 0.07mg/kg (up to 5mg total) once daily. The recommended dose for heart failure is 5mg once daily; the dose may be increased as tolerated to 40mg daily. The recommended dose for acute myocardial infarction is 5mg within 24 hours of myocardial infarction, followed by 5mg after 24 hours, then 10mg once daily.

Recommendations

The College of Pharmacy recommends the prior authorization of Byvalson™ (nebivolol/valsartan) and Qbrelis™ (lisinopril oral solution) with the following criteria:

Byvalson™ (Nebivolol/Valsartan) Approval Criteria:

1. A patient-specific, clinically significant reason the member cannot use the individual components, nebivolol (Bystolic®) and valsartan (Diovan®); and
2. A quantity limit of 30 tablets per 30 days will apply.

Qbrelis™ (Lisinopril Oral Solution) Approval Criteria:

1. A patient-specific, clinically significant reason why the member cannot use lisinopril oral tablets in place of the oral solution formulation even when the tablets are crushed.

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[1] Byvalson™ (Nebivolol/Valsartan) Prescribing Information. Allergan. Available online at: https://www.allergan.com/assets/pdf/byvalson_pi. Last revised 06/2016. Last accessed 05/02/2017.
[2] Qbrelis™ Prescribing Information. Silvergate Pharmaceuticals, Inc. Available online at: http://silvergatepharma.com/wp-content/uploads/2016/07/QBRELIS-PI-7-8-2016-Font-change-7-20-2016-002.pdf. Last revised 07/2016. Last accessed 05/02/2017.

Appendix E

Vote to Prior Authorize Giazo® (Balsalazide Disodium Tablets)

Oklahoma Health Care Authority
May 2017

Introduction[1]

Giazo® (balsalazide tablets) is a locally acting aminosalicylate indicated for the treatment of mildly-to-moderately active ulcerative colitis (UC) in male patients 18 years of age and older.

- Limitations of Use:
  - Effectiveness in female patients was not demonstrated in clinical trials.
  - Safety and effectiveness of Giazo® beyond eight weeks have not been established.

Cost:

Medication	Cost Per Unit*	Cost Per Day	Cost Per 8 Weeks
Giazo® (balsalazide disodium) 1.1g tablet	**$5.28**	**$31.68**	**$1,774.08**
balsalazide disodium 750mg capsule	$0.47	$1.41	$78.96
sulfasalazine 500mg tablet	$0.17	$1.36	$76.16

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

Recommendations

The College of Pharmacy recommends the prior authorization of Giazo® (balsalazide) with the following criteria:

Giazo® (Balsalazide) Approval Criteria:

1. An FDA approved diagnosis of mildly-to-moderately active ulcerative colitis (UC); and
2. Member must be 18 years of age or older; and
3. Member must be male (effectiveness of Giazo® was not demonstrated in female patients in clinical trials); and
4. A patient-specific, clinically significant reason why the member cannot use generic balsalazide 750mg capsules or other products available without prior authorization*; and
5. Approvals will be for the duration of eight weeks. After eight weeks of treatment the prescriber must document a patient-specific, clinically significant reason the member needs a longer duration of treatment.

***The following medications do not require prior authorization:** sulfasalazine 500mg tablets, sulfasalazine delayed-release 500mg tablets, Rowasa® (mesalamine) rectal suspension enemas, Lialda® (mesalamine) delayed-release capsules, Colazal® (balsalazide) capsules, Dipentum® (olsalazine) capsules, Pentasa® (mesalamine) 250mg controlled-release capsules, Canasa® (mesalamine) suppositories, Apriso® (mesalamine) extended-release capsules, Delzicol® (mesalamine) delayed-release capsules, and hydrocortisone enemas.

[1] Giazo® Prescribing Information. Valeant Pharmaceuticals International, Inc. Available online at: https://shared.salix.com/shared/pi/giazo-pi.pdf. Last revised 06/2016. Last accessed 04/2017.

Appendix F

Vote to Prior Authorize Invokamet® XR (Canagliflozin/ Metformin Extended-Release), Jentadueto® XR (Linagliptin/ Metformin Extended-Release), Adlyxin® (Lixisenatide), Xultophy® 100/3.6 (Insulin Degludec/Liraglutide), Soliqua™ 100/33 (Insulin Glargine/Lixisenatide), Synjardy® XR (Empagliflozin/Metformin Extended-Release), and Qtern® (Dapagliflozin/Saxagliptin)

Oklahoma Health Care Authority
May 2017

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

- **Invokamet® XR (canagliflozin/metformin extended-release [ER])** is a sodium-glucose co-transporter-2 (SGLT-2) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (DM) when treatment with both canagliflozin and metformin is appropriate.
- **Jentadueto® XR (linagliptin/metformin ER)** is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM when treatment with both linagliptin and metformin is appropriate.
- **Adlyxin® (lixisenatide)** is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM.
- **Xultophy® 100/3.6 (insulin degludec 100 units/mL and liraglutide 3.6mg/mL injection)** is a combination of insulin degludec, a long-acting human insulin analog, and liraglutide, a GLP-1 receptor agonist, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM inadequately controlled on basal insulin (less than 50 units daily) or liraglutide (less than or equal to 1.8mg daily).
- **Soliqua™ 100/33 (insulin glargine 100 units/mL and lixisenatide 33mcg/mL injection)** is a combination of a long-acting human insulin analog with a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM inadequately controlled on basal insulin (less than 60 units daily) or lixisenatide.
- **Synjardy® XR (empagliflozin/metformin ER)** is a combination of empagliflozin, a SGLT-2 inhibitor and metformin ER, a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM when treatment with both empagliflozin and metformin is appropriate. Empagliflozin is indicated to reduce the risk of cardiovascular (CV) death in adults with type 2 DM and established CV disease. However, the effectiveness of Synjardy® XR on reducing the risk of CV death in adults with type 2 DM and CV disease has not been established.

- **Qtern® (dapagliflozin/saxagliptin)** is a SGLT-2 inhibitor and a DPP-4 inhibitor combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin.
- In December 2016, the U.S. Food and Drug Administration (FDA) approved a new indication for **Jardiance® (empagliflozin)** to reduce the risk of CV death in adult patients with type 2 DM and CV disease. The FDA's decision was based on a post-marketing study required by the FDA when Jardiance® was originally approved in 2014 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 DM. Jardiance® was studied in a post-market clinical trial of more than 7,000 patients with type 2 DM and CV disease. It was shown to reduce the risk of CV death compared to placebo when added to standard of care therapies for DM and atherosclerotic CV disease.

Recommendations

The College of Pharmacy recommends the following:

1. The placement of Invokamet® XR (canagliflozin/metformin extended-release), Jentadueto® XR (linagliptin/metformin extended-release), and Synjardy® XR (empagliflozin/metformin extended-release) into the Special Prior Authorization (PA) Tier of the Diabetes Medications Product Based Prior Authorization (PBPA) category.
2. The placement of Adlyxin® (lixisenatide), Xultophy® 100/3.6 (insulin degludec/ liraglutide), Soliqua™ 100/33 (insulin glargine/lixisenatide), and Qtern® (dapagliflozin/saxagliptin) into Tier-3 of the Diabetes Medications PBPA category.
3. A clinical exception will apply for medications with the FDA approved diagnosis to reduce the risk of cardiovascular (CV) death in adult patients with type 2 diabetes mellitus (DM) and established CV disease. Tier structure rules for this indication will apply.

Diabetes Medications*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Alpha-Glucosidase Inhibitors acarbose (Precose®)	**DPP-4 Inhibitors** linagliptin (Tradjenta®) linagliptin/metformin (Jentadueto®) saxagliptin (Onglyza®) saxagliptin/metformin (Kombiglyze®) sitagliptin (Januvia®) sitagliptin/metformin (Janumet®) sitagliptin/metformin ER (Janumet XR®)	**Alpha-Glucosidase Inhibitors** miglitol (Glyset®)	**Amylinomimetics** pramlintide (Symlin®)
Biguanides metformin (Glucophage®) metformin SR (Glucophage XR®) metformin/glipizide (Metaglip®) metformin/glyburide (Glucovance®)	**Glinides** nateglinide (Starlix®) repaglinide/metformin (Prandimet®)	**Dopamine Agonists** bromocriptine (Cycloset®)	**Biguanides** metformin ER (Fortamet®, Glumetza®) metformin solution (Riomet®)
Glinides repaglinide (Prandin®)		**DPP-4 Inhibitors** alogliptin (Nesina®) alogliptin/metformin (Kazano®) alogliptin/pioglitazone (Oseni®)	**DPP-4 Inhibitors** **linagliptin/metformin ER (Jentadueto® XR)**
			SGLT-2 Inhibitors **canagliflozin/metformin ER (Invokamet® XR)** **empagliflozin/metformin ER (Synjardy® XR)**

Diabetes Medications*			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
Sulfonylureas chlorpropamide glimepiride (Amaryl®) glipizide (Glucotrol®) glipizide SR (Glucotrol XL®) glyburide (Diabeta®) glyburide micronized (Micronase®) tolbutamide **Thiazolidinediones** pioglitazone (Actos®)	**GLP-1 Agonists** exenatide (Byetta®) liraglutide (Victoza®) **SGLT-2 Inhibitors** canagliflozin (Invokana®) canagliflozin/metformin (Invokamet®)	**GLP-1 Agonists** albiglutide (Tanzeum®) dulaglutide (Trulicity®) exenatide (Bydureon®) **lixisenatide (Adlyxin™)** **GLP-1 Agonists/Insulin** **insulin degludec/ liraglutide (Xultophy® 100/3.6)** **insulin glargine/ lixisenatide (Soliqua™ 100/33)** **SGLT-2 Inhibitors** dapagliflozin (Farxiga®) dapagliflozin/metformin ER (Xigduo® XR) empagliflozin (Jardiance®) empagliflozin/metformin (Synjardy®) **SGLT-2/DPP-4 Inhibitors** **dapagliflozin/saxagliptin (Qtern®)** empagliflozin/linagliptin (Glyxambi®) **Thiazolidinediones** pioglitazone/glimepiride (Duetact®) pioglitazone/metformin (Actoplus Met®, Actoplus Met XR®) rosiglitazone (Avandia®) rosiglitazone/glimepiride (Avandaryl®) rosiglitazone/metformin (Avandamet®)	

*Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
SR = sustained-release, ER = extended-release, DPP-4 = dipeptidyl peptidase-4, GLP-1 = glucagon-like peptide-1, SGLT-2 = sodium-glucose cotransporter-2

[1] Invokamet® XR Prescribing Information. Janssen Pharmaceuticals. Available online at: https://www.invokanahcp.com/sites/www.invokanahcp.com/files/prescribing-information-invokamet-xr.pdf. Last revised 09/2016. Last accessed 04/2017.

[2] Jentodueto® XR Prescribing Information. Boehringer Ingelheim Pharmaceuticals. Available online at: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Jentadueto%20XR/Jentadueto%20XR.pdf. Last revised 12/2016. Last accessed 04/2017.

[3] Adlyxin® Prescribing Information. Sanofi-Aventis U.S. LLC. Available online at: http://products.sanofi.us/adlyxin/adlyxin.pdf. Last revised 07/2016. Last accessed 04/2017.

[4] Xultophy® Prescribing Information. Novo Nordisk. Available online at: http://www.novo-pi.com/xultophy10036.pdf. Last revised 11/2016. Last accessed 04/2017.

[5] Soliqua® Prescribing Information. Sanofi-Aventis U.S. LLC. Available online at: http://products.sanofi.us/Soliqua100-33/Soliqua100-33.pdf. Last revised 11/2016. Last accessed 04/2017.

[6] Synjardy® XR Prescribing Information. Boehringer Ingelheim Pharmaceuticals. Available online at: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Synjardy/Synjardy.pdf. Last revised 12/2016. Last accessed 04/2017.

[7] Qtern® Prescribing Information. AstraZeneca Pharmaceuticals. Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209091s000lbl.pdf. Last revised 02/2017. Last accessed 04/2017.

[8] U.S. Food and Drug Administration (FDA). News Release: FDA Approves Jardiance to Reduce Cardiovascular Death in Adults with Type 2 Diabetes. Available online at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm531517.htm. Issued 12/2016. Last accessed 04/2017.

Appendix G

Fiscal Year 2016 Annual Review of Lung Cancer Medications and 30-Day Notice to Prior Authorize Tarceva® (Erlotinib), Gilotrif® (Afatinib), Tagrisso™ (Osimertinib), Xalkori® (Crizotinib), Zykadia® (Ceritinib), Alecensa® (Alectinib), Cyramza® (Ramucirumab), Tecentriq® (Atezolizumab), and Alunbrig™ (Brigatinib)

Oklahoma Health Care Authority
May 2017

Introduction

The American Cancer Society estimates that approximately 222,500 new lung cancer cases will be diagnosed in 2017.[1] Lung cancer is the leading cause of cancer death accounting for 25% of all cancer-related deaths among both males and females. Lung cancer is most commonly diagnosed in older people with the average age at diagnosis being 70 years. Over 95% of all lung cancer cases are classified as either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC). Defining the cell type is essential as the prognosis and treatment of the two types differs substantially. NSCLC is more common than SCLC accounting for 80 to 85% of all lung cancer diagnoses. In actuality, there are many subtypes of NSCLC including adenocarcinomas, squamous cell carcinomas, and large cell carcinomas but these subtypes are often grouped together under the broad term of NSCLC as the approach to initial treatment of localized disease is similar among the subtypes.

Treatment decisions are guided by the stage of the disease, histology, and molecular features of the tumor.[2] Patient-specific factors such as performance status and comorbid conditions are also considered when determining treatment plans. Surgical resection provides the best chance for cure in patients with stage I to II NSCLC and can be used in combination with cisplatin-based systemic chemotherapy and radiation. Chemotherapy is the treatment of choice for stage III to IV NSCLC. The role of molecularly targeted-therapy and immunotherapy continues to develop and is quickly becoming a part of standard-of-care treatment plans in select patients with NSCLC. SCLC differs in that there is no role for surgery in the treatment of this histology. Chemotherapy and radiation are the treatments of choice for SCLC.[2]

Current Prior Authorization Criteria

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

1. A diagnosis of metastatic NSCLC; and
2. The member has not previously failed other PD-1 inhibitors [e.g., Opdivo® (nivolumab)]; and
3. Tumors express PD-L1 (FDA approved test); and
4. Member meets one of the following:

a. New diagnosis as first-line therapy (patient has not received chemotherapy to treat disease) if:
    i. Tumor does not express sensitizing Epidermal Growth Factor Receptor (EGFR) mutations or Anaplastic Lymphoma Kinase (ALK) translocations; and
    ii. Member has a ECOG performance status of 0 to 1
b. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin):
    i. Patients with EGFR-mutation-positive should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
        1. Examples of drugs for EGFR-mutation-positive tumors: osimertinib, eroltinib, afatinib, or gefitinib
    ii. Patients with ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. *This does not apply if tumors do not have these mutations*; and
        1. Examples of drugs for ALK-mutation-positive tumors: crizotinib, ceritinib, or alectinib
    iii. Member has a ECOG performance status of 0 to 2.

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. Nivolumab must be used as a single-agent; and
4. Disease progression on or after platinum-containing chemotherapy (cisplatin or carboplatin); and
5. Member has a ECOG performance status of 0 to 2; and
6. The patient has not previously failed other PD-1 inhibitors [e.g., Keytruda® (pembrolizumab)]; and
7. Dose as follows: Single-agent: 240mg every two weeks.

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

1. One of the following criteria is met:
    a. Disease relapsed within six months of initial chemotherapy; or
    b. Disease is progressive on initial chemotherapy; and
2. Nivolumab must be used as a single-agent or in combination with ipilimumab; and
3. Member has a ECOG performance status of 0 to 2; and
4. The patient has not previously failed other PD-1 inhibitors (e.g., Keytruda® (pembrolizumab)].

Utilization of Lung Cancer Medications: Fiscal Year 2016

Comparison of Fiscal Years: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	19	126	$697,726.90	$5,537.52	$365.49	3,568	1,909
2016	17	70	$429,295.93	$6,132.80	$294.24	3,260	1,459
% Change	**-10.50%**	**-44.40%**	**-38.50%**	**10.70%**	**-19.50%**	**-8.60%**	**-23.60%**
Change	**-2**	**-56**	**-$268,430.97**	**$595.28**	**-$71.25**	**-308**	**-450**

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

Fiscal Year 2016 Utilization: Medical Claims

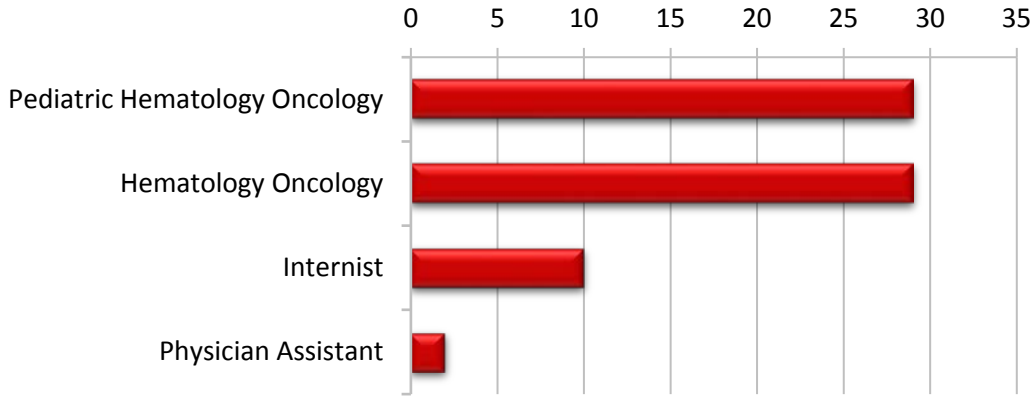
*Total Members	Total Claims	Total Cost	Cost/Claim
290	1,017	$2,362,488.54	$2,323.00

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

Demographics of Members Utilizing Lung Cancer Medications: Pharmacy Claims

- Due to the small number of members utilizing lung cancer medications during fiscal year 2016, detailed demographic information could not be provided.

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



Market News and Updates

National Comprenhensive Cancer Network (NCCN) guidelines for the treatment of NSCLC and SCLC are continually updated, but the major indications are reflected in the product summaries section of this report.

The U.S. Food and Drug Administration (FDA) Orange Book indicates the following patent expiration dates for each of the products:

- Gilotrif® (afatinib): July 29, 2018
- Tarceva® (erlotinib): November 8, 2018
- Zykadia® (ceritinib): February 26, 2021
- Cyramza® (ramucirumab): April 2021
- Xalkori® (crizotinib): August 26, 2025
- Alecensa® (alectinib): March 4, 2032
- Tagrisso™ (osimertinib): August 8, 2032

Lung Cancer Medication Product Summaries

Alecensa® (Alectinib)

- **Therapeutic Class:** Anaplastic Lymphoma Kinase (ALK) inhibitor
- **Indication(s):** Treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib
- **How Supplied:** 150mg capsules
- **Dose:** 600mg orally twice daily
- **Cost:** 150mg (240): $15,976.33

Xalkori® (Crizotinib)

- **Therapeutic Class:** ALK inhibitor
- **Indication(s):** Treatment of patients with metastatic NSCLC whose tumors are ALK-positive (as detected by an approved test) or are proto-oncogene tyrosine-protein kinase ROS (ROS1)-positive
- **How Supplied:** 200mg, 250mg capsule
- **Dose:** 250mg orally twice daily
- **Cost:** 200mg (60): $17,815.04 or 250mg (60): $17,815.04

Tagrisso™ (Osimertinib)

- **Therapeutic Class:** Epidermal Growth Factor Receptor (EGFR) inhibitor
- **Indication(s):** Treatment of metastatic EGFR T790M mutation-positive NSCLC, as detected by an approved test, in patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy
- **How Supplied:** 40mg, 80mg tablets
- **Dose:** 80mg orally once daily
- **Cost:** 40mg (30): $17,028.90 or 80mg (30): $17,028.90

Tarceva® (Erlotinib)

- **Therapeutic Class:** EGFR inhibitor
- **Indication(s):**
    - Treatment of metastatic NSCLC in tumors with EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test either as first-line, maintenance, or as second or greater line treatment after progression following at least one prior chemotherapy regimen
    - First-line treatment of locally advanced, unresectable, or metastatic pancreatic cancer (in combination with gemcitabine)

- **How Supplied:** 25mg, 100mg, 150mg tablets
- **Dose:** 150mg orally once daily
- **Cost:** 25mg (30): $3,022.66 or 100mg (30): $8,302.25 or 150mg (30): $9,390.44

Gilotrif® (Afatinib)

- **Therapeutic Class:** EGFR inhibitor
- **Indication(s):**
    - First-line treatment of metastatic NSCLC in patients whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an approved test
    - Treatment of previously treated metastatic squamous cell NSCLC which has progressed following platinum-based chemotherapy
- **How Supplied:** 20mg, 30mg, 40mg tablets
- **Dose:** 40mg orally once daily
- **Cost:** 20mg (30): $9,060.85 or 30mg (30): $9,060.85 or 40mg (30): $9,060.85

Zykadia® (Ceritinib)

- **Therapeutic Class:** ALK inhibitor
- **Indication(s):** Treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib
- **How Supplied:** 150mg capsules
- **Dose:** 750mg orally once daily
- **Cost:** 150mg (70): $8,444.58

Cyramza® (Ramucirumab)

- **Therapeutic Class:** Vascular Endothelial Growth Factor (VEGF) Inhibitor
- **Indication(s):**
    - Treatment (in combination with docetaxel) of metastatic NSCLC in patients with disease progression on or after platinum-based chemotherapy; patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving ramucirumab
    - Treatment (in combination with FOLFIRI [irinotecan, leucovorin, and fluorouracil]) of metastatic colorectal cancer (mCRC) in patients with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine
    - Treatment (single-agent or in combination with paclitaxel) of advanced or metastatic gastric or gastroesophageal junction adenocarcinoma in patients with disease progression on or following fluoropyrimidine- or platinum-containing chemotherapy
- **How Supplied:** 100mg/10mL (10mL), 500mg/50mL (50mL) solution for IV infusion
- **Dose:** 10mg/kg on day one every 21 days in combination with docetaxel; continue until disease progression or unacceptable toxicity
- **Cost:** 100mg/10mL (10mL): $1,298.96 or 500mg/50mL (50mL): $6,494.82

Alunbrig™ (Brigatinib)

- **Therapeutic Class:** ALK inhibitor
- **Indication(s):** Treatment of patients with ALK-positive, metastatic NSCLC who have progressed on or are intolerant to crizotinib
- **How Supplied:** 30mg, 90mg tablets
- **Dose:** 90mg orally once daily for the first 7 days then, if tolerated, increase to 180mg orally once daily
- **Cost:** $14,250 per month

Recommendations

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

1. A 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 must be used as a single-agent only.

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

1. A diagnosis of metastatic NSCLC (first-line or subsequent therapy); and
2. Anaplastic lymphoma kinase (ALK) or ROS1 positivity; or
3. MET amplification; and
4. Crizotinib must be used as a single-agent only.

Xalkori® (Crizotinib) Approval Criteria [Soft Tissue Sarcoma – Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation Diagnosis]:

1. A diagnosis of soft tissue sarcoma – IMT; and
2. Anaplastic lymphoma kinase (ALK) positivity; and
3. Crizotinib must be used as a single-agent only.

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

1. A diagnosis of NSCLC; and
2. Epidermal growth factor receptor (EGFR) T790M mutation-positive disease; and
3. Following progression on erlotinib, afatinib, or gefitinib for asymptomatic disease, symptomatic brain lesions, or multiple symptomatic systemic lesions; and
4. Osimertinib must be used for subsequent therapy only.

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

1. A diagnosis of NSCLC; and
2. Recurrence or metastatic disease; and
3. Epidermal growth factor receptor (EGFR) mutation detected; and
4. Erlotinib must be used as a single-agent only.

Tarceva® (Erlotinib) Approval Criteria [Pancreatic Cancer Diagnosis]:

1. A diagnosis of pancreatic cancer; and
2. Locally advanced unresectable or metastatic disease; and

3. Member must have good performance status; and
4. Erlotinib must be used as a first-line agent only; and
5. Erlotinib must be used in combination with gemcitabine.

Tarceva® (Erlotinib) Approval Criteria [Kidney Cancer Diagnosis]:

1. A diagnosis of kidney cancer; and
2. Non-clear cell type; and
3. Relapsed disease or for surgically unresectable stage IV disease; and
4. Erlotinib must be used as a single-agent only.

Tarceva® (Erlotinib) Approval Criteria [Bone Cancer – Chordoma Diagnosis]:

1. A diagnosis of bone cancer – Chordoma; and
2. Recurrent disease; and
3. Erlotinib must be used as a single-agent only.

Tarceva® (Erlotinib) Approval Criteria [Pancreatic Adenocarcinoma Diagnosis]:

1. A diagnosis of pancreatic adenocarcinoma; and
2. Locally advanced unresectable disease or metastatic disease; and
3. Member must have good performance status; and
4. Erlotinib must be used in combination with gemcitabine.

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

The following criteria must be met when used in the <u>first-line setting:</u>

1. A diagnosis of metastatic NSCLC; and
2. Epidermal growth factor receptor (EGFR) mutation detected; and
3. Afatinib when used in the first-line setting must be used as a single-agent only.

The following criteria must be met when used in the <u>second-line setting:</u>

1. A diagnosis of metastatic NSCLC; and
2. Progressed following platinum-based chemotherapy; and
3. Afatinib when used in the second-line setting may be used as a single-agent or in combination with cetuximab in patients with a known sensitizing EGFR mutation who are T790M negative.

Gilotrif® (Afatinib) Approval Criteria [Head and Neck Cancer Diagnosis]:

1. A diagnosis of head and neck cancer; and
2. Disease progression on or after platinum containing chemotherapy; and
3. Non-nasopharyngeal cancer must be one of the following:
    a. Newly diagnosed T4b, any N, M0 disease, unresectable nodal disease with no metastases, or for patients who are unfit for surgery and performance status (PS) 3; or
    b. Metastatic (M1) disease at initial presentation, recurrent/persistent disease with distant metastases, or unresectable locoregional recurrence or second primary with prior radiation therapy (RT) and PS 0 to 2; or
    c. Unresectable locoregional recurrence without prior RT and PS 3; and
4. Afatinib must be used as a single-agent.

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

1. A diagnosis of metastatic NSCLC; and
2. Anaplastic lymphoma kinase (ALK) positivity; and
3. Must have progressed on or be intolerant to crizotinib; or
4. Must have asymptomatic disease with rapid radiologic progression or threatened organ function on crizotinib therapy; and
5. Ceritinib must be used as a single-agent only.

Zykadia® (Ceritinib) Approval Criteria [Soft Tissue Sarcoma – Inflammatory Myofibroblastic Tumor (IMT) with Anaplastic Lymphoma Kinase (ALK) Translocation Diagnosis]:

1. A diagnosis of soft tissue sarcoma – IMT; and
2. ALK positivity; and
3. Ceritinib must be used as a single-agent only.

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

1. A diagnosis of NSCLC; and
2. Subsequent therapy for metastatic disease after progression; and
3. Member must have an ECOG performance status of 0 to 2; and
4. Ramucirumab must be used in combination with docetaxel.

Cyramza® (Ramucirumab) Approval Criteria [Colorectal Cancer Diagnosis]:

1. A diagnosis of colorectal cancer; and
2. Subsequent therapy for metastatic disease after progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine; and
3. Ramucirumab must be used in combination with an irinotecan based regimen.

Cyramza® (Ramucirumab) Approval Criteria [Esophageal Cancer Diagnosis]:

1. A diagnosis of unresectable, locally advanced, recurrent or metastatic esophageal or esophagogastic junction adenocarcinoma; and
2. Member must have a Karnofsky performance score greater than or equal to 60% or an ECOG performance score of 0 to 2; and
3. Ramucirumab must be used as a single-agent or in combination with paclitaxel.

Cyramza® (Ramucirumab) Approval Criteria [Gastric Cancer Diagnosis]:

1. A diagnosis of gastric cancer; and
2. Member is not a surgical candidate or has unresectable, locally advanced, recurrent or metastatic disease; and
3. Member has a Karnofsky performance score of greater than or equal to 60% or an ECOG performance score of 0 to 2; and
4. Ramucirumab must be used as a single-agent or in combination with paclitaxel.

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

1. A diagnosis of metastatic NSCLC; and
2. Anaplastic lymphoma kinase (ALK) positivity; and
3. Progressed on or intolerant to crizotinib; and
4. Brigatnib must be used as a single-agent only.

Utilization Details of Lung Cancer Medications: Fiscal Year 2016

Pharmacy Claims: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
ERLOTINIB PRODUCTS					
TARCEVA TAB 150MG	15	4	$108,556.68	3.75	$7,237.11
TARCEVA TAB 25MG	9	3	$57,097.08	3	$6,344.12
TARCEVA TAB 100MG	9	4	$56,207.84	2.25	$6,245.32
SUBTOTAL	**33**	**10**	**$221,861.60**	**3.3**	**$6,723.08**
BEVACIZUMAB PRODUCTS					
AVASTIN INJ 400/16ML	14	4	$50,439.41	3.5	$3,602.82
AVASTIN INJ	7	1	$14,643.44	7	$2,091.92
SUBTOTAL	**21**	**4**	**$65,082.85**	**5.25**	**$3,099.18**
AFATINIB PRODUCTS					
GILOTRIF TAB 40MG	12	2	$84,762.89	6	$7,063.57
SUBTOTAL	**12**	**2**	**$84,762.89**	**6**	**$7,063.57**
CRIZOTINIB PRODUCTS					
XALKORI CAP 250MG	3	1	$42,658.29	3	$14,219.43
XALKORI CAP 200MG	1	1	$14,930.30	1	$14,930.30
SUBTOTAL	**4**	**2**	**$57,588.59**	**2**	**$14,397.15**
TOTAL	**70**	**17***	**$429,295.93**	**4.12**	**$6,132.80**

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

Medical Claims: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM
J9035 BEVACIZUMAB INJECTION	910	266	$1,908,298.91	$2,097.03
J9271 PEMBROLIZUMAB INJECTION	8	3	$69,677.25	$8,709.66
J9299 NIVOLUMAB INJECTION	94	25	$362,909.18	$3,860.74
J9308 RAMUCIRUMAB INJECTION	7	3	$21,603.20	$3,086.17
TOTAL	**1,017+**	**290***	**$2,362,488.54**	**$2,323.00**

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

[1] American Cancer Society. Key statistics for lung cancer. Available online at: https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/key-statistics.html. Last revised 01/05/2017. Last accessed 04/20/2017.
[2] National Comprehensive Cancer Network. Non-small cell lung cancer and small cell lung cancer. (Version 5.2017). http://www.nccn.org/professionals/physician_gls/pdf/bone.pdf. Last revised 11/07/2016. Last accessed 04/13/2017.

Appendix H

30-Day Notice to Prior Authorize Kuvan® (Sapropterin)

Oklahoma Health Care Authority
May 2017

Phenylketonuria[1,2,3,4]

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. 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, NutraSweet® and Equal®, must be avoided as they also contain Phe. Phe-free formula for newborns, Phe-free protein substitutes, and low-protein foods such as vegetables, fruits, and some grains are recommended. Phe blood levels should be maintained between 120 to 360µmol/L (2 to 6mg/dL) for life.

In December 2007, the U.S. Food and Drug Administration (FDA) approved Kuvan® (sapropterin), the first and only specific drug therapy approved for the treatment of PKU. Sapropterin is a PAH activator indicated to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU in conjunction with a Phe-restricted diet. BH4 is a required cofactor for PAH activity and accounts for the disposal of approximately 75% of dietary phenylalanine, 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. To determine if there is a response to sapropterin, the recommended starting dose in patients 1 month to 6 years of age is 10mg/kg/day taken once daily for up to a month. If there is no response, the drug dose may be increased to 20mg/kg/day for up to a month. In patients 7 years and older, the recommended starting dose is 10 to 20mg/kg/day once daily. If the 20mg/kg/day starting dose is used, then response to therapy is determined by change in blood Phe following a treatment period of one month. Treatment should be discontinued in patients who do not respond to Kuvan®. The dose may be adjusted within a range of 5 to 20mg/kg/day in patients who respond to sapropterin. In clinical trials, a response to sapropterin treatment was defined as greater than or equal to a 30%

decrease in blood Phe from baseline. The safety and efficacy of sapropterin was evaluated in five clinical studies in patients with PKU. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with sapropterin.

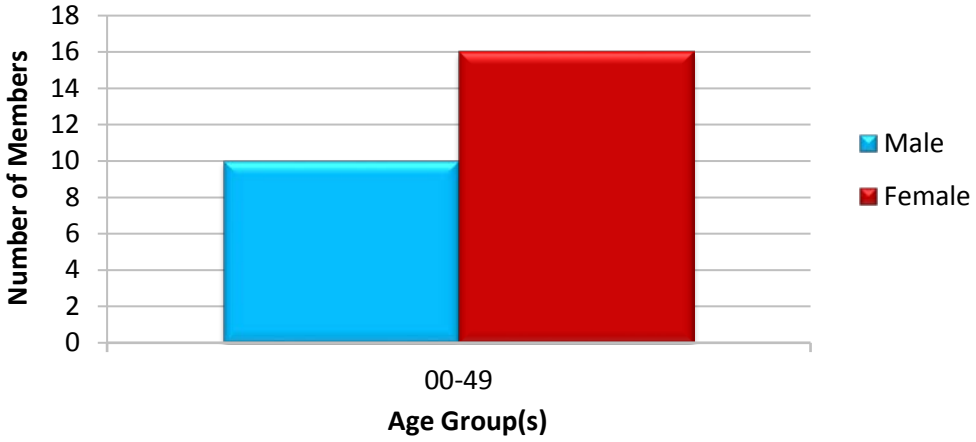
Utilization of Kuvan® (Sapropterin): Calendar Year 2016

Comparison of Calendar Years

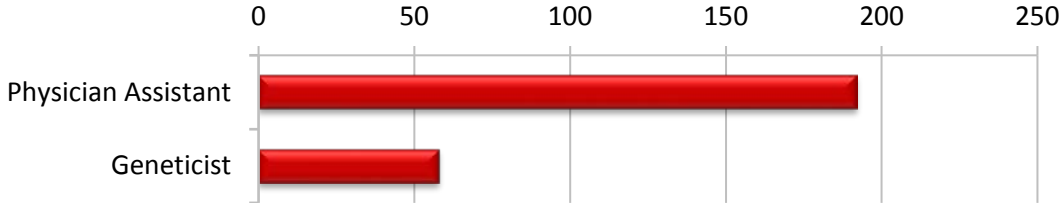
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	24	171	$1,046,702.97	$6,121.07	$204.04	33,885	5,130
2016	26	250	$1,468,182.41	$5,872.73	$195.81	37,710	7,498
% Change	**8.30%**	**46.20%**	**40.30%**	**-4.10%**	**-4.00%**	**11.30%**	**46.20%**
Change	**2**	**79**	**$421,479.44**	**-$248.34**	**-$8.23**	**3,825**	**2,368**

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

Demographics of Members Utilizing Kuvan® (Sapropterin)



Top Prescriber Specialties of Kuvan® (Sapropterin) by Number of Claims



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

Anticipated Patent Expiration(s): Kuvan® (sapropterin): May 2026

News:

- **March 2016:** BioMarin Pharmaceutical announced positive results from their Phase 3 PRISM-2 study of pegvaliase (pegylated recombinant phenylalanine ammonia lyase), an investigational enzyme substitution therapy for PKU. Pegvaliase met its primary endpoint of change in Phe blood levels compared with placebo in PKU patients.

Pegvaliase is currently being studied in ongoing Phase 3 clinical trials to evaluate the safety, tolerability, and efficacy for people with PKU who have not received the treatment in the past as well as to evaluate long-term treatment. The treatment has designated Orphan Drug status in the United States and European Union. BioMarin anticipates submitting a New Drug Application (NDA) for pegvaliase to the FDA in the second quarter of 2017.

- **April 2017:** BioMarin Pharmaceutical Inc. announced a settlement agreement with Par Pharmaceutical that resolves patent litigation in the United States over Kuvan® (sapropterin) tablets and powder. BioMarin will grant Par a non-exclusive license to its patents related to Kuvan® (sapropterin) to allow Par to market a generic version of sapropterin tablets and powder for oral solution in the United States for the FDA approved indications beginning October 1, 2020 or earlier under certain circumstances which are currently confidential.

Kuvan® (Sapropterin) Product Summary[9]

Indications: Kuvan® (sapropterin) is a PAH activator indicated to reduce blood Phe levels in patients with HPA due to BH4-responsive PKU. Sapropterin is to be used in conjunction with a Phe-restricted diet.

Dosing:

- Kuvan® is available as 100mg soluble tablets, 100mg powder for oral solution, and 500mg powder for oral solution.
- The recommended starting dose of sapropterin in patients 1 month to 6 years of age is 10mg/kg once daily with a meal. In patients 7 years of age and older, the recommended starting dose is 10 to 20mg/kg once daily with a meal.
- Dose adjustments may be made in the range of 5 to 20mg/kg once daily and blood Phe must be monitored regularly.
- Sapropterin tablets should be swallowed whole or after mixing in a small amount of soft foods or dissolving in recommended liquid. Sapropterin oral solution should be swallowed after mixing the powder in a small amount of soft food or dissolving in recommended liquids.

Mechanism of Action: Sapropterin is a synthetic form of BH4, the cofactor for the enzyme PAH. PAH hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with PKU, PAH activity is absent or deficient. Treatment with BH4 can activate residual PAH enzyme activity, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients.

Contraindications: None.

Warnings and Precautions:

- Hypersensitivity Reactions: Hypersensitivity reactions including anaphylaxis have occurred with sapropterin.
- Gastritis: Gastritis was reported in clinical trials with sapropterin. Patients should be monitored for signs of gastritis.

- Risk of Low Phe Blood Levels: Children younger than 7 years of age treated with sapropterin doses of 20mg/kg per day are at increased risk for low levels of blood Phe compared with children 7 years of age and older.
- Monitor Blood Phe Levels: Blood Phe levels should be monitored during treatment to ensure adequate blood Phe control.
- Sapropterin Non-responders: Non-responders to sapropterin treatment should be identified. Not all patients with PKU respond to treatment with sapropterin.
- Phe-Restricted Diet: All patients should be treated with a Phe-restricted diet. The initiation of sapropterin therapy does not eliminate the need for ongoing dietary management.
- Monitor Liver Function Tests: Liver function tests should be monitored in patients with liver impairment who are receiving sapropterin.
- Monitor for Drug Interactions: Patients co-administering sapropterin with medications known to inhibit folate metabolism, or with levodopa should be monitored. Patients should be monitored for hypotension when co-administering sapropterin with medications known to affect nitric oxide-mediated vasorelaxation.
- Hyperactivity: There have been post-marketing reports of hyperactivity with administration of sapropterin. Patients should be monitored for hyperactivity.

Adverse Reactions: The most common adverse reactions (incidence ≥4%) in patients treated with sapropterin are headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.

Efficacy: The safety and efficacy of sapropterin was evaluated in five clinical studies in patients with PKU. In clinical trials, approximately 20% to 56% of PKU patients responded to treatment with sapropterin. Study 2 evaluated 88 patients with PKU who were responders to sapropterin in Study 1. After a washout period from Study 1, patients were randomized to either sapropterin 10mg/kg or placebo daily for six weeks. At six weeks, the change in adjusted baseline mean in blood Phe level was -239 and +6 for the sapropterin and placebo groups. The difference between the groups was statistically significant ($p<0.001$).

Cost:

Medication	Cost Per Month¥	Cost Per Year¥
Kuvan® (sapropterin) all strengths/formulations	**$15,825.00**	**$189,900.00**

Costs do not reflect rebated prices or net costs.
Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
¥Costs based on 75kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Kuvan® (sapropterin) with the following 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 greater than or equal to a 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 greater than or equal to a 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 greater than or equal to a 30% decrease in blood phenylalanine levels from baseline.
5. Subsequent approvals will be for the duration of one year.

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[1] Bodamer, Olaf. Overview of Phenylketonuria. *UpToDate*. Available online at: http://www.uptodate.com/contents/overview-of-phenylketonuria?source=search_result&search=phenylalanine&selectedTitle=1%7E150. Last revised 06/2016. Last accessed 04/2017.

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Appendix I

30-Day Notice to Prior Authorize Lumizyme® (Alglucosidase Alfa Injection)

Oklahoma Health Care Authority
May 2017

Pompe Disease (Acid Alpha-Glucosidase Deficiency)[1,2,3]

Acid alpha-glucosidase (GAA) deficiency, also known as Pompe disease, is an autosomal recessive, genetic, neuromuscular disorder with an incidence of approximately 1 in 40,000 people in the United States with variances among different ethnic groups. Pompe disease is classified as a glycogen storage disease type II and leads to the accumulation of glycogen within the lysosomes in all tissues. The lyosomal GAA enzyme defect affects lyosomal-mediated degradation of glycogenesis leading to accumulation of glycogen in lysosomes and cytoplasm resulting in tissue destruction. GAA deficiency is caused by mutations in the gene encoding lyosomal acid alpha-1,4-glucosidase and more than 500 mutations causing the disorder have been found. There are two classifications: infantile-onset and late-onset form.

The classic GAA infantile form is typically present within the first few months of life, with a median age of onset of 4 months of age. It is characterized by cardiomegaly, severe, generalized hypotonia (floppy baby), respiratory distress, muscle weakness, feeding difficulties, and failure to thrive. Facial features include enlarged tongue, wide open mouth and eyes, and poor facial muscle tone. Hepatomegaly may be present secondary to heart failure. Most patients with infantile-onset do not survive beyond the first year or two of life without treatment.

The late-onset form, also known as juvenile and adult form, can present at any age with variable clinical symptoms from asymptomatic to severe, progressive myopathy leading to respiratory failure. Children usually present with delayed gross-motor development, delayed milestones, and progressive muscle weakness in the limb-girdle distribution and diaphragm. Adult patients also present with progressive limb-girdle distribution myopathy and diaphragm involvement. Older children and adults usually do not have cardiomegaly or cardiac involvement, however, the diaphragmatic involvement leads to respiratory distress and failure.

The symptoms of Pompe disease can vary widely between persons; therefore, care and treatment must be individualized for each patient's needs. Most patients require some level of respiratory support during the course of disease and a multidisciplinary care team with support from rehabilitation, cardiology, pulmonology, orthopedics, nutrition, physical, occupational, and speech therapy. The primary treatment for GAA deficiency is enzyme replacement therapy (ERT) with recombinant human alglucosidase alfa derived from Chinese hamster ovary cells.

In April 2006, the U.S. Food and Drug Administration (FDA) approved Myozyme® (alglucosidase alfa) for use in patients with infantile-onset Pompe disease. Lumizyme® (alglucosidase alfa), produced from the same cell line as Myozyme® but with a larger volume bioreactor to scale-up production, was FDA approved in May 2010 for treatment of late-onset Pompe disease. In

August 2014, the FDA expanded the approval of Lumizyme® to all patients with Pompe disease with no limitation of age or phenotype following supportive data from the ADVANCE trial and biochemical analysis demonstrating alglucosidase alfa 4,000L (Lumizyme®) is comparable to alglucosidase alfa 160L (Myozyme®). Sanofi Genzyme, the makers of both products, announced in October 2014 that as of December 31, 2014, Myozyme® will no longer be available and all resources will shift to the production of Lumizyme®.

Utilization of Lumizyme® (Alglucosidase Alfa): Calendar Year 2016

Utilization Details of Lumizyme® (Alglucosidase Alfa): Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
LUMIZYME® INJECTION	5	1	$151,300.55	$1,080.72	$30,260.11	100%
TOTAL	**5**	**1***	**$151,300.55**	**$1,080.72**	**$30,260.11**	**100%**

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

- There was no use of Lumizyme® (alglucosidase alfa) during calendar year 2015.
- There were no medical claims for Lumizyme® (alglucosidase alfa) during calendar year 2016.

Demographics of Members Utilizing Lumizyme® (Alglucosidase Alfa)

- Due to the small number of members utilizing Lumizyme® (alglucosidase alfa) during calendar year 2016, detailed demographic information could not be provided.

Top Prescriber Specialties of Lumizyme® (Alglucosidase Alfa) by Number of Claims

- The only prescriber specialty listed on paid pharmacy claims for Lumizyme® (alglucosidase alfa) during calendar year 2016 was geneticist.

Market News and Updates[4,5]

Patent Expiration(s):

- Lumizyme® (alglucosidase alfa) exclusivity end date: 04/2013; currently there is no approved biosimilar.

News:

- **March 2017:** The *Molecular Therapy* journal published a recent Phase 2a, open-label study demonstrating the investigational drug duvoglustat HCl (AT2220, 1-deoxynojirimycin) that works as a chaperone of GAA by increasing exposure of active GAA levels in plasma and skeletal muscle leading to greater substrate reduction in muscle. The Phase 2a study demonstrated a further 1.2 to 2.8-fold increase in GAA activity and plasma concentration compared to GAA alone in 25 Pompe patients.

Lumizyme® (Alglucosidase Alfa) Product Summary[6]

Indications: Lumizyme® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency).

Dosing:

- Lumizyme® is available as an intravenous (IV) injection supplied as 50mg alglucosidase alfa lyophilized powder in a single-use vial for reconstitution.
- The recommended dosing of alglucosidase alfa is 20mg per kilogram (kg) of body weight administered every two weeks as an IV infusion.

Mechanism of Action: Pompe disease is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA. Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule. After which alglucosidase alfa is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

Contraindications: None.

Warnings and Precautions:

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If anaphylaxis or severe hypersensitivity reactions occur, the infusion should be immediately discontinued and appropriate medical treatment should be initiated.
- Immune-Mediated Reactions: Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs.
- Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion.
- Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

Adverse Reactions: The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

Efficacy: The safety and efficacy of alglucosidase alfa in Pompe disease was studied in 57 treatment-naïve infantile-onset patients in three open-label clinical trials and in one randomized, double-blind, placebo-controlled trial in 90 patients with late-onset disease.

Infantile-Onset Studies:

- Study 1 randomized equally 18 infantile-onset patients 7 months of age or younger at time of first infusion with clinical signs of Pompe disease and cardiac hypertrophy, who did not require ventilator support at study entry to receive either alglucosidase alfa 20mg/kg or 40mg/kg every two weeks, with length of treatment ranging from 52 to 106 weeks, until the patient reached 18 months of age. Efficacy was accessed comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months with the mortality experience of a historical cohort. By 18 months of age, 15 of the 18 (83%) patients were alive without invasive ventilator support and 3 (17%) required invasive ventilator support compared to only 1 of the 61 (2%) historical control patients was alive. There were no differences in outcome between 20mg/kg and 40mg/kg doses.
- Study 2 enrolled 21 infantile-onset Pompe disease patients 3 months to 3.5 years of age at first infusion; 5 of the 21 patients were receiving invasive ventilator support at time of first infusion. All patients received 20mg/kg alglucosidase alfa every other week for up to 104 weeks. The primary outcome was the proportion of patients alive at the conclusion of treatment. At the 52-week interim analysis, 16 of 21 patients were alive. Of the 16 patients not on invasive ventilator support at time of first infusion, 4 died and 2 required invasive ventilator support. Of the 5 patients who were receiving invasive ventilator support at baseline, 1 died and 4 remained on invasive ventilator support at Week 52.
- Study 3 enrolled 18 infantile-onset Pompe disease patients who had a confirmed diagnosis as identified through a newborn screening program. All patients were Cross Reactive Immunologic Material (CRIM) positive and treated with alglucosidase alfa prior to 6 months of age (0.2 months to 5.8 months at time of first infusion). A total of 16 patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

Late-Onset Study:

- A total of 90 patients with late-onset Pompe disease 10 to 70 years of age were accessed in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa treated patient was 16 years of age and the youngest placebo-treated patient was 10 years of age. Patients were randomized 2:1 to receive 20mg/kg alglucosidase alfa or placebo every other week for 18 months (78 weeks). At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30% and 79% predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded. At baseline, the mean FVC% in the sitting position for all patients was about 55%. After 78 weeks, the mean percent predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased for placebo-treated patients to 52.8% indicating an alglucosidase alfa treatment effect of 3.4% (95% CI: [1.3% to 5.5%]; p=0.004). Stabilization of percent predicted FVC in the alglucosidase

alfa-treated patients was observed. At study entry, the mean 6 minute walk test (6MWT) among all patients was 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% CI: [-1 to 52 meters]; p=0.06).

Cost:

Medication	Cost Per Unit*	Cost Per Treatment¥	Cost Per Year¥
Lumizyme® (alglucosidase alfa) 50mg vial	**$754.00**	**$21,112.00**	**$548,912.00**

Costs do not reflect rebated prices or net costs.
*Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
¥Costs based on 70kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Lumizyme® (alglucosidase alfa) with the following criteria:

Lumizyme® (Alglucosidase Alfa) Infantile-Onset Approval Criteria:

1. An FDA approved diagnosis of infantile-onset Pompe disease (acid alpha-glucosidase [GAA] deficiency); and
2. Documentation of diagnosis confirmation of GAA enzyme deficiency through specific genetic laboratory test(s); and
3. Lumizyme® must be prescribed by a geneticist or a physician that specializes in the treatment of Pompe disease and/or inherited genetic disorders; and
4. Member's weight must be provided and have been taken within the last four weeks to ensure accurate dosing.

Lumizyme® (Alglucosidase Alfa) Late-Onset (Non-Infantile) Approval Criteria:

1. An FDA approved diagnosis of late-onset (non-infantile) Pompe disease (acid alpha-glucosidase [GAA] deficiency); and
2. Documentation of diagnosis confirmation of GAA enzyme deficiency through specific genetic laboratory test(s); and
3. Provider must document presence of symptoms; and
4. Lumizyme® must be prescribed by a geneticist or a physician that specializes in the treatment of Pompe disease and/or inherited genetic disorders; and
5. Member's weight must be provided and have been taken within the last four weeks to ensure accurate dosing.
6. Initial approval will be for the duration of six months, at that time compliance and information regarding efficacy, such as improvement or stabilization in Forced Vital Capacity (FVC) and/or 6-minute walk test (6MWT), will be required for continued approval. Additional authorization will be for the duration of one year.

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Appendix J

30-Day Notice to Prior Authorize Alpha$_1$-Proteinase Inhibitors: Aralast NP™, Glassia™, Prolastin®-C, and Zemaira®

Oklahoma Health Care Authority
May 2017

Alpha$_1$ Antitrypsin Deficiency[1,2]

Alpha$_1$ antitrypsin deficiency (AATD) also referred to as Alpha$_1$-proteinase inhibitor deficiency, is an inherited disorder affecting the lungs, liver, and rarely, skin. AATD is inherited by autosomal co-dominant transmission, meaning that affected individuals have inherited an abnormal alpha$_1$ antitrypsin (AAT) gene from each parent. The gene that encodes AAT is called *SERPINA1* (formerly known as Pi). Nearly 24 variants of the alpha$_1$-antiprotease molecule have been identified, and all are inherited as codominant alleles. The most common form of AATD is associated with allele Z, or homozygous PiZ (ZZ). Serum levels of AAT in these patients are about 3.4 to 7µmol/L, 10% to 15% of normal serum levels. Serum levels greater than 11µmol/L appear to be protective (further explained below). AAT is a protease inhibitor of the proteolytic enzyme elastase and also of the proteases trypsin, chymotrypsin, and thrombin. It is part of a larger family of structurally unique **ser**ine **p**rotease **in**hibitors, referred to as serpins. In the lungs, AATD causes chronic obstructive pulmonary disease (COPD). This is thought to result from an imbalance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin. In the liver, the pathogenesis is quite different. Liver disease results from the accumulation within the hepatocyte of variant AAT protein. The accumulation of intrahepatic AAT is thought to result in apoptosis of hepatocytes. This initially can manifest as laboratory abnormalities, but also can progress to hepatitis, followed by fibrosis and cirrhosis. The incidence of liver disease increases with age.

AATD is generally considered to be rare; however, estimates that 80,000 to 100,000 individuals in the United States have severe deficiency of AAT suggest that the disease is under-recognized. The prevalence of AATD varies considerably from one country to another; however, it is estimated that more than three million people worldwide have allele combinations associated with severe deficiency of AAT.

Slowly progressive dyspnea is the primary symptom, though many patients initially have symptoms of cough, sputum production, or wheezing. Treatment involves smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen when indicated, and physical rehabilitation in a program similar to that designed for patients with smoking-related COPD. Another option may include surgical management using lung volume reduction surgery. In patients with advanced lung disease or end-stage hepatic disease, solid organ transplantation may be an option. Additionally, intravenous (IV) augmentation therapy with AAT benefits some patients. IV augmentation via the infusion of AAT is currently the most direct and efficient means of elevating AAT levels in the plasma and lung interstitium. The goal of AAT

augmentation is to slow the progression of emphysema. There are currently four pooled human plasma AAT products available: Aralast NP™, Glassia™, Prolastin®-C, and Zemaira®. These products work by restoring serum and alveolar AAT concentrations to protective levels; restoring the balance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin.

Utilization of Alpha$_1$-Proteinase Inhibitors: Calendar Year 2016

Utilization of Alpha$_1$-Proteinase Inhibitors: Medical Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Total Units
2016	2	5	$11,750.38	$2,350.08	2,556

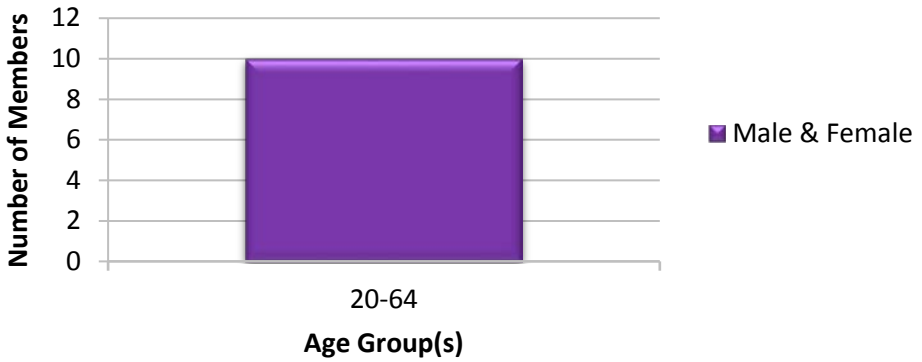
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Comparison of Calendar Years: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	6	53	$347,477.95	$6,556.19	$234.15	798,916	1,484
2016	10	76	$623,160.05	$8,199.47	$292.84	1,330,836	2,128
% Change	**66.70%**	**43.40%**	**79.30%**	**25.10%**	**25.10%**	**66.60%**	**43.40%**
Change	**4**	**23**	**$275,682.10**	**$1,643.28**	**$58.69**	**531,920**	**644**

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

Demographics of Members Utilizing Alpha$_1$-Proteinase Inhibitors



Top Prescriber Specialties of Alpha$_1$-Proteinase Inhibitors by Number of Claims

- The only prescriber specialty listed on paid pharmacy claims for alpha$_1$-proteinase inhibitors during calendar year 2016 was pulmonary disease specialist.

Market News and Updates[3]

Guidelines Update(s):

- **February 2016:** The *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* published clinical practice guidelines entitled "The Diagnosis and Management of Alpha$_1$ Antitrypsin Deficiency in the Adult." To update the 2003 guidance, a systematic review was performed to identify citations related to AATD that were published since the 2003 comprehensive review, specifically evaluating publications between January 2002 and December 2014.
  - The major recommendations continue to endorse and reinforce the importance of testing for AATD in all adults with symptomatic fixed airflow obstruction, whether clinically labeled as COPD or asthma. Individuals with unexplained bronchiectasis or liver disease also should be tested. Family testing of first-degree relatives is currently the most efficient detection technique.
  - In general, individuals with AATD and emphysema, bronchiectasis, and/or liver disease should be managed according to usual guidelines for these clinical conditions.
  - In countries where IV augmentation therapy with purified pooled human plasma-derived AAT is available, recent evidence now provides strong support for its use in appropriate individuals with lung disease due to AATD. This includes patients with a forced expiratory volume in one second (FEV_1) less than or equal to 65% predicted. It excludes individuals with lung disease due to AATD who continue to smoke, and with AATD and emphysema or bronchiectasis who do not have airflow obstruction. In regard to augmentation therapy, weekly doses higher than the current U.S. Food and Drug Administration (FDA) approved dose and monitoring of trough AAT blood levels to evaluate the adequacy of AAT augmentation dosing are not recommended.

Alpha$_1$-Proteinase Inhibitors Class Summary[4,5,6,7]

Products: Aralast NP™, Glassia™, Prolastin®-C, and Zemaira®

Indications: Alpha$_1$-proteinase inhibitors (human) (Alpha$_1$-PI) are indicated for chronic augmentation therapy in adults with clinically evident emphysema due to severe congenital deficiency of Alpha$_1$-PI. They increase antigenic and functional (anti-neutrophil elastase capacity, ANEC) serum levels and antigenic lung epithelial lining fluid (ELF) levels of Alpha$_1$-PI. The effect of augmentation therapy with any of the Alpha$_1$-PI products on pulmonary exacerbations and on the progression of emphysema in AATD has not been conclusively demonstrated in randomized, controlled clinical trials. Clinical data demonstrating the long-term effects of chronic augmentation and maintenance therapy of individuals using these products is not available. Alpha$_1$-PIs are not indicated as therapy for lung disease in patients in whom severe Alpha$_1$-PI deficiency has not been established.

Dosing:

	Aralast NP™	Glassia™	Prolastin®-C	Zemaira®
Weekly IV dose: 60mg/kg	X	X	X	X
Infusion rate: 0.2mL/kg/minute	X	X		
Infusion rate: 0.08mL/kg/minute			X	X
Lyophilized powder in single-use 500mg vial*	X			
Lyophilized powder in single-use 1g vial*	X		X	X
Sterile, ready-to-use, single-dose 1g/50mL vial		X		
Option to self-administer+		X		
Healthcare provider administration only	X		X	X

***Powder for reconstitution comes in a kit containing a suitable volume of sterile water for injection, USP diluent and other items for reconstitution/infusion as determined by the manufacturer.

+Self-administered by the patient/caregiver only after appropriate training.

IV= Intravenous

Contraindications:

- Immunoglobulin A (IgA) deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity.

Warnings and Precautions:

- Hypersensitivity Reactions: These products may contain trace amounts of IgA. Patients with known antibodies to IgA, which can be present in patients with selective or severe IgA deficiency, have a greater risk of developing severe hypersensitivity and anaphylactic reactions. The recommended infusion rates should be closely followed and vital signs should be continuously monitored. The infusion should be discontinued if hypersensitivity symptoms occur and appropriate emergency treatment administered. It is recommended that epinephrine and other appropriate supportive therapy are available for the treatment of any acute anaphylactic or anaphylactoid reaction.
- Transmission of Infectious Agents: These products are made from human plasma; therefore, they may carry a risk of transmitting infectious agents, such as viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmitting an infectious agent has been minimized through various methods; however, these products may still potentially transmit human pathogenic agents.

Adverse Reactions: The most common adverse reactions occurring in at least 5% of infusions in clinical studies included the following:

	Aralast NP™	Glassia™	Prolastin®-C	Zemaira®
Asthenia				X
Bronchitis				X
Fever				X
Headache	X	X	X	X
Increased Cough				X
Injection Site Bruise	X			
Injection Site Hemorrhage				X
Musculoskeletal Discomfort	X			
Nausea	X			
Rhinitis				X
Rhinorrhea	X			
Sinusitis				X
Sore Throat				X
Upper Respiratory Infection		X		X
Vasodilation				X

Use in Special Populations:

- Pregnancy: Animal reproduction studies have not been conducted with these products. It is also not known whether these products can cause fetal harm when administered to pregnant women or can affect reproductive capacity. Alpha$_1$-PIs should be given to a pregnant woman only if clearly needed.
- Lactation: It is not known whether Alpha$_1$-PI is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when any of these products are administered to a nursing woman.
- Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
- Geriatric Use: Safety and effectiveness in patients over 65 years of age have not been established.

Production: Each Alpha$_1$-PI product is produced from pooled human plasma using the cold ethanol fractionation process. The product then undergoes further purification steps with processes which may include polyethylene glycol and zinc chloride precipitations and ion exchange chromatography. To reduce the risk of viral transmission, the manufacturing process may also include treatment with a solvent detergent mixture and a nanofiltration step.

Efficacy: The clinical efficacy of any Alpha$_1$-PI product in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

	Aralast NP™	Glassia™	Prolastin®-C*	Zemaira®
Number of subjects in the trial	13	50	23	44
8 Weeks of treatment	X			
24 Weeks of treatment		X		X
26 Weeks of treatment			X	
Statistically significant increase in ANEC of the ELF of the lower respiratory tract of the lung after treatment			X	
Mean plasma Alpha$_1$-PI levels > 11µmol/L after treatment	X	X	X	X

*Prolastin® was the first FDA approved Alpha$_1$-PI; all other product approvals based on comparability to Prolastin®.
ANEC = anti-neutrophil elastase capacity; ELF = epithelial lining fluid

Cost:

Medication	Cost Per mg	Cost Per Month$^{\Delta}$	Cost Per Year$^{\Delta}$
Aralast NP™	$0.52	$9,360.00	$112,320.00
Glassia™	$0.52	$9,360.00	$112,320.00
Prolastin®-C	$0.49	$8,820.00	$105,840.00
Zemaira®	$0.52	$9,360.00	$112,320.00

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.
$^{\Delta}$Cost for treatment based on dosing of 60mg/kg for 75kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Aralast NP™, Prolastin®-C, Zemaira®, and Glassia™ (alpha$_1$-proteinase inhibitor [human]) with the following criteria based, in part, on cost after rebates:

Prolastin®-C (Alpha$_1$-Proteinase Inhibitor [Human]) Approval Criteria:

1. An FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha$_1$-antitrypsin (AAT) with clinical evidence of emphysema; and
2. Diagnosis confirmed by all of the following:
    a. Genetic confirmation of PiZZ, PiZ(null) or Pi(null, null) phenotype alpha$_1$-antitrypsin deficiency (AATD) or other alleles determined to increase risk of AATD; and
    b. Serum levels of AAT less than 11µmol/L; and
    c. Documented emphysema with airflow obstruction; and
3. Prescriber must document that member's forced expiratory volume in one second (FEV$_1$) is less than or equal to 65% predicted; and
4. Must be prescribed by a pulmonary disease specialist or advanced care practitioner specializing in pulmonary disease; and
5. The prescriber must verify the member is a non-smoker; and
6. The prescriber must verify the member does not have antibodies to IgA; and

7. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Aralast NP™ and Glassia™ (Alpha$_1$-Proteinase Inhibitor [Human]) Approval Criteria:

1. An FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha$_1$-antitrypsin (AAT) with clinical evidence of emphysema; and
2. Diagnosis confirmed by all of the following:
    a. Genetic confirmation of PiZZ, PiZ(null) or Pi(null, null) phenotype alpha$_1$-antitrypsin deficiency (AATD) or other alleles determined to increase risk of AATD; and
    b. Serum levels of AAT less than 11µmol/L; and
    c. Documented emphysema with airflow obstruction; and
3. Prescriber must document that member's forced expiratory volume in one second (FEV_1) is less than or equal to 65% predicted; and
4. Must be prescribed by a pulmonary disease specialist or advanced care practitioner specializing in pulmonary disease; and
5. The prescriber must verify the member is a non-smoker; and
6. The prescriber must verify the member does not have antibodies to IgA; and
7. A patient-specific, clinically significant reason why the member cannot use Prolastin®-C; and
8. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Zemaira® (Alpha$_1$-Proteinase Inhibitor [Human]) Approval Criteria:

1. An FDA approved indication for augmentation and maintenance therapy of patients 18 years of age or older with severe hereditary deficiency of alpha$_1$-antitrypsin (AAT) with clinical evidence of emphysema; and
2. Diagnosis confirmed by all of the following:
    a. Genetic confirmation of PiZZ, PiZ(null) or Pi(null, null) phenotype alpha$_1$-antitrypsin deficiency (AATD) or other alleles determined to increase risk of AATD; and
    b. Serum levels of AAT less than 11µmol/L; and
    c. Documented emphysema with airflow obstruction; and
3. Prescriber must document that member's forced expiratory volume in one second (FEV_1) is less than or equal to 65% predicted; and
4. Must be prescribed by a pulmonary disease specialist or advanced care practitioner specializing in pulmonary disease; and
5. The prescriber must verify the member is a non-smoker; and
6. The prescriber must verify the member does not have antibodies to IgA; and
7. A patient-specific, clinically significant reason why the member cannot use Prolastin®-C, Aralast NP™, or Glassia™; and

8. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Utilization Details of Alpha$_1$-Proteinase Inhibitors: Calendar Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
PROLASTIN-C INJ 1000MG	71	9	$596,016.00	$299.81	$8,394.59	95.64%
ZEMAIRA INJ 1000MG	5	1	$27,144.05	$193.89	$5,428.81	4.36%
TOTAL	**76**	**10***	**$623,160.05**	**$292.84**	**$8,199.47**	**100.00%**

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

[1] Stoller, JK. *Up-To-Date*. Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency. Available online at: http://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-natural-history-of-alpha-1-antitrypsin-deficiency?source=search_result&search=alpha+1+antitrypsin+deficiency&selectedTitle=1%7E90. Last revised 03/17/2016. Last accessed 04/12/2017.

[2] Izaguirre-Anariba, DE. Alpha1-Antitrypsin Deficiency Clinical Presentation. *Medscape*. Available online at: http://emedicine.medscape.com/article/295686-clinical#b5. Last revised 02/10/2017. Last accessed 04/12/2017.

[3] Sandhaus RA, Turino G, Brantly ML, et al. The diagnosis and management of alpha-1 antitrypsin deficiency in the adult. *Chronic Obstr Pulm Dis (Miami)*. 2016; 3(3): 668-682.

[4] Aralast NP™ Prescribing Information. Baxalta US Inc. Available online at: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=a9a5b46e-04da-41bd-bb5f-c4936b664fef&type=display%20-%20section-11. Last revised 09/2016. Last accessed 04/12/2017.

[5] Prolastin®-C Prescribing Information. Grifols Therapeutics Inc. Available online at: http://www.prolastin.com/documents/24987357/0/prolastinPI/b436e646-0787-4aad-a3d5-b5e004cc92c6. Last revised 08/2016. Last accessed 04/12/2017.

[6] Glassia™ Prescribing Information. Shire US Inc. Available online at: http://www.shirecontent.com/PI/PDFs/GLASSIA_USA_ENG.pdf. Last revised 06/2016. Last accessed 04/12/2017.

[7] Zemaira® Prescribing Information. CSL Behring LLC. Available online at: http://labeling.cslbehring.com/PI/US/Zemaira/EN/Zemaira-Prescribing-Information.pdf. Last revised 09/2015. Last accessed 04/12/2017.

Appendix K

Fiscal Year 2016 Annual Review of Antiparasitic Medications and 30-Day Notice to Prior Authorize Impavido® (Miltefosine)

Oklahoma Health Care Authority
May 2017

Current Prior Authorization Criteria

Albenza® (Albendazole) Approval Criteria:

1. A quantity of six tablets will process without prior authorization. For infections requiring additional doses, a prior authorization will need to be submitted and the following criteria will apply:
    a. An FDA approved diagnosis of one of the following:
        i. Treatment of parenchymal neurocysticercosis due to active lesions caused by larval forms of the pork tapeworm, *Taenia solium*; or
        ii. Treatment of cystic hydatid disease of the liver, lung, and peritoneum, caused by the larval form of the dog tapeworm, *Echinococcus granulosus*.

Emverm™ (Mebendazole) Approval Criteria:

1. An FDA approved diagnosis of any of the following:
    a. Treatment of *Enterobius vermicularis* (pinworm); or
    b. Treatment of *Trichuris trichiura* (whipworm); or
    c. Treatment of *Ascaris lumbricoides* (common roundworm); or
    d. Treatment of *Ancylostoma duodenale* (common hookworm); or
    e. Treatment of *Necator americanus* (American hookworm); and
2. For the treatment of *Enterobius vermicularis* (pinworm), *Ascaris lumbricoides* (common roundworm), *Ancylostoma duodenale* (common hookworm), or *Necator americanus* (American hookworm), a patient-specific, clinically significant reason why a more cost-effective anthelmintic therapy, such as albendazole or pyrantel pamoate, cannot be used must be provided.
3. The following quantity limits will apply:
    a. *Enterobius vermicularis (*pinworm): 2 tablets per approval
    b. *Trichuris trichiura* (whipworm): 6 tablets per approval
    c. *Ascaris lumbricoides* (common roundworm): 6 tablets per approval
    d. *Ancylostoma duodenale* (common hookworm): 6 tablets per approval
    e. *Necator americanus* (American hookworm): 6 tablets per approval

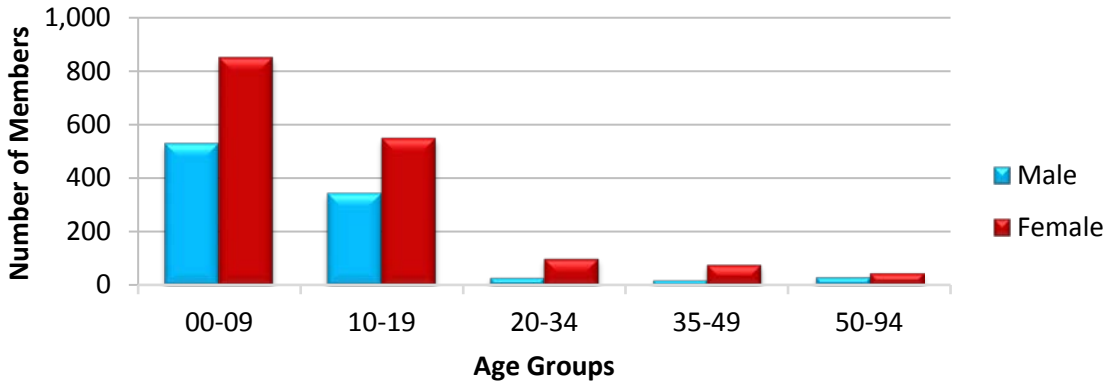
Utilization of Antiparasitic Medications: Fiscal Year 2016

Comparison of Fiscal Years

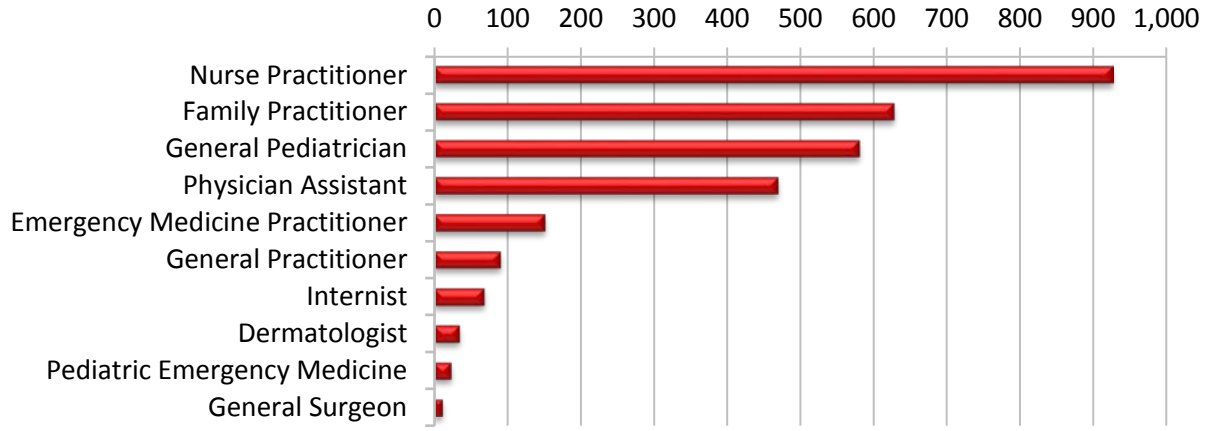
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	2,164	2,536	$817,571.70	$322.39	$39.50	12,132	20,699
2016	2,579	3,046	$1,102,039.71	$361.80	$43.57	13,466	25,293
% Change	**19.20%**	**20.10%**	**34.80%**	**12.20%**	**10.30%**	**11.00%**	**22.20%**
Change	**415**	**510**	**$284,468.01**	**$39.41**	**$4.07**	**1,334**	**4,594**

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

Demographics of Members Utilizing Antiparasitic Medications

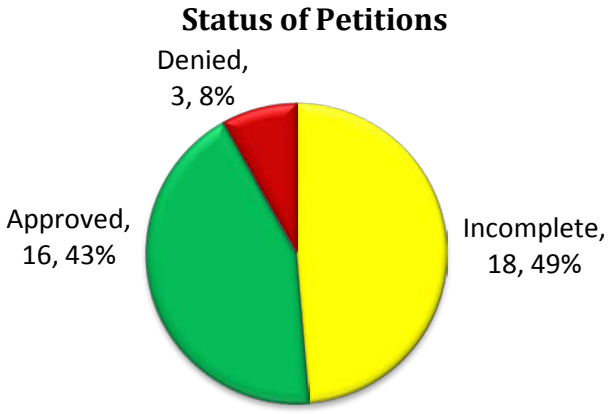


Top Prescriber Specialties of Antiparasitic Medications by Number of Claims



Prior Authorization of Antiparasitic Medications

There were 37 prior authorization requests submitted for antiparasitic medications during fiscal year 2016. The following chart shows the status of the submitted petitions.



Leishmaniasis Background Information[1,2,3]

Leishmaniasis is a parasitic disease that is caused by infection with *Leishmania* parasites. The parasites are transmitted by the bite of sandflies. There are several different forms of leishmaniasis; the most common forms are cutaneous leishmaniasis, which causes skin lesions, and visceral leishmaniasis, which can cause complications such as splenomegaly, thrombocytopenia, and anemia. Mucosal leishmaniasis is a less common form and can cause sores in the mucous membranes of the nose, mouth, or throat. It is estimated that the number of cutaneous leishmaniasis cases world-wide ranges from approximately 700,000 to 1,200,000 and the number of visceral leishmaniasis cases world-wide ranges from approximately 200,000 to 400,000. Leishmaniasis is found in parts of the tropics, subtropics, and southern Europe. Overall, leishmaniasis is found in more than 90 countries. Leishmaniasis is not usually found in the United States and almost all of the cases diagnosed in the United States were in people who became infected while traveling or living in other countries. However, there have been occasional cases of cutaneous leishmaniasis acquired in Texas and Oklahoma.

Prior to beginning treatment, the first step is to make sure the diagnosis is correct. Health care providers may consult with Centers for Disease Control and Prevention (CDC) staff about individual treatment decisions. Factors that need to be considered include the form of leishmaniasis, the species of *Leishmania* responsible for the infection, the potential severity of the infection, and the individual patient's co-morbid conditions. According to the CDC, not all cases of cutaneous leishmaniasis require treatment; however, in general, all clinically manifested cases of visceral and mucosal leishmaniasis should be treated. With cutaneous leishmaniasis the skin sores may heal on their own without treatment, but potential consequences of no treatment or suboptimal treatment include scarring, superinfection, persistence of a chronic wound, and for some species of *Leishmania*, mucosal leishmaniasis can be destructive or disfiguring. With visceral leishmaniasis, severe cases are typically fatal if left untreated; the fatality rate can be as high as 100% within two years in developing countries if the disease is not treated. Treatment approaches and regimens depend in part on host and parasite factors as some treatments are effective only against certain *Leishmania* species and only in particular geographic regions. Furthermore, the data from clinical trials is not necessarily generalizable to other settings. Additionally, special patient populations (e.g., pediatric, geriatric, pregnant/lactating women, immunocompromised) may require different

medications or treatment regimens. In the United States, special considerations also apply due to the availability of particular medications to treat leishmaniasis. For example, pentavalent antimonial compounds, which have been used for treating leishmaniasis since the 1940s, are not licensed for commercial use in the United States. However, Pentostam®, a pentavalent antimonial, is available through the CDC Drug Service under an Investigational New Drug (IND) protocol approved by the U.S. Food and Drug Administration (FDA). Liposomal amphotericin B, which is administered by an intravenous infusion, is FDA-approved for the treatment of visceral leishmaniasis. In 2014, the FDA approved Impavido® (miltefosine) for the treatment of cutaneous, mucosal, and visceral leishmaniasis caused by particular *Leishmania* species in adults and adolescents at least 12 years of age who weigh at least 30kg. Other treatment options available in the United States that might be used for treating selected cases of leishmaniasis but are not FDA approved for this indication include pentamidine, amphotericin B deoxycholate, as well as the "azoles" (ketoconazole, itraconazole, and fluconazole).

Impavido® (Miltefosine) Product Summary[4]

Indications: Impavido® (miltefosine) is an antileishmanial drug indicated in adults and adolescents 12 years of age and older weighing 30kg (66lbs) or more for treatment of:

- Visceral leishmaniasis due to *Leishmania donovani*
- Cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, and *Leishmania panamensis*
- Mucosal leishmaniasis due to *Leishmania braziliensis*

Limitations of use: *Leishmania* species evaluated in clinical trials were based on epidemiologic data. There may be geographic variation in the response of the same *Leishmania* species to miltefosine. The efficacy of miltefosine in the treatment of other *Leishmania* species has not been evaluated.

Dosing:

- Impavido® is available as a 50mg capsule.
- The recommended dosage for patients weighing 30 to 44kg is one 50mg capsule twice daily with food. For patients weighing 45kg or greater, the recommended dosage is one 50mg capsule three times daily with food. The treatment duration is 28 consecutive days.

Mechanism of Action: The specific mode of action of miltefosine against *Leishmania* species is unknown. Miltefosine's mechanism of action is likely to involve interaction with lipids, inhibition of cytochrome c oxidase, and apoptosis-like cell death.

Boxed Warning: Embryo-Fetal Toxicity

- Miltefosine may cause fetal harm. Fetal death and teratogenicity occurred in animals administered miltefosine at doses lower than the recommended human dose. A serum or urine pregnancy test should be obtained in females of reproductive potential prior to prescribing miltefosine. Females of reproductive potential should be advised to use effective contraception during miltefosine therapy and for 5 months after therapy. Miltefosine should not be administered to pregnant women.

Contraindications:

- Pregnancy
- Sjögren-Larsson-Syndrome
- Hypersensitivity to miltefosine or any of its excipients

Adverse Reactions: The most common adverse reactions occurring in ≥2% of patients treated with miltefosine include:

- Nausea
- Vomiting
- Diarrhea
- Headache
- Decreased appetite
- Dizziness
- Abdominal pain
- Pruritus
- Somnolence
- Elevated transaminases
- Elevated creatinine

Use in Specific Populations:

- Pregnancy: Miltefosine is Pregnancy Category D. Miltefosine may cause fetal harm. Human pregnancy data are not available; however, embryo-fetal toxicity including death and teratogenicity was observed in embryo-fetal studies in rats and rabbits administered oral miltefosine during organogenesis at doses that were 0.06 and 0.2 times the maximum recommended human dose (MRHD), respectively, based on body surface area comparison. Miltefosine should not be administered to pregnant women.
- Lactation: It is not known whether miltefosine is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from miltefosine, a decision should be made to either discontinue nursing or discontinue the medication, taking into account the importance of the medication to the mother. Breastfeeding should be avoided for five months after miltefosine therapy.
- Pediatric Use: The safety and effectiveness of miltefosine in pediatric patients under 12 years of age have not been established. Juvenile rats were more sensitive to the miltefosine-induced effects, especially retinal and kidney effects, than adult rats.
- Geriatric Use: Clinical studies of miltefosine did not include a sufficient number of patients 65 years of age and over to determine whether they respond differently than younger patients.
- Renal Impairment: Patients with serum creatinine or blood urea nitrogen levels ≥1.5 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with renal impairment.
- Hepatic Impairment: Patients with serum levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3 times the upper limit of normal and bilirubin levels ≥2 times the upper limit of normal were excluded from the clinical studies. Miltefosine pharmacokinetics have not been studied in patients with hepatic impairment.
- Females and Males of Reproductive Potential: Miltefosine may cause fetal harm when used during pregnancy. Females of reproductive potential should be advised to use effective contraception during miltefosine therapy and for five months after therapy is completed. Vomiting and/or diarrhea occurring during miltefosine therapy may affect absorption of oral contraceptives and therefore may compromise their efficacy. Females who use oral contraceptives should be advised to use additional non-hormonal

or alternative method(s) of effective contraception during miltefosine therapy if vomiting and/or diarrhea occurs. Furthermore, miltefosine caused impaired fertility in rats and caused reversible follicular atresia and diestrus in dogs at doses approximately 1.0 and 0.2 times respectively the MRHD. Miltefosine also caused reduced viable sperm counts and impaired fertility in rats at doses approximately 0.4 times the MRHD. A higher dose in rats caused testicular atrophy and impaired fertility that did not fully reverse ten weeks after drug administration ended. Men and women should be advised of the animal fertility findings and that the potential for impaired fertility with miltefosine therapy has not been adequately studied.

Efficacy:

- Treatment of Visceral Leishmaniasis: The efficacy of miltefosine in the treatment of visceral leishmaniasis was evaluated in a randomized, open-label, active-controlled study. The study was conducted in Bihar, India, an area where *L. donovani* is known epidemiologically to be the prevalent infecting species. Patients 12 years of age and older with clinical signs and symptoms compatible with visceral leishmaniasis confirmed by the presence of *Leishmania* amastigotes in aspirates of spleen or bone marrow were randomized to receive oral miltefosine or intravenous amphotericin B deoxycholate in a 3:1 ratio. Patients weighing 25kg and greater received miltefosine 50mg with meals twice a day and patients weighing less than 25kg received miltefosine 50mg with meals once a day in the morning. Patients were hospitalized for the duration of treatment. Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at six months follow up. During the study, 299 patients received miltefosine and 99 patients received amphotericin B given intravenously over six continuous hours at 1mg/kg every other day for 15 doses. Approximately 70% of patients in each arm had previously failed treatment with pentavalent antimony. In each treatment arm 98% of patients achieved an initial cure. At six months after therapy 88 (29.5%) of miltefosine patients and 12 (12.1%) of amphotericin B patients continued to have signs and symptoms suggestive of visceral leishmaniasis. These signs and symptoms were attributed to alternative diagnosis in 73 patients. The remaining 27 patients, all in the miltefosine arm, underwent evaluation with splenic or bone marrow aspiration and nine were positive for *Leishmania* amastigotes, indicating relapse. The final cure rate for miltefosine was 94% and for amphotericin B was 97%.
- Treatment of Cutaneous Leishmaniasis: A placebo controlled study was performed in Columbia where *L. panamensis* and *L. braziliensis* are epidemiologically known to be the prevalent infecting *Leishmania* species, and in Guatemala where *L. braziliensis* is epidemiologically known to be the prevalent infecting species. The study included male and female patients older than 12 years of age who had newly diagnosed or relapsing cutaneous leishmaniasis without mucosal involvement, parasitologically confirmed, presenting with at least one skin ulcer with minimum area of $50mm^2$. Patients were randomized to receive miltefosine or placebo in a 2:1 allocation. Patients who weighed less than 45kg received miltefosine 50mg twice a day and patients who weighed 45kg or greater received miltefosine 50mg three times a day. Definite cure was defined as apparent (complete epithelialization of all lesions) or partial cure (incomplete epithelialization, no enlargement by more than 50% in lesions, no appearance of new

lesions, and negative parasitology if done) at two weeks after end of therapy and complete epithelialization of all ulcers at six months after end of therapy. The definite cure rate for miltefosine was statistically significantly higher than the cure rate for placebo; the difference between groups was 36.8% ($p<0.0001$).

- Treatment for Mucosal Leishmaniasis: A single arm study was conducted in Bolivia where *L. braziliensis* is epidemiologically the most prevalent species to evaluate the efficacy of miltefosine for the treatment of mucosal leishmaniasis. There were 79 patients 18 years of age and older with a cutaneous leishmaniasis scar plus parasites observed or cultured from lesion material or a positive skin test, and no clinically significant concomitant disease included in the study. Patients received miltefosine at a target dose of 2.5mg/kg/day for 28 days. By 12 months after the end of therapy, 49 patients had complete resolution of edema, erythema, infiltration, and erosion from the involved mucosal sites.

Cost: The wholesale acquisition cost of Impavido® is $577.17 per capsule, resulting is a cost per treatment of $32,321.52 to $48,482.28, depending on patient's weight.

Recommendations

The College of Pharmacy recommends the prior authorization of Impavido® (miltefosine) with the following criteria:

Impavido® (Miltefosine) Approval Criteria:

1. An FDA approved indication for treatment of:
    a. Visceral leishmaniasis due to *Leishmania donovani*; or
    b. Cutaneous leishmaniasis due to *Leishmania braziliensis*, *Leishmania guyanensis*, or *Leishmania panamensis*; or
    c. Mucosal leishmaniasis due to *Leishmania braziliensis*; and
2. Female members must not be pregnant and must have a pregnancy test prior to therapy initiation. Female members must be willing to use effective contraception while on therapy and for five months after completion of therapy; 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.
4. A quantity limit of 84 capsules per 28 days will apply.

Utilization Details of Antiparasitic Medications: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
ALBENZA TAB 200MG	1,788	1,589	$1,063,045.53	$59.83	$594.54	96.46%
IVERMECTIN TAB 3MG	1,238	1,002	$29,030.02	$3.98	$23.45	2.63%
BILTRICIDE TAB 600MG	11	11	$2,434.36	$16.12	$221.31	0.22%
EMVERM CHW 100MG	5	5	$7,421.60	$200.58	$1,484.32	0.67%
STROMECTOL TAB 3MG	4	4	$108.20	$2.52	$27.05	0.01%
TOTAL	**3,046**	**2,611***	**$1,102,039.71**	**$43.57**	**$361.80**	**100%**

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

[1] Leishmaniasis. Centers for Disease Control and Prevent (CDC). Available online at: https://www.cdc.gov/parasites/leishmaniasis/. Last revised 12/09/2016. Last accessed 04/21/2017.
[2] Anderson N. Cutaneous Leishmaniasis: Treatment. *UpToDate*. Available online at: http://www.uptodate.com/contents/cutaneous-leishmaniasis-treatment?source=search_result&search=leishmaniasis&selectedTitle=3%7E98#H113484778. Last revised 01/04/2017. Last accessed 04/25/2017.
[3] Visceral Leishmaniasis. World Health Organization (WHO). Available online at: http://www.who.int/leishmaniasis/visceral_leishmaniasis/en/. Last accessed 04/26/2017.
[4] Impavido® (Miltefosine) Prescribing Information. Profounda, Inc. Available online at: http://media.wix.com/ugd/a54292_eb861bfce29a43a185892ee0a7b15edb.pdf. Last revised 10/2015. Last accessed 04/17/2017.

Appendix L

Calendar Year 2016 Annual Review of Bowel Preparation Medications and 30-Day Notice to Prior Authorize ColPrep™ Kit (Sodium Sulfate/Potassium Sulfate/Magnesium Sulfate)

Oklahoma Health Care Authority
May 2017

Current Prior Authorization Criteria

OsmoPrep®, Prepopik®, Suclear®, and SUPREP® Approval Criteria:

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

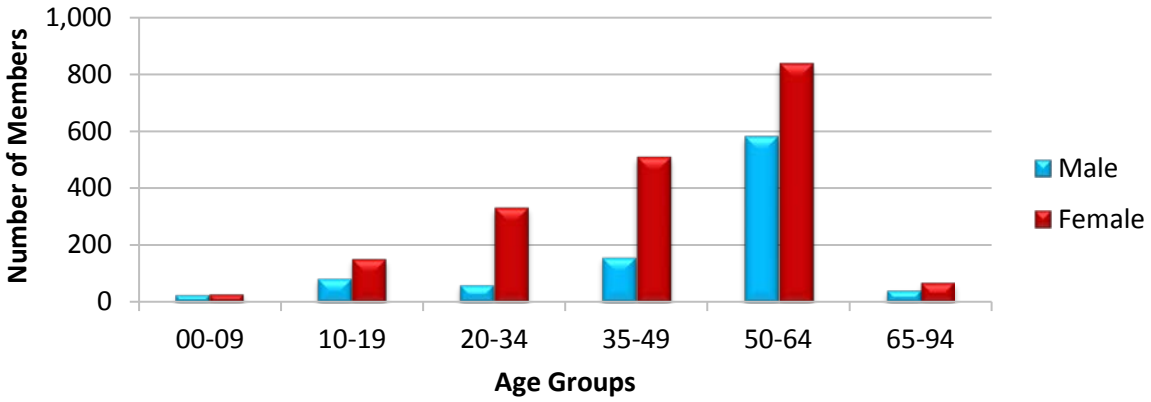
Utilization of Bowel Preparation Medications: Calendar Year 2016

Comparison of Calendar Years

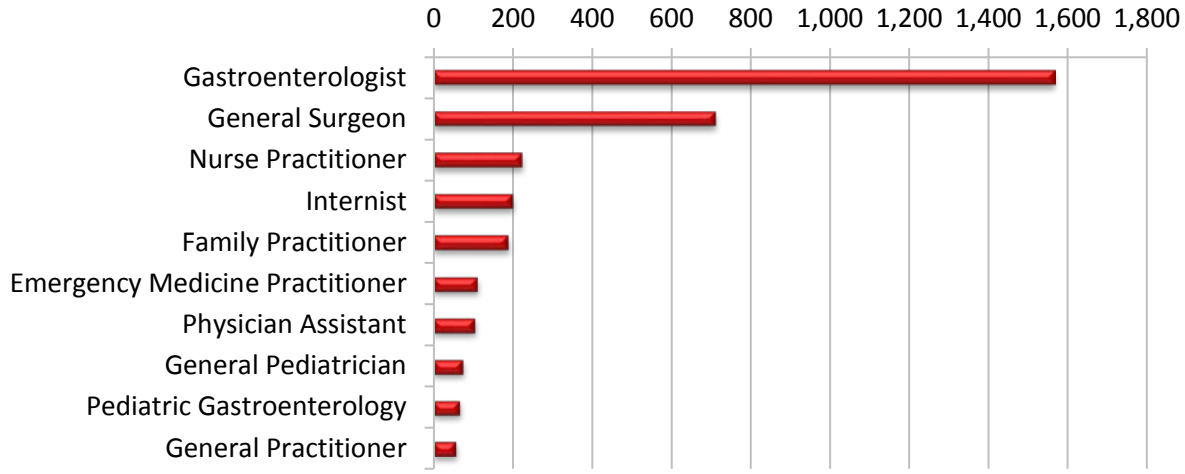
Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	2,962	3,323	$178,661.04	$53.76	$14.62	6,703,828	12,221
2016	2,887	3,267	$137,768.44	$42.17	$12.24	8,838,495	11,255
% Change	**-2.50%**	**-1.70%**	**-22.90%**	**-21.60%**	**-16.30%**	**31.80%**	**-7.90%**
Change	**-75**	**-56**	**-$40,892.60**	**-$11.59**	**-$2.38**	**2,134,667**	**-966**

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

Demographics of Members Utilizing Bowel Preparation Medications



Top Prescriber Specialties of Bowel Preparation Medications by Number of Claims



Market News and Updates[1,2]

Anticipated Patent Expiration(s):

- SUPREP® (sodium sulfate/potassium sulfate/magnesium sulfate): March 2023
- MoviPrep® (PEG-3350/sodium sulfate/sodium chloride/potassium chloride/sodium ascorbate/ascorbic acid): September 2024
- OsmoPrep® (sodium phosphate monobasic/sodium phosphate dibasic): June 2028
- Prepopik® (sodium picosulfate/magnesium oxide/citric acid): October 2028

News:

- **August 2015:** The U.S. Food and Drug Administration (FDA) announced Suclear® (sodium sulfate/potassium sulfate/magnesium sulfate/PEG-3350/sodium chloride/sodium bicarbonate/potassium chloride) has been discontinued from marketing and that the product was not discontinued or withdrawn for safety or efficacy reasons.

New FDA Approval(s):

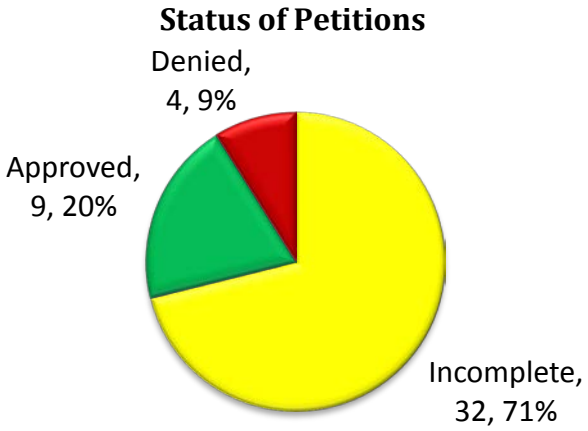
- **December 2016:** The FDA approved ColPrep™ Kit (sodium sulfate/potassium sulfate/magnesium sulfate), an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults. ColPrep™ Kit is a low-volume (1L) sodium sulfate-based bowel preparation which is to be taken as a split-dose regimen, with each dose to be taken with an additional 32-oz of water.

Pipeline Update(s):

- **PLENVU™ (NER1006):** In October 2016, Norgine B.V. reported positive results of a United States-based Phase 3 clinical trial for PLENVU™, a novel, low-volume (1L) polyethylene glycol based bowel preparation that has been developed to provide whole bowel cleansing, with an additional focus on the ascending colon. The study met its primary endpoints demonstrating non-inferiority to SUPREP® (sodium sulfate/potassium sulfate/magnesium sulfate) when used as a 2-day split-dosing regimen and a rating of "Excellent plus Good" cleansing of the ascending colon using the Harefield Cleansing Scale (HCS).

Prior Authorization of Bowel Preparation Medications

There were 45 prior authorization requests submitted for bowel preparation medications during calendar year 2016. The prior authorization criteria did not go into effect until September 29, 2016. The following chart shows the status of the submitted petitions for calendar year 2016.



ColPrep™ Kit (Sodium Sulfate/Potassium Sulfate/Magnesium Sulfate) Product Summary[3]

FDA Approved: December 27, 2016

Indications: ColPrep™ Kit (sodium sulfate/potassium sulfate/magnesium sulfate) is an osmotic laxative indicated for cleansing of the colon in preparation for colonoscopy in adults.

Dosing:

- ColPrep™ Kit is available as a kit containing two 200mL bottles of oral solution (each containing sodium sulfate 17.5g, potassium sulfate 3.13g, and magnesium sulfate 1.6g) and one 20-oz mixing container with a 16-oz fill line.
- Each bottle of ColPrep™ Kit oral solution should be administered as 16-oz of diluted ColPrep™ Kit solution with an additional 32-oz of water taken orally.
- ColPrep™ Kit should be taken as a split-dose oral regimen:
    - Day prior to colonoscopy: Early in the evening prior to colonoscopy patients should pour the contents of one bottle of ColPrep™ Kit into the mixing container provided, dilute with water to the 16-oz fill line, and drink the entire amount. Patients should then drink two additional containers filled to the 16-oz line with water over the next hour.
    - Day of colonoscopy: The morning of colonoscopy (10 to 12 hours after the evening dose) patients should prepare the bottle of ColPrep™ Kit, and drink the entire amount. Patients should then drink two additional containers filled to the 16-oz line with water over the next hour.

Cost/Launch Date: ColPrep™ Kit cost information and launch information are unknown at this time.

Recommendations

The College of Pharmacy recommends the prior authorization of ColPrep™ Kit with criteria similar to the other prior authorized bowel preparation medications with the following criteria:

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

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

Utilization Details of Bowel Preparation Medications: Calendar Year 2016

Product Utilized	Total Claims	Total Members	Total Cost	Claims/ Member	Cost/ Claim
Polyethylene Glycol Electrolyte Solution Products					
GAVILYTE-G SOL	929	791	$14,972.59	1.17	$16.12
PEG 3350 SOL ELECTROL	345	321	$4,119.97	1.07	$11.94
MOVIPREP SOL	306	303	$27,609.20	1.01	$90.23
GAVILYTE-N SOL FLAV PK	274	255	$5,039.35	1.07	$18.39
PEG-3350/KCL SOL /SODIUM	203	196	$3,944.36	1.04	$19.43
PEG-3350 SOL ELECTROL	189	146	$3,485.60	1.29	$18.44
GAVILYTE-C SOL	85	76	$1,232.66	1.12	$14.50
TRILYTE SOL	80	76	$1,547.79	1.05	$19.35
GOLYTELY SOL	18	16	$268.62	1.13	$14.92
COLYTE/FLAVR SOL PACKS	1	1	$48.39	1	$48.39
Subtotal	**2,430**	**2,116**	**$62,268.53**	**1.15**	**$27.17**
Sodium Sulfate Products					
SUPREP BOWEL SOL PREP	770	748	$66,201.25	1.03	$85.98
Subtotal	**770**	**748**	**$66,201.25**	**1.03**	**$85.98**
Sodium Picosulfate/Magnesium Oxide/Anhydrous Citric Acid Products					
PREPOPIK PAK	42	41	$5,058.79	1.02	$120.45
Subtotal	**42**	**41**	**$5,058.79**	**1.02**	**$120.45**
Sodium Phosphate Oral Products					
OSMOPREP TAB 1.5GM	25	25	$4,239.87	1	$169.55
Subtotal	**25**	**25**	**$4,239.87**	**1**	**$169.55**
Total	**3,267**	**2,887***	**$137,768.44**	**1.13**	**$42.17**

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

[1] U.S. Food and Drug Administration (FDA): Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 01/25/2017. Last accessed 04/2017.

[2] Norgine B.V. Postive US Phase III Data Show Efficacy of PLENVU™ (NER1006), A Low Volume, PEG Based Bowel Cleansing Solution. Available online at: http://www.norgine.com/media/press-release/positive-us-phase-iii-data-show-efficacy-of-plenvu-ner1006-a-low-volume-peg-based-bowel-cleansing-solution. Last revised 10/2016. Last accessed 04/2017.

[3] ColPrep™ Kit Prescribing Information. Gator Pharmaceuticals, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/204553s001lbl.pdf. Last revised 12/2016. Last accessed 04/2017.

Appendix M

30-Day Notice to Prior Authorize Elaprase® (Idursulfase)

Oklahoma Health Care Authority
May 2017

Introduction[1,2]

Hunter syndrome, also known as mucopolysaccharidosis type II or MPS II, is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. This enzyme cleaves the terminal 2-*O*-sulfate moieties from the mucopolysaccharides, also known as glycosaminoglycans (GAGs), dermatan sulfate and heparin sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAGs progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction. The vast majority of affected individuals are male. Hunter syndrome is a progressively debilitating disorder; however, age of onset, disease severity, and rate of progression vary significantly among affected males.

In those with early progressive disease, central nervous system (CNS) involvement (manifested primarily by progressive cognitive deterioration), progressive airway disease, and cardiac disease usually result in death in the first or second decade of life. In those with slowly progressive disease, the CNS is not (or is minimally) affected, although the effect of GAG accumulation on other organ systems may be early progressive to the same degree as in those who have progressive cognitive decline. Survival into the early adult years with normal intelligence is common in the slowly progressing form of the disease. The early progressive CNS form of Hunter syndrome may be more than twice as prevalent as the slowly progressive form; however, accurate prevalence rates are not available. Additional findings in both forms of Hunter syndrome include coarsening of facial features, short stature, macrocephaly with or without communicating hydrocephalus, macroglossia, hoarse voice, conductive and sensorineural hearing loss, hepatosplenomegaly, dysostosis multiplex, spinal stenosis, and carpal tunnel syndrome.

It is estimated that Hunter syndrome occurs in approximately 1 in 100,000 to 1 in 170,000 males.[3] The diagnosis of Hunter syndrome cannot be made on clinical findings alone, as the specific combination of signs and symptoms and their physical manifestation vary widely, depending on disease severity. Urine GAG analysis will show large concentrations of the GAGs dermatan sulfate and heparin sulfate; however, these findings are not specific to Hunter syndrome (MPS II), as the profile is similar to that seen in mucopolysaccharidosis type I (MPS I). Establishing the diagnosis of Hunter syndrome requires documentation of absent or reduced iduronate-2-sulfatase enzyme activity or molecular genetic testing for identification of a hemizygous pathogenic variant of the *IDS* gene.

Treatment of the complications in Hunter syndrome is symptomatic. The involvement of specialists for each affected organ is required to monitor and treat specific problems. Developmental, occupational, and physical therapy are often necessary for patients with

Hunter syndrome. Hematopoietic stem cell transplantation (HSCT) using umbilical cord blood or bone marrow is a potential way of providing sufficient enzyme activity to slow or stop the progression of the disease; however, the use of HSCT is controversial because of the associated high risk of morbidity and mortality. The U.S. Food and Drug Administration (FDA) approved Elaprase® (idursulfase) in 2006 as an orphan drug for long-term enzyme replacement therapy for patients with Hunter syndrome. Idursulfase is a recombinant form of human iduronate-2-sulfatase.

Utilization of Elaprase® (Idursulfase): Fiscal Year 2016

Fiscal Year 2016 Utilization: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim
2016	3	10	$445,747.48	$44,574.75

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

Fiscal Year 2016 Utilization: Medical Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim
2016	1	3	$36,350.64	$12,116.88

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

Demographics of Members Utilizing Elaprase® (Idursulfase)

- Due to the small number of members utilizing Elaprase® (idursulfase) during fiscal year 2016, detailed demographic information could not be provided.

Top Prescriber Specialties of Elaprase® (Idursulfase) by Number of Claims

- The only prescriber specialty listed on paid claims for Elaprase® (idursulfase) during fiscal year 2016 was general pediatrician.

Elaprase® (Idursulfase) Product Summary[4,5]

FDA Approval: 2006

Indications: Elaprase® (idursulfase) is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).

Dosing:

- Elaprase® is available as a 2mg/mL injection for intravenous (IV) use in 3mL (6mg/3mL) single-use vials.
- The recommended dosage regimen of idursulfase is 0.5mg per kilogram (kg) of body weight administered once weekly as an IV infusion.

- The calculated volume of idursulfase solution (based on the patient's weight) should be added to a 100mL bag of 0.9% sodium chloride injection for IV infusion.
- The diluted idursulfase solution should be administered to patients using a low-protein-binding infusion set equipped with a low-protein-binding 0.2µm in-line filter.
- The total volume of infusion should be administered over a period of three hours, which may be gradually reduced to one hour if no hypersensitivity reactions are observed. Patients may require longer infusion times if hypersensitivity reactions occur; however, infusion times should not exceed eight hours. Idursulfase should not be infused with other products in the infusion tubing.
- Elaprase® does not contain preservatives; therefore, after dilution with saline, the infusion bags should be used immediately. If immediate use is not possible, the diluted solution should be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours.

Boxed Warning: Risk of Anaphylaxis

- Life-threatening anaphylactic reactions have occurred in some patients during and up to 24 hours after idursulfase infusions. Anaphylaxis, presenting as respiratory distress, hypoxia, hypotension, urticaria, and/or angioedema of the throat or tongue have been reported to occur during and after idursulfase infusions, regardless of duration of the course of treatment. Patients should be closely observed during and after idursulfase administration and should seek immediate medical care should symptoms occur. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory conditions due to hypersensitivity reactions, and require additional monitoring.

Mechanism of Action: Hunter syndrome is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. Elaprase® is a formulation of idursulfase, a purified form of human iduronate-2-sulfatase. Idursulfase is produced by recombinant DNA technology in a human cell line and is intended to provide exogenous enzyme for uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide chains allow binding of the enzyme to the M6P receptors on the cell surface, leading to cellular internalization of the enzyme, targeting to intracellular lysosomes, and subsequent catabolism of accumulated GAGs.

Contraindications: None.

Safety:

- Hypersensitivity Reactions Including Anaphylaxis: Serious hypersensitivity reactions, including anaphylaxis, have occurred during and up to 24 hours after idursulfase infusion. Some of these reactions were life-threatening and included respiratory distress, hypoxia, hypotension, urticaria, and angioedema of the throat or tongue, regardless of duration of the course of treatment. If anaphylactic or other acute reactions occur, the idursulfase infusion should be immediately discontinued and appropriate medical treatment should be initiated. Due to the potential for severe reactions, appropriate medical support should be readily available when idursulfase is administered, and patients should be closely observed for signs and symptoms of anaphylaxis for an appropriate period of time

after administration of idursulfase. When severe reactions have occurred during clinical trials, subsequent infusions were managed with antihistamines and/or corticosteroids prior to and during infusions, a slower rate of idursulfase infusion, and/or early discontinuation of the idursulfase infusion. In postmarketing reports, patients receiving idursulfase experienced anaphylactic reactions up to several years after initiating treatment. Medical management included treatment with antihistamines, inhaled beta-adrenergic agonists, corticosteroids, oxygen, and vasopressors. Treatment was discontinued for some patients, while others continued treatment with premedication and a slower infusion rate. Patients should be informed of the signs and symptoms of anaphylaxis and instructed to seek immediate medical care should signs and symptoms occur.

- Risk of Hypersensitivity, Serious Adverse Reactions, and Antibody Development in Hunter Syndrome Patients with Severe Genetic Mutations: In an open-label clinical trial of male Hunter syndrome patients aged 7 years and younger, patients with complete gene deletion, large gene rearrangement, nonsense, frameshift, or splice site mutations experienced a higher incidence of hypersensitivity reactions, serious adverse reactions, and anti-idursulfase antibody development than Hunter syndrome patients with missense mutations. In patients who were persistently antibody positive, the presence of anti-idursulfase antibody was associated with reduced systemic exposure of idursulfase and a less pronounced decrease in urinary GAG levels.
- Risk of Acute Respiratory Complications: Patients with compromised respiratory function or acute febrile or respiratory illness at the time of idursulfase infusion may be at higher risk of life-threatening complications from hypersensitivity reactions. Careful consideration should be given to the patient's clinical status prior to administration of idursulfase and if necessary to delaying the idursulfase infusion.
- Risk of Acute Cardiorespiratory Failure: Caution should be exercised when administering idursulfase to patients susceptible to fluid overload, or to patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function for whom fluid restriction is indicated. These patients may be at risk of serious exacerbation of their cardiac or respiratory status during infusions. Appropriate medical support and monitoring measures should be readily available during idursulfase infusion, and some patients may require prolonged observation times based on the individual needs of the patient.
- Pediatric Use: The safety and efficacy of idursulfase in pediatric patients less than 16 months of age have not been established. Clinical trials were conducted in 96 patients with Hunter syndrome, ages 5 to 31 years old, with the majority of the patients in the pediatric age group (median age 15 years). In addition, an open-label, uncontrolled clinical trial was conducted in 28 patients with Hunter syndrome, ages 16 months to 7.5 years. Patients 16 months to 5 years of age demonstrated reduction in spleen volume that was similar to that of adults and children 5 years and older; however, there are no data to support improvement in disease-related symptoms or long-term clinical outcomes in patients 16 months to 5 years of age.
- Geriatric Use: Clinical studies of idursulfase did not include patients older than 31 years of age. It is not known whether older patients respond differently than younger patients.

Adverse Reactions: In clinical trials, the most common adverse reactions (>10%) following idursulfase treatment were hypersensitivity reactions and included rash, urticaria, pruritus, flushing, pyrexia, and headache. Most hypersensitivity reactions requiring intervention were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, with or without administering additional treatments including antihistamines, corticosteroids, or both prior to or during infusions. In clinical trials, the most frequent serious adverse reaction following idursulfase treatment was hypoxic episodes.

Efficacy: The safety and efficacy of idursulfase were evaluated in a 53-week, randomized, double-blind, placebo-controlled clinical trial of 96 patients with Hunter syndrome.

- The trial included patients with deficiency in iduronate-2-sulfatase enzyme activity and a percent predicted forced vital capacity (%-predicted FVC) less than 80%. The age of the patients ranged from 5 to 31 years.
- Patients received idursulfase 0.5mg/kg once per week (n = 32), idursulfase 0.5mg/kg once every other week (n = 32), or placebo (n = 32).
- The primary efficacy outcome assessment was a two-component composite score based on the sum of the ranks of the change from baseline to week 53 in distance walked in six minutes (6-minute walk test) and the ranks of the change in %-predicted FVC. This two-component composite primary endpoint differed statistically significantly between the three groups, and the difference was greatest between the placebo group and the once weekly treatment group (once weekly idursulfase vs. placebo, p=0.0049).
- Examination of the individual components of the composite score showed that, in the adjusted analysis, the weekly idursulfase treatment group experienced a 35 meter greater mean increase in distance walked in six minutes compared to placebo. The changes in %-predicted FVC were not statistically significant. The long-term effect of idursulfase on pulmonary function in Hunter syndrome patients is unclear.
- Pharmacodynamic assessments including urinary GAG levels and changes in liver and spleen size were performed. Urinary GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean urinary GAG levels were reduced in the idursulfase once weekly group, although GAG levels still remained above the upper limit of normal in half of the idursulfase-treated patients. Urinary GAG levels remained elevated and essentially unchanged in the placebo group. Sustained reductions in both liver and spleen volumes were observed in the idursulfase once weekly group through week 53 compared to placebo. There were essentially no changes in liver and spleen volume in the placebo group.

Cost: The wholesale acquisition cost (WAC) of Elaprase® (idursulfase) is $3,135.84 per 6mg/3mL single-use vial for IV use.

Patient Weight	Dosing Regimen	Vials Per Infusion	Cost Per Weekly Infusion	Cost Per Year
10kg	5mg once weekly	1	$3,135.84	$163,063.68
20kg	10mg once weekly	2	$6,271.68	$326,127.36
55kg	27.5mg once weekly	5	$15,679.20	$815,318.40

Costs based on WAC and do not reflect rebated prices or net costs. Cost per year based on 52 weekly infusions.

Recommendations

The College of Pharmacy recommends the prior authorization of Elaprase® (idursulfase) with the following criteria:

Elaprase® (Idursulfase) Approval Criteria:

1. An FDA approved diagnosis of Hunter syndrome (mucopolysaccharidosis type II; MPS II) confirmed by:
    a. Enzyme assay demonstrating a deficiency of iduronate-2-sulfatase enzyme activity; or
    b. Molecular genetic testing confirming a hemizygous pathogenic variant in the *IDS* gene; and
2. 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.

[1] U.S. National Library of Medicine. MedlinePlus: Hunter Syndrome. Available online at: https://medlineplus.gov/ency/article/001203.htm. Last revised 04/20/2015. Last accessed 04/20/2017.
[2] Scarpa M. Mucopolysaccharidosis Type II. *GeneReviews®*. Available online at: https://www.ncbi.nlm.nih.gov/books/NBK1274/. Last revised 03/26/2015. Last accessed 04/20/2017.
[3] U.S. National Library of Medicine. Genetics Home Reference: Mucopolysaccharidosis Type II. Available online at: https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-ii#statistics. Last revised 12/2008. Last accessed 04/20/2017.
[4] Elaprase® Package Insert. MedLibrary.org. Available online at: http://medlibrary.org/lib/rx/meds/elaprase-1/. Last revised 03/10/2016. Last accessed 04/20/2017.
[5] Elaprase® Prescribing Information. Shire Human Genetic Therapies, Inc. Available online at: http://pi.shirecontent.com/PI/PDFs/Elaprase_USA_ENG.pdf. Last revised 06/2013. Last accessed 04/20/2017.

Appendix N

Fiscal Year 2016 Annual Review of Botulinum Toxins

Oklahoma Health Care Authority
May 2017

Current Prior Authorization Criteria

Botulinum Toxins Approval Criteria:

1. Cosmetic indications will not be covered.
2. A diagnosis of chronic migraine (tension headaches are not a covered diagnosis), non-neurogenic overactive bladder, and neurogenic overactive bladder will require manual review (see specific criteria below).
3. The following indications listed below have been determined to be appropriate and are covered:

Covered Indications
▪ Spasticity associated with: • Cerebral Palsy • Paralysis • Generalized weakness/incomplete paralysis • Larynx • Anal fissure • Esophagus (achalasia and cardiospasms) • Eye and eye movement disorders ▪ Cervical Dystonia

Botulinum toxins are billed through the medical claims system and require a manual prior authorization for any covered diagnosis to ensure appropriate reimbursement for the billing provider. Prior authorization requests for botulinum toxins are first reviewed by a clinical pharmacist and if necessary, the prior authorization request is sent to Oklahoma Health Care Authority (OHCA) for a second review from an OHCA physician. Botulinum toxin claims are denied if submitted through the pharmacy point of sale system. There are four covered products in this class: Botox® (onabotulinumtoxinA), Dysport® (abobotulinumtoxinA), Xeomin® (incobotulinumtoxinA), and Myobloc® (rimabotulinumtoxinB).

Botox® is the only botulinum toxin product indicated for the prevention of migraine headaches and for the treatment of non-neurogenic overactive bladder and neurogenic overactive bladder. Approval criteria for Botox® for the prevention of chronic migraine headaches, non-neurogenic overactive bladder, and neurogenic overactive bladder were developed internally by medical staff at OHCA in collaboration with two SoonerCare contracted neurologists. Due to the modest effect, high cost, and potential for severe adverse reactions, Botox® should be reserved for patients who have failed all available recommended therapies.

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, and central venous thrombosis); or
    b. Decreased intracranial pressure (e.g. post-lumbar puncture headache and dural tear after trauma); and
2. Migraine headache exacerbation secondary to other medication conditions or therapies have been ruled out and/or treated. This includes but is not limited to:
    a. Hormone replacement therapy or hormone-based contraceptives; and
    b. Chronic insomnia; and
    c. Obstructive sleep apnea; and
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 days per month; and
        ii. Duration of four hours per day or longer; and
5. The member has failed medical migraine preventative therapy including at least three agents in three or more categories, but not limited to:
    a. Select antihypertensive therapy such as beta-blocker therapy; or
    b. Select anticonvulsant therapy; or
    c. Select antidepressant therapy [e.g. tricyclic antidepressants (TCA) or 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); and
    b. Combination analgesics containing caffeine and/or butalbital (> 5 days/month); and
    c. Opioids; and
    d. Analgesic medications including acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs); and
    e. Ergotamine-containing medications (> 8 days/month); and
    f. Triptans (> 8 days/month); 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.

Approval Criteria for Botox® for Non-Neurogenic Overactive Bladder *(other botulinum toxins will not be approved for this diagnosis)*:

1. Member must have severe disease (≥ 5 urinary incontinence episodes per day on medication) and specific pathology determined via urodynamic studies; and
2. Member must have participated in behavioral therapy for at least 12 weeks that did not yield adequate clinical results; and
3. Member must have had compliant use of at least three anti-muscarinic or beta-3 adrenoceptor agonist medications for at least 12 weeks each, alone or in combination with behavioral therapy, that did not yield adequate clinical results. One of those trials must have been an extended-release formulation; and
4. Member must be 18 years of age or older and have adequate hand function and sufficient cognitive ability to know when the bladder needs emptying and to self-catheterize, or have a caregiver able to catheterize the member when necessary; and
5. Botox® must be administered by an urologist.

Approval Criteria for Botox® for Neurogenic Overactive Bladder (*other botulinum toxins will not be approved for this diagnosis)*:

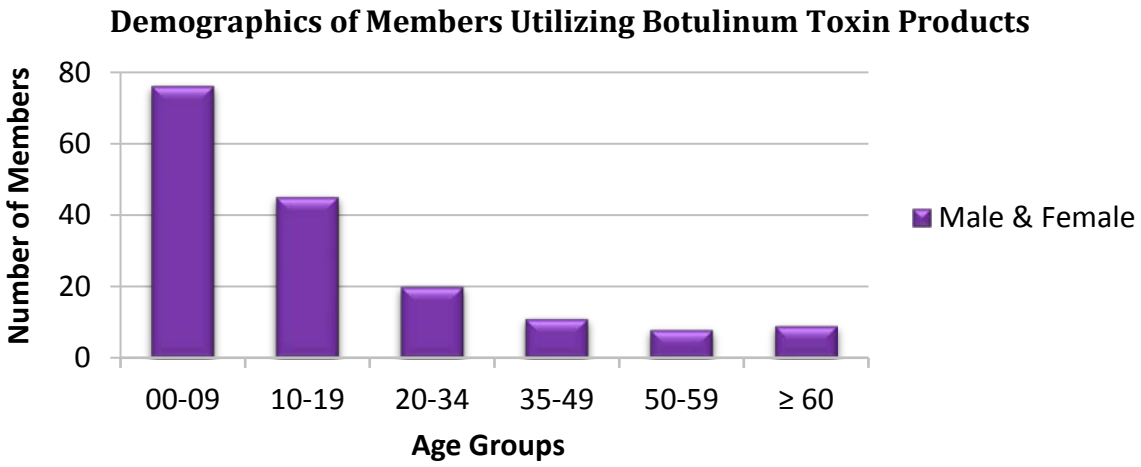
1. Diagnosis of neurogenic bladder including underlying pathological dysfunction subtype confirmed by:
    a. Urodynamic studies to determine pathology and serve to provide objective evidence of bladder and external sphincter function; and
    b. A diary of fluid intake, incontinence, voiding, and catheterization times and amounts to provide a record of actual occurrences; and
2. Member must have a clinically significant reason why anticholinergic medications are no longer an option for the member; and
3. Member must be 18 years of age or older and have adequate hand function and sufficient cognitive ability to know when the bladder needs emptying and to self-catheterize, or have a caregiver able to catheterize the member when necessary; and
4. Botox® must be administered by an urologist.

Utilization of Botulinum Toxin Products: Fiscal Year 2016

Comparison of Fiscal Years: Botulinum Toxin Products

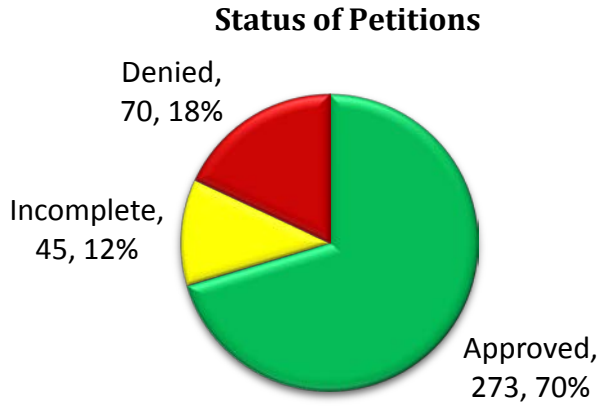
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Claims/ Member
2015	152	301	$398,583.43	$1,324.20	1.98
2016	169	298	$424,361.65	$1,424.03	1.76
% Change	**11.18%**	**-1.00%**	**6.47%**	**7.54%**	**-10.96%**
Change	**17**	**-3**	**$25,778.22**	**$99.83**	**-0.22**

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



Prior Authorization of Botulinum Toxin Products

There were 388 prior authorization requests submitted for botulinum toxin products during fiscal year 2016. The following chart shows the status of the submitted petitions.



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

New FDA Approved Indication(s):

- **July 2016:** The U.S. Food and Drug Administration (FDA) approved Dysport® (abobotulinumtoxinA) for the treatment of lower limb spasticity in patients age 2 years and older, making it the first and only FDA-approved botulinum toxin product for the treatment of pediatric lower limb spasticity. Dysport® was first FDA approved in 2009 for the treatment of cervical dystonia in adult patients and for the temporary improvement in the appearance of glabellar lines in adult patients, and then in 2015 for the treatment of upper limb spasticity in adult patients. The current approval criteria and covered diagnosis codes for botulinum toxins include lower limb spasticity.

Guideline Update(s):

- **April 2016:** The American Academy of Neurology (AAN) updated its 2008 guidelines on the use of botulinum toxin for spasticity in adults, cervical dystonia, blepharospasm, and headache based on recent research. Four preparations of botulinum toxin are available

in the United States and are not interchangeable; therefore, the guidelines assessed each formulation separately for each condition. To develop the guidelines, researchers reviewed all available scientific studies on the topic. The guidelines determined that botulinum toxin is generally safe and effective for treating spasticity in adults, cervical dystonia, blepharospasm, and chronic migraine. Significant recommendations and conclusions from the updated guidelines include:

- **Spasticity:** For *upper limb spasticity*, Dysport®, Xeomin®, and Botox® are effective at reducing excess muscle tone and should be offered. Myobloc® is probably effective and should be considered. For *lower limb spasticity*, Dysport® and Botox® are effective and should be offered.
- **Cervical Dystonia:** Dysport® and Myobloc® are effective for cervical dystonia and should be offered. Botox® and Xeomin® are probably effective and should be considered.
- **Blepharospasm:** Few well-designed studies have been done on blepharospasm. Botox® and Xeomin® are probably effective and should be considered. Dysport® is possibly effective and may be considered.
- **Headache:** Previously, in the 2008 guidelines, there was not enough evidence available to make any recommendation on the use of botulinum toxin for chronic migraine. Now there are well-designed studies that support the effectiveness of Botox® to reduce how often migraine headaches occur; however, the studies showed that the benefit from the drug was small. In four weeks after the first treatments, patients had about 15% fewer days of headache compared with a placebo or dummy injection. For chronic migraine, the guidelines conclude that Botox® is effective and should be offered to increase headache-free days and is probably effective and should be considered to improve health-related quality of life. However, Botox® is ineffective and should not be offered for episodic migraine and is probably ineffective for chronic tension-type headaches.

Other News:

- **December 2015:** A retrospective analysis of a United States-based insurance claims database compared the effectiveness of Botox® versus oral migraine prophylactic medications on headache-related resource utilization in the management of chronic migraine. Headache-related health care utilization was assessed at 6, 9, and 12 months pre- and post-treatment. When compared with similar patients who initiated treatment with oral migraine prophylactic medications, Botox® was associated with a significantly lower likelihood of headache-related emergency department visits and hospitalizations.
- **October 2016:** In a randomized clinical trial, a single injection of Botox® was more effective than sacral neuromodulation (InterStim®) in reducing urgency urinary incontinence episodes over 6 months in women with refractory overactive bladder (OAB). The small daily improvement in episodes with Botox® therapy was statistically significant, but is of uncertain clinical importance. Botox® therapy was associated with a three-fold increased risk of urinary tract infection (UTI). There were no differences in convenience, adverse effects, and treatment preference. However, the increased rate

of UTI and need for intermittent catheterization with Botox® injections could influence treatment choices for refractory OAB in some cases.

Recommendations

The College of Pharmacy does not recommend any changes to the botulinum toxins prior authorization criteria at this time.

Utilization Details of Botulinum Toxin Products: Fiscal Year 2016

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	PERCENT COST
ONABOTULINUMTOXINA PRODUCTS						
BOTOX®	295	167*	$422,393.20	$1,431.84	1.77	99.54%
INCOBOTULINUMTOXINA PRODUCTS						
XEOMIN®	2	1*	$514.70	$257.35	2.00	0.12%
RIMABOTULINUMTOXINB PRODUCTS						
MYOBLOC®	1	1*	$1,453.75	$1,453.75	1.00	0.34%
TOTAL	**298**	**169***	**$424,361.65**	**$1,424.03**	**1.76**	**100.00%**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Dysport® (abobotulinumtoxinA) had no utilization in fiscal year 2016.

[1] U.S. Food and Drug Administration (FDA) sBLA Approval: Dysport® (AbobotulinumtoxinA). Available online at: http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/125274Orig1s105ltr.pdf. Issued 07/29/2016. Last accessed 03/01/2017.

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[3] Brooks M. FDA Clears Dysport for Lower-Limb Spasticity in Kids. *Medscape.* Available online at: http://www.medscape.com/viewarticle/867063. Issued 08/03/2016. Last accessed 03/01/2017.

[4] Dysport® Prescribing Information. Ipsen Biopharmaceuticals, Inc. Available online at: https://www.dysport.com/pdfs/Dysport_Full_Prescribing_Information.pdf. Last revised 12/2016. Last accessed 03/01/2017.

[5] Simpson D, Hallett M, et al. Practice Guideline Update Summary: Botulinum Neurotoxin for the Treatment of Blepharospasm, Cervical Dystonia, Adult Spasticity, and Headache. *Neurology®.* Available online at: http://www.neurology.org/content/86/19/1818.full. Issued 04/18/2016. Last accessed 03/02/2017.

[6] Hepp Z, Rosen N, et al. Comparative Effectiveness of OnabotulinumtoxinA versus Oral Migraine Prophylactic Medications on Headache-Related Resource Utilization in the Management of Chronic Migraine: Retrospective Analysis of a U.S.-Based Insurance Claims Database. *Cephalalgia*. Available online at: http://journals.sagepub.com/doi/10.1177/0333102415621294. Issued 12/20/2015. Last accessed 03/02/2017.

[7] Amundsen C, Richter H, et al. OnabotulinumtoxinA vs Sacral Neuromodulation on Refractory Urgency Urinary Incontinence in Women. *JAMA®.* Available online at: http://jamanetwork.com/journals/jama/fullarticle/2565290. Issued 10/04/2016. Last accessed 03/03/2017.

Appendix O

Calendar Year 2016 Annual Review of Gaucher Disease Medications

Oklahoma Health Care Authority
May 2017

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

Gaucher disease (GD) is one of the most common lysosomal storage disorders and occurs in approximately 1 in 75,000 births worldwide. In the mid-1990s, there were approximately 20,000 individuals with GD in the United States.[1] GD is an inherited disorder that affects many of the body's organs and tissues. GD is sub-divided into three subtypes according to the presence or absence of neurological involvement. The most prevalent is Type 1 GD (GD1) and occurs with greater frequency in the Ashkenazi-Jewish population. It usually does not affect the central nervous system. Type 2 and 3 are less common and are characterized by neurological involvement.

GD results from a deficiency of a lysosomal enzyme glucocerebrosidase (also known as glucosylceramidase or acid beta-glucosidase [GBA]) in the body. The enzyme deficiency causes lipid-laden macrophages to accumulate in the spleen, liver, bone marrow, bone, and other tissues/organs.

The presenting features are quite variable and may occur at any age with varying severity. GD can cause anemia, fatigue, easy bruising, nosebleeds, osteoporosis, bone pain and easily broken bones, and swollen stomach due to enlarged liver or spleen. Features seen only in Type 2 and Type 3 GD include developmental delay, strabismus, nonimmune hydrops, and congenital ichthyosis.

There is no cure for GD; however, there are a number of treatments available to help control symptoms, prevent irreversible damage, and improve quality of life for patients with certain types of GD. There are currently no effective treatment options available for Type 2. Current pharmacologic treatment includes enzyme replacement therapy (ERT) or substrate-reduction therapy (SRT). There are three ERTs, Cerezyme® (imiglucerase), Elelyso® (taliglucerase alfa), and Vpriv® (velaglucerase alfa), and two SRTs, Cerdelga® (eliglustat) and Zavesca® (miglustat).

Current Prior Authorization Criteria

Cerezyme® (Imiglucerase), Elelyso® (Taliglucerase Alfa), and Vpriv® (Velaglucerase Alfa) Approval Criteria:

1. A diagnosis of symptomatic (e.g., anemia, thrombocytopenia, bone disease, splenomegaly, or hepatomegaly) Type 1 or Type 3 Gaucher disease (GD); and
2. Member's weight (kg) must be provided and have been taken within the last four weeks to ensure accurate weight-based dosing; and

3. Prescriber must verify that the member will not take requested therapy concurrently with another therapy for GD.
4. Approvals will be for the duration of six months, at which time the prescriber must verify the patient is responding to the medication.

Cerdelga® (Eliglustat) Approval Criteria:

1. An FDA approved indication of Type 1 Gaucher disease (GD1); and
2. Member is classified as one of the following as detected by an FDA-cleared test:
    a. CYP2D6 extensive metabolizers (EMs); or
    b. CYP2D6 intermediate metabolizers (IMs); or
    c. CYP2D6 poor metabolizers (PMs); and
3. Prescriber must verify that the member will not take Cerdelga® concurrently with another therapy for GD1.
4. For CYP2D6 EMs and IMs, a quantity limit of 56 capsules per 28 days will apply. For CYP2D6 PMs, a quantity limit of 28 capsules per 28 days will apply.
5. Approvals will be for the duration of six months, at which time the prescriber must verify the patient is responding to the medication.

Zavesca® (Miglustat) Approval Criteria:

1. An FDA approved indication of mild/moderate Type 1 Gaucher disease (GD1); and
2. A patient-specific, clinically significant reason why the member cannot use one of the following enzyme replacement therapies:
    a. Cerezyme® (imiglucerase); or
    b. Elelyso® (taliglucerase alfa); or
    c. Vpriv® (velaglucerase alfa); and
3. Prescriber must verify that the member will not take Zavesca® concurrently with another therapy for GD1.
4. A quantity limit of 90 capsules per 30 days will apply.
5. Approvals will be for the duration of six months, at which time the prescriber must verify the patient is responding to the medication.

Utilization of Gaucher Disease Medications: Calendar Year 2016

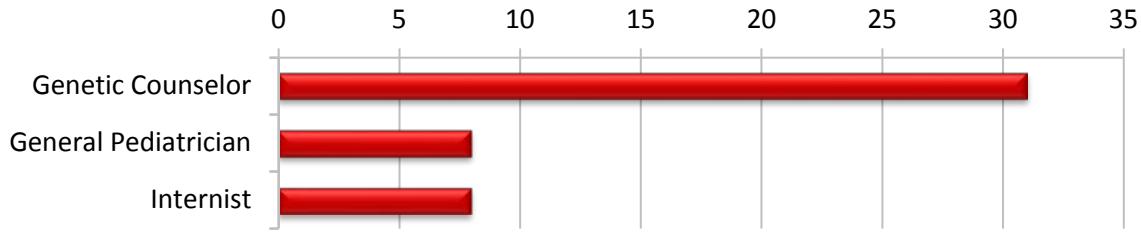
Gaucher Disease Medications Comparison of Calendar Years: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	5	57	$912,561.79	$16,009.86	$557.12	2,434	1,638
2016	5	47	$881,946.83	$18,764.83	$661.13	2,176	1,334
% Change	**0.00%**	**-17.50%**	**-3.40%**	**17.20%**	**18.70%**	**-10.60%**	**-18.60%**
Change	**0**	**-10**	**-$30,614.96**	**$2,754.97**	**$104.01**	**-258**	**-304**

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

- There were no pharmacy claims for Cerdelga® (eliglustat), Elelyso® (taliglucerase alfa), or Vpriv® (velaglucerase alfa) during calendar year 2016.
- There were no medical claims for Elelyso® (taliglucerase alfa) or Cerezyme® (imiglucerase) during calendar year 2016. Details of medical claims for Vpriv® (velaglucerase alfa) during calendar year 2016 can be found at the end of the report.

Top Prescriber Specialties of Gaucher Disease Medications by Number of Claims



Prior Authorization of Gaucher Disease Medications

There were seven prior authorization requests submitted for Gaucher disease medications during calendar year 2016. All requests were approved.

Market News and Updates[6]

Anticipated Patent Expiration(s):

- Cerdelga® (eliglustat): April 2022
- Elelyso® (taliglucerase alfa): October 2025

Recommendations

The College of Pharmacy does not recommend any changes to the Gaucher disease medication prior authorization criteria at this time.

Utilization Details of Gaucher Disease Medications: Calendar Year 2016

Calendar Year 2016: Pharmacy Claims

Product Utilized	Total Claims	Total Members	Total Cost	Cost/ Day	Cost/ Claim	% Cost
CEREZYME INJ 400UNIT	31	3	$881,064.83	$1,031.69	$28,421.45	99.90%
ZAVESCA CAP 100MG	16	2	$882.00	$1.84	$55.13	0.10%
Total	**47**	**5***	**$881,946.83**	**$661.13**	**$18,764.83**	**100.00%**

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

Calendar Year 2016: Medical Claims

Product Utilized	J-code	Total Claims	Total Members	Total Cost	Cost/Claim
VPRIV INJ 400 UNIT	J3385	48	2	$318,323.36	$6,631.74
Total	**J3385**	**48**	**2***	**$318,323.36**	**$6,631.74**

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

[1] Hughes, D. Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis. *UpToDate*. Available online at: http://www.uptodate.com/contents/gaucher-disease-pathogenesis-clinical-manifestations-and-diagnosis?source=search_result&search=gaucher+disease&selectedTitle=1%7E55. Last revised 04/2017. Last accessed 04/14/2017.

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[3] Gaucher's disease. Mayo Clinic. Available online at: http://www.mayoclinic.org/diseases-conditions/gauchers-disease/basics/definition/con-20031396. Last revised 07/2015. Last accessed 04/14/2017.

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[6] 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/default.cfm?resetfields=1. Last revised 02/2017. Last accessed 03/17/2017.

Appendix P

Fiscal Year 2016 Annual Review of Gonadotropin-Releasing Hormone (GnRH) Medications

Oklahoma Health Care Authority
May 2017

Introduction[1,2,3,4]

Gonadotropin-releasing hormone (GnRH) medications work by providing continuous stimulation to the pituitary gonadotrophs. Continuous stimulation leads to desensitization of the gonadotroph cells and suppression of gonadotropins resulting in decreased sex steroid production or pituitary-gonadal axis suppression. U.S. Food and Drug Administration (FDA) approved indications for these medications include advanced prostate cancer, endometriosis, precocious puberty, and uterine fibroids, depending on the specific agent.

FDA Approved GnRH Options for Treatment of Central Precocious Puberty or Endometriosis[5,6,7,8]

GnRH Agonist/Analog	Method of Administration and Frequency	Indication(s)
goserelin (Zoladex®)	3.6mg subcutaneously every 28 days	Prostate cancer, endometriosis, dysfunctional uterine bleeding, advanced breast cancer
histrelin (Supprelin® LA)	50mg subcutaneous implant every 12 months	Central precocious puberty (CPP)
leuprolide (Lupron Depot®)	3.75mg monthly 11.25mg every 3 months	Anemia due to vaginal bleeding from fibroids, endometriosis
leuprolide (Lupron Depot-Ped®)	7.5mg, 11.25mg, or 15mg monthly 11.25mg or 30mg every 3 months	Central precocious puberty
leuprolide/norethindrone (Lupaneta Pack™)	3.75mg intramuscularly monthly 11.25mg intramuscularly every 3 months (both with daily, oral norethindrone 5mg)	Endometriosis
nafarelin (Synarel®)	CPP: 1600-1800mcg (8-9 sprays) intranasally divided 2-3 times daily Endometriosis: 400mcg (2 sprays) divided twice daily	Endometriosis, central precocious puberty

*Products only indicated for the diagnosis of prostate cancer are not included in the table; this includes specific medication strengths that only have a prostate cancer indication.

Current Prior Authorization Criteria

Gonadotropin-Releasing Hormone (GnRH) Medications		
Tier-1	**Tier-2**	**Tier-3**
leuprolide (Lupron® Depot)	histrelin (Supprelin® LA)	nafarelin (Synarel®)
leuprolide (Lupron Depot-Ped®)		
leuprolide depot/norethindrone tablets (Lupaneta Pack™)		

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

Lupron Depot® (Leuprolide), Supprelin® LA (Histrelin), and Synarel® (Nafarelin)
Approval Criteria:

1. An FDA approved diagnosis of central precocious puberty confirmed by submitting the following:
    a. Documentation of onset of symptoms less than 8 years of age in females and 9 years of age in males; and
    b. Documentation that bone age is advanced 1 year beyond the chronological age; and
    c. Lab assessment:
        i. Documentation of abnormal basal gonadotropin levels; or
        ii. Documentation of pubertal response to a gonadotropin releasing hormone analog stimulation test; and
2. Approvals may be granted with documentation of failed trials of lower tiered products or an FDA approved indication not covered by a lowered tiered product.

Utilization of GnRH Medications: Fiscal Year 2016

Comparison of Fiscal Years for GnRH Medications: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2015	199	466	$1,447,676.63	$3,106.60	$52.96	473	27,336
2016	177	451	$1,443,190.43	$3,199.98	$55.65	478	25,932
% Change	**-11.10%**	**-3.20%**	**-0.30%**	**3.00%**	**5.10%**	**1.10%**	**-5.10%**
Change	**-22**	**-15**	**-$4,486.20**	**$93.38**	**$2.69**	**5**	**-1,404**

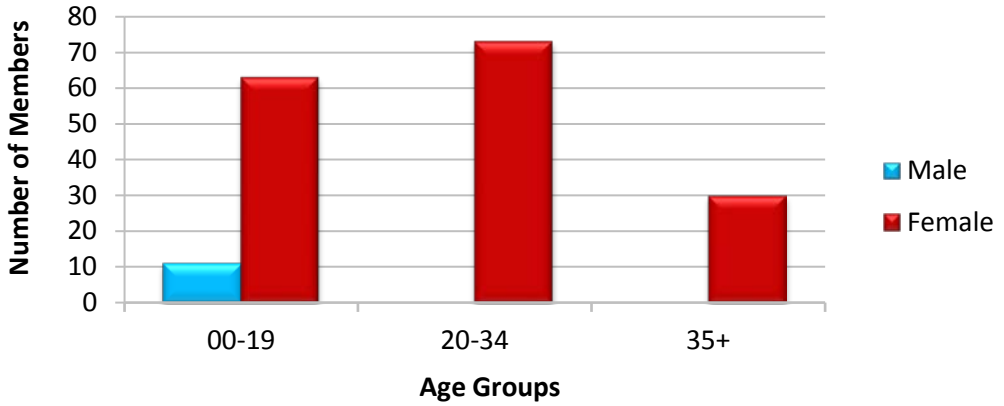
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Utilization of GnRH Medications: Medical Claims

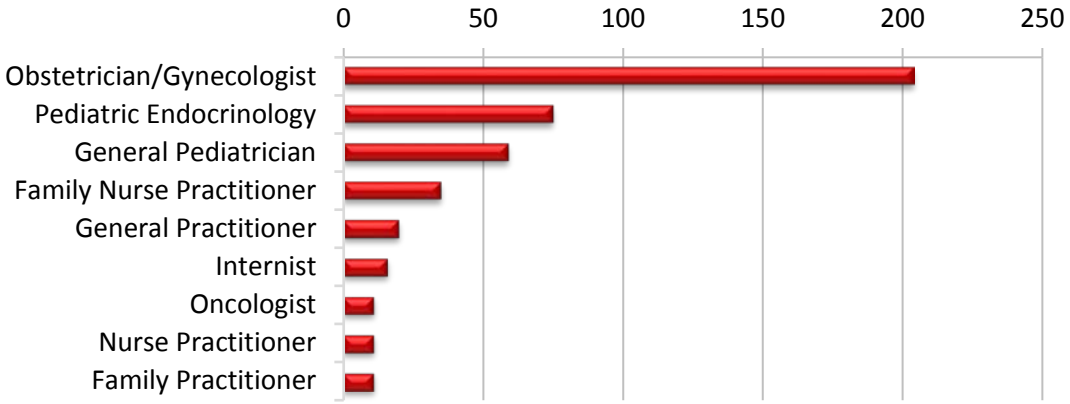
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/Claim
2016	72	150	$100,502.51	$670.02

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

Demographics of Members Utilizing GnRH Medications: Pharmacy Claims



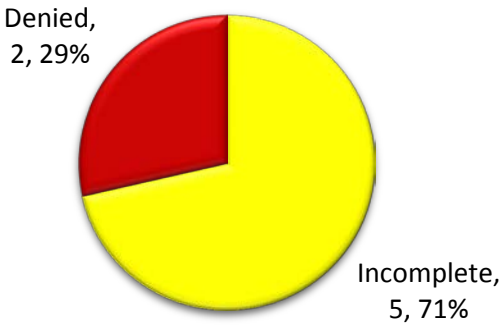
Top Prescriber Specialties of GnRH Medications by Number of Claims: Pharmacy Claims



Prior Authorization of GnRH Medications

There were 7 prior authorization requests submitted for the GnRH medications during fiscal year 2016. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[9,10,11,12,13]

Patent Expiration(s):

- Lupron Depot® and Lupron Depot-Ped® (leuprolide): December 2016
- Lupaneta Pack® (leuprolide depot/norethindrone tablets): December 2016
- Supprelin® LA (histrelin): June 2026

Pipeline Update(s):

- **October 2016:** AbbVie announced positive Phase 3 data from two clinical trials evaluating elagolix (ABT-620), a GnRH receptor antagonist, in premenopausal women with endometriosis. Patients treated with elagolix reported statistically significant reductions in scores for menstrual pain (dysmenorrhea, DYS) and non-menstrual pelvic pain (NMPP) associated with endometriosis as measured by the Daily Assessment of Endometriosis Pain scale compared to placebo at month three and month six.
- **January 2017:** Myovant Sciences announced the initiation of two Phase 3 clinical trials to evaluate relugolix, an oral GnRH receptor antagonist, in women with heavy menstrual bleeding associated with uterine fibroids. Each trial is expected to have a 24-week blinded period followed by an additional 24-week active treatment extension with a primary efficacy outcome of clinically-meaningful reduction in menstrual blood loss. Blood loss will be assessed based upon the alkaline hematin method, a standardized centrally-assessed quantitative measurement of menstrual blood loss.

Guideline Update(s):

- **January 2016:** The American Academy of Pediatrics released a clinical report titled "Evaluation and Referral of Children with Signs of Early Puberty." The report is intended to serve as a guide for physicians to help distinguish which signs of early sexual maturation require only observation and which require referral to a pediatric endocrinology specialist. According to the authors of the report, signs of early sexual maturation can vary with a patient's ethnicity or obesity status.

Recommendations

The College of Pharmacy does not recommend any changes to the gonadotropin-releasing hormone medication prior authorization criteria at this time.

Utilization Details of GnRH Medications: Fiscal Year 2016

GnRH Medications: Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM
LEUPROLIDE DEPOT PRODUCTS					
LUPRON DEPOT INJ 3.75MG	171	62	$186,290.35	$35.00	$1,089.42
LUPRON DEPOT INJ 11.25MG	92	66	$287,891.70	$38.26	$3,129.26
LUPRON DEPOT INJ 7.5MG	11	1	$6,555.84	$21.29	$595.99
LUPRON DEPOT INJ 30MG	3	1	$14,800.96	$54.82	$4,933.65
LUPRON DEPOT INJ 22.5MG	1	1	$3,956.20	$47.10	$3,956.20
SUBTOTAL	**278**	**123**	**$499,495.05**	**$36.98**	**$1,796.74**
LEUPROLIDE DEPOT PEDIATRIC PRODUCTS					
LUPR DEP-PED INJ 30MG	82	31	$566,683.57	$80.98	$6,910.78
LUPR DEP-PED INJ 11.25MG	47	15	$323,819.18	$79.84	$6,889.77
LUPR DEP-PED INJ 7.5MG	19	3	$24,052.64	$45.21	$1,265.93
LUPR DEP-PED INJ 15MG	16	4	$22,376.15	$48.86	$1,398.51
LUPR DEP-PED INJ 11.25MG	5	2	$6,045.30	$19.63	$1,209.06
SUBTOTAL	**169**	**52**	**$942,976.84**	**$76.34**	**$5,579.74**
LEUPROLIDE INJECTION PRODUCTS					
LEUPROLIDE INJ 1MG/0.2	4	2	$718.54	$9.98	$179.64
SUBTOTAL	**4**	**2**	**$718.54**	**$9.98**	**$179.64**
TOTAL	**451**	**177***	**$1,443,190.43**	**$55.65**	**$3,199.98**

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

GnRH Medications: Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM
LEUPROLIDE PRODUCTS				
LEUPROLIDE DEPOT 3.75MG (J1950)	36	11	$42,031.72	$1,167.55
LEUPROLIDE DEPOT 7.5MG (J9217)	63	34	$47,566.90	$755.03
LEUPROLIDE ACETATE INJ 1MG (J9218)	20	20	$412.68	$20.63
GOSERELIN ACETATE PRODUCTS				
GOSERELIN IMPLANT 3.6MG (J9202)	31	8	$10,491.21	$338.43
TOTAL	**150**	**72***	**$100,502.51**	**$670.02**

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

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[5] Zoladex® Prescribing Information. AstraZeneca Pharmaceuticals. Available online at: http://www.azpicentral.com/zoladex-36/zoladex3_6.pdf#page=1. Last revised 02/2016. Last accessed 04/21/2017.
[6] Supprelin® LA Prescribing Information. Endo Pharmaceuticals Inc. Available online at: http://www.endo.com/file%20library/products/prescribing%20information/supprelinla_prescribing_information.html. Last revised 06/2013. Last accessed 04/21/2017.
[7] Lupron Depot® and Depot-Ped® Prescribing Information. AbbVie Inc. Available online at: http://www.lupron.com/prescribing-information.aspx. Last revised 06/2013. Last accessed 04/21/2017.
[8] Lupaneta Pack™ Prescribing Information. AbbVie Inc. Available online at: http://www.rxabbvie.com/pdf/lupaneta_11_25_pi.pdf. Last revised 06/2015. Last accessed 04/21/2017.
[9] U.S. Food and Drug Administration (FDA): Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 03/2017. Last accessed 04/18/2017.
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Appendix Q

FDA & DEA Updates (additional information can be found at http://www.fda.gov/Drugs/default.htm)

FDA NEWS RELEASE

For Immediate Release: April 7th, 2017

FDA approves two hepatitis C drugs for pediatric patients

The U.S. Food and Drug Administration approved supplemental applications for Sovaldi (sofosbuvir) and Harvoni (ledipasvir and sofosbuvir) to treat hepatitis C virus (HCV) in children ages 12 to 17. Harvoni and Sovaldi were previously approved to treat HCV in adults.

These are the first direct-acting antiviral treatments approved for children and adolescents with HCV. Direct-acting antiviral drugs reduce the amount of HCV in the body by preventing the virus from multiplying, and in most cases, they cure HCV.

These approvals provide pediatric treatment options for six major genotypes, or strains, of HCV. Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 77 pounds (35 kilograms) with HCV genotype 1, 4, 5 or 6 infection without cirrhosis or with mild cirrhosis. Sovaldi in combination with ribavirin is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 77 pounds (35 kilograms) with genotype 2 or 3 HCV infection without cirrhosis or with mild cirrhosis.

HCV is a viral disease that causes inflammation of the liver that can lead to diminished liver function or liver failure. According to the Centers for Disease Control and Prevention, an estimated 2.7 to 3.9 million people in the United States have chronic HCV, and children born to HCV-positive mothers are at risk for HCV infection. It is estimated that there are 23,000 to 46,000 children in the United States with HCV infection.

The safety, pharmacokinetics and efficacy of Harvoni for the treatment of HCV genotype 1 infection were established in an open-label, multicenter clinical trial that included 100 pediatric patients 12 years of age and older. The results were comparable to those observed in adults and demonstrated that 98 percent of patients had no virus detected in the blood 12 weeks after finishing treatment, suggesting the patients' infections were cured.

The safety and efficacy of Harvoni for treatment of HCV genotypes 4, 5 or 6 infection in pediatric patients 12 years of age and older is based on data showing similar exposures to Harvoni in adults and adolescents with HCV genotype 1 infection, as well as similar efficacy and exposures to Harvoni across HCV genotypes 1, 4, 5 and 6 in adults.

The most common adverse reactions observed with treatment with Harvoni were fatigue and headache.

Sovaldi in combination with ribavirin was evaluated in an open-label clinical trial that included 50 pediatric patients 12 years of age and older. The results were comparable to those observed in adults and 100 percent of patients with HCV genotype 2, and 97 percent of patients with HCV genotype 3 had no virus detected in the blood 12 weeks after finishing treatment.

The most common adverse events observed with Sovaldi in combination with ribavirin were fatigue and headache. All contraindications to ribavirin also apply to Sovaldi combination therapy.

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

Harvoni and Sovaldi are marketed by Gilead Sciences, Inc.

FDA NEWS RELEASE

For Immediate Release: April 11th, 2017

FDA approves first drug to treat tardive dyskinesia

The U.S. Food and Drug Administration approved Ingrezza (valbenazine) capsules to treat adults with tardive dyskinesia. This is the first drug approved by the FDA for this condition.

Tardive dyskinesia is a neurological disorder characterized by repetitive involuntary movements, usually of the jaw, lips and tongue, such as grimacing, sticking out the tongue and smacking the lips. Some affected people also experience involuntary movement of the extremities or difficulty breathing.

Tardive dyskinesia is a serious side effect sometimes seen in patients who have been treated with antipsychotic medications, especially the older medications, for long periods to treat chronic conditions, such as schizophrenia and bipolar disorder. Tardive dyskinesia can also occur in patients taking antipsychotic medications for depression and certain medications for gastrointestinal disorders and other conditions. It is unclear why some people who take these medications develop tardive dyskinesia yet others do not.
The efficacy of Ingrezza was shown in a clinical trial of 234 participants that compared Ingrezza to placebo. After six weeks, participants who received Ingrezza had improvement in the severity of abnormal involuntary movements compared to those who received placebo.
Ingrezza may cause serious side effects including sleepiness and heart rhythm problems (QT prolongation). Its use should be avoided in patients with congenital long QT syndrome or with abnormal heartbeats associated with a prolonged QT interval. Those taking Ingrezza should not drive or operate heavy machinery or do other dangerous activities until it is known how the drug affects them.
The FDA granted this application Fast Track, Priority Review and Breakthrough Therapy designations.
The FDA granted approval of Ingrezza to Neurocrine Biosciences, Inc.

Safety Announcements

FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women

[4/20/2017] The Food and Drug Administration (FDA) is restricting the use of codeine and tramadol medicines in children. Codeine is approved to treat pain and cough, and tramadol is approved to treat pain. These medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. Single-ingredient codeine and all tramadol-containing products are FDA-approved only for use in adults. The FDA is also recommending against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.
As a result, the FDA is requiring several changes to the labels of all prescription medicines containing these drugs. These new actions further limit the use of these medicines beyond the FDA's 2013 restriction of codeine use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids. The FDA is now adding:

- FDA's strongest warning, called a *Contraindication*, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new *Contraindication* to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new *Warning* to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened *Warning* to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.

Caregivers and patients should always read the label on prescription bottles to find out if a medicine contains codeine or tramadol. Patients can also ask their child's health care provider or a pharmacist and should watch closely for signs of breathing problems in a child of any age who is taking these medicines or in infants exposed to codeine or tramadol through breastmilk. These signs include slow or shallow breathing, difficulty or noisy breathing, confusion, more than usual sleepiness, trouble breastfeeding, or limpness. If patients notice any of these signs, they should stop giving the medicine and seek medical attention immediately by going to an emergency room or calling 911.
Health care professionals should be aware that tramadol and single-ingredient codeine medicines are FDA-approved only for use in adults. Consideration should be given to recommending over-the-counter (OTC) or other FDA-approved prescription medicines for cough and pain management in children younger than 12 years and in adolescents younger than 18 years, especially those with certain genetic factors, obesity, or obstructive sleep apnea and other breathing problems. Cough is often secondary to infection, not serious, and usually will get better on its own so treatment may not be necessary.
Codeine and tramadol are a type of narcotic medicine called an opioid. Codeine is used to treat mild to moderate pain and also to reduce coughing. It is usually combined with other medicines, such as

acetaminophen, in prescription pain medicines. It is frequently combined with other drugs in prescription and over-the-counter (OTC) cough and cold medicines. Tramadol is a prescription medicine approved only for use in adults to treat moderate to moderately severe pain. However, data show it is being used in children and adolescents despite the fact that it is not approved for use in these patients.

In early 2013, FDA added a *Boxed Warning* to the codeine drug label cautioning against prescribing codeine to children of any age to treat pain after surgery to remove tonsils or adenoids. The FDA also issued Drug Safety Communications in July 2015 and September 2015 warning about the risk of serious breathing problems in some children who metabolized codeine and tramadol much faster to their active form than usual (called ultra-rapid metabolism), causing potentially dangerously high levels in their bodies too quickly. At that time, the FDA said they would continue to evaluate this safety issue. As part of that safety review, the codeine-related safety issues were discussed at an FDA Advisory Committee meeting in December 2015.

The FDA's review of several decades of adverse event reports submitted to FDA from January 1969 to May 2015 identified 64 cases of serious breathing problems, including 24 deaths, with codeine-containing medicines in children younger than 18 years. This includes only reports submitted to FDA, so there may be additional cases about which the FDA is unaware. The FDA also identified nine cases of serious breathing problems, including three deaths, with the use of tramadol in children younger than 18 years from January 1969 to March 2016. The majority of serious side effects with both codeine and tramadol occurred in children younger than 12 years, and some cases occurred after a single dose of the medicine.

In the FDA's review of the medical literature for data regarding codeine use during breastfeeding, the FDA found numerous cases of excess sleepiness and serious breathing problems in breastfed infants, including one death. A review of the available medical literature for data regarding tramadol use during breastfeeding did not reveal any cases of adverse events. However, tramadol and its active form are also present in breast milk, and tramadol has the same risks associated with ultra-rapid metabolism as codeine.

The FDA will continue to monitor this safety issue. The FDA is considering additional regulatory action for the OTC codeine products that are available in some states. OTC codeine products are available in combination with other medicines for cough and cold symptoms. The FDA is also considering an FDA Advisory Committee meeting to discuss the role of prescription opioid cough-and-cold medicines, including codeine, to treat cough in children.

The FDA urges patients and health care professionals to report side effects involving codeine-and tramadol-containing medicines to the FDA MedWatch program.

Current Drug Shortages Index (as of April 24th, 2017):

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

Albuterol Sulfate Inhalation Solution (0.5%, 0.021%, and 0.042%)	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Bleomycin Sulfate for Injection	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Dihydroergotamine Mesylate Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Estradiol Valerate Injection, USP	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Hydroxyamphetamine Hydrobromide/Tropicamide (Paremyd)	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***
Indigotindisulfonate Sodium (Indigo Carmine) 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***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Mecasermin [rDNA origin] (Increlex) Injection	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methylprednisolone Sodium Succinate for Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nitrous Oxide, Gas	***Currently in Shortage***
Penicillin G Benzathine (Bicillin L-A) Injection	***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***
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***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Rocuronium Bromide Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine (Transderm Scop) Transdermal System Patch	***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***
Sterile Talc Powder	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***