Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
March 14, 2018
4:00pm

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

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review (DUR) Board Members

FROM: Bethany Holderread, Pharm.D.

SUBJECT: Packet Contents for Board Meeting – March 14th, 2018

DATE: March 01, 2018

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 March 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/U.S. Food and Drug Administration Safety Alerts – Appendix B

Action Item – Vote to Prior Authorize Tymlos™ (Abaloparatide) – Appendix C

Action Item – Vote to Prior Authorize Prevymis™ (Letermovir Tablets and Injection) – Appendix D

Action Item – Vote to Prior Authorize Rhopressa® (Netarsudil Ophthalmic Solution) and Vyzulta™ (Latanoprostene Bunod Ophthalmic Solution) – Appendix E

Action Item – Vote to Prior Authorize Mepsevii™ (Vestronidase Alfa-vjbk) – Appendix F

Action Item – Vote to Prior Authorize Ergomar® (Ergotamine Sublingual Tablets) – Appendix G

Action Item – Vote to Prior Authorize Xadago® (Safinamide) and Gocovri™ (Amantadine Extended-Release) – Appendix H

Annual Review of Chronic Lymphocytic Leukemia (CLL) Medications and 30-Day Notice to Prior Authorize Arzerra® (Ofatumumab), Gazyva® (Obinutuzumab), Imbruvica® (Ibrutinib), Venclexta™ (Venetoclax), and Zydelig® (Idelalisib) – Appendix I

Action Item – Annual Review of Erythropoietin Stimulating Agents (ESAs) – Appendix J

30-Day Notice to Prior Authorize Luxturna™ (Voretigene Neparvovec-rzyl) – Appendix K

Action Item – Annual Review of Spinraza® (Nusinersen) – Appendix L

Annual Review of Multiple Sclerosis (MS) Medications and 30-Day Notice to Prior Authorize Ocrevus™ (Ocrelizumab) – Appendix M

Annual Review of Alpha$_1$-Proteinase Inhibitors and 30-Day Notice to Prior Authorize Prolastin®-C Liquid [Alpha$_1$-Proteinase Inhibitor (Human)] – Appendix N

Industry News and Updates – Appendix O

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

Future Business

Adjournment

Oklahoma Health Care Authority

Drug Utilization Review Board
(DUR Board)
Meeting – March 14, 2018 @ 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. Acknowledgment of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. February 14, 2018 DUR Minutes – Vote

B. February 14, 2018 DUR Recommendations Memorandum

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

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

A. Medication Coverage Activity for February 2018

B. Pharmacy Help Desk Activity for February 2018

C. U.S. Food and Drug Administration Safety Alerts

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

5. Action Item – Vote to Prior Authorize Tymlos™ (Abaloparatide) – See Appendix C

A. Introduction

B. College of Pharmacy Recommendations

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

6. Action Item – Vote to Prior Authorize Prevymis™ (Letermovir Tablets and Injection) – See Appendix D

A. Introduction

B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Rhopressa® (Netarsudil Ophthalmic Solution) and Vyzulta™ (Latanoprostene Bunod Ophthalmic Solution) – See Appendix E

A. Introduction

B. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Mepsevii™ (Vestronidase Alfa-vjbk) – See Appendix F

A. Introduction

B. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize Ergomar® (Ergotamine Sublingual Tablets) – See Appendix G

A. Introduction

B. College of Pharmacy Recommendations

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

10. Action Item – Vote to Prior Authorize Xadago® (Safinamide) and Gocovri™ (Amantadine Extended-Release) – See Appendix H

A. Introduction
B. College of Pharmacy Recommendations

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

11. Annual Review of Chronic Lymphocytic Leukemia (CLL) Medications and 30-Day Notice to Prior Authorize Arzerra® (Ofatumumab), Gazyva® (Obinutuzumab), Imbruvica® (Ibrutinib), Venclexta™ (Venetoclax), and Zydelig® (Idelalisib) – See Appendix I

A. Introduction
B. Utilization of CLL Medications
C. Market News and Updates
D. Product Summaries
E. Recommendations
F. Utilization Details of CLL Medications

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

12. Action Item – Annual Review of Erythropoietin Stimulating Agents (ESAs) – See Appendix J

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

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

13. 30-Day Notice to Prior Authorize Luxturna™ (Voretigene Neparvovec-rzyl) – See Appendix K

A. Introduction
B. Market News and Updates
C. Luxturna™ (Voretigene Neparvovec-rzyl) Product Summary
D. College of Pharmacy Recommendations

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

14. Action Item – Annual Review of Spinraza® (Nusinersen) – See Appendix L

A. Current Prior Authorization Criteria
B. Utilization of Spinraza® (Nusinersen)
C. Prior Authorization of Spinraza® (Nusinersen)
D. Market News and Updates
E. College of Pharmacy Recommendations

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

15. Annual Review of Multiple Sclerosis (MS) Medications and 30-Day Notice to Prior Authorize Ocrevus™ (Ocrelizumab) – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of MS Medications
C. Prior Authorization of MS Medications
D. Market News and Updates
E. Institute for Clinical Effectiveness and Economic Review (ICER): Disease Modifying Therapies for MS
F. Ocrevus™ (Ocrelizumab) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of MS Medications

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

16. Annual Review of Alpha$_1$-Proteinase Inhibitors and 30-Day Notice to Prior Authorize Prolastin®-C Liquid [Alpha$_1$-Proteinase Inhibitor (Human)] – See Appendix N

A. Alpha$_1$-Antitrypsin Deficiency
B. Current Prior Authorization Criteria
C. Utilization of Alpha$_1$-Proteinase Inhibitors
D. Prior Authorization of Alpha$_1$-Proteinase Inhibitors
E. Market News and Updates
F. Prolastin®-C Liquid [Alpha$_1$-Proteinase Inhibitor (Human)] Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Alpha$_1$-Proteinase Inhibitors

Non-Presentation; Questions Only:

17. Industry News and Updates – See Appendix O

A. Introduction
B. News and Updates

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

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

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

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

A. Annual Review of Pharmacy Benefit
B. Diabetic Medications
C. Antihypertensive Medications
D. Benlysta® (Belimumab)

**Future business subject to change.*

20. Adjournment

Appendix A

OKLAHOMA HEALTH CARE AUTHORITY
DRUG UTILIZATION REVIEW BOARD MEETING
MINUTES OF MEETING OF FEBRUARY 14, 2018

BOARD MEMBERS:	PRESENT	ABSENT
Stephen Anderson, Pharm.D.	x	
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	

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., BCGP; 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): N/A		

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Melody Anthony, Deputy State Medicaid Director	x	
Marlene Asmussen, R.N.; Population Care Management Director	x	
Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.; Assistant Pharmacy Director	x	
Kelli Brodersen, Marketing Coordinator		x
Robert Evans, M.D.; Sr. Medical Director	x	
Michael Herndon, D.O.; Chief Medical Officer		x
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Thomas Nunn, D.O.; Medical Director		x
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist		x
Garth Splinter, M.D.; M.B.A.; Deputy Chief Executive Officer		x
Joseph Young, J.D.; Deputy General Counsel IV	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Megan Loftis, Ultragenyx	Jeff O'Dell, Ultragenyx	Brandon Ross, Merck
Craig Schilling, AstraZeneca	Karen Ladusau, UCO School of Nursing	Chi Kohlhoff, Braeburn
Kristi Kemp, Allergan	Erica Brumleve, GSK	Steve Curry, ACK
Dan Doyle, Trividia	Mai Duong, Novartis	Matt Forney, Merck
Chris Stanfield, Supernus	Kari Suttee, Novartis	Gwendolyn Caldwell, PhRMA
Brent Hildebrand, Gilead	Clint Degner, Novartis Oncology	Brian Maves, Pfizer
Aaron Shaw, BI	Amber Schrantz, Lilly	

PRESENT FOR PUBLIC COMMENT:	
Craig Schilling	AstraZeneca

AGENDA ITEM NO. 1: CALL TO ORDER

1A: ROLL CALL

Dr. Muchmore called the meeting to order. Roll call by Dr. Cothran established the presence of a quorum.

ACTION: NONE REQUIRED

AGENDA ITEM NO. 2: PUBLIC COMMENT FORUM

2A: AGENDA ITEM NO. 6 SPEAKER: CRAIG SCHILLING

ACTION: NONE REQUIRED

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

3A: DECEMBER 13, 2017 DUR MINUTES – VOTE

3B: DECEMBER 13, 2017 DUR RECOMMENDATIONS MEMORANDUM

3C: JANUARY 10, 2018 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Cothran

Ms. Varalli-Claypool moved to approve; seconded by Dr. Preslar

ACTION: MOTION CARRIED

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

4A: MEDICATION COVERAGE ACTIVITY FOR JANUARY 2018

4B: PHARMACY HELP DESK ACTIVITY FOR JANUARY 2018

4C: CHRONIC MEDICATION ADHERENCE PROGRAM UPDATE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: VOTE TO PRIOR AUTHORIZE ZERVIATE™ (CETIRIZINE OPHTHALMIC SOLUTION)

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE ARMONAIR™ RESPICLICK® (FLUTICASONE PROPIONATE), TRELEGY™ ELLIPTA® (FLUTICASONE FUROATE/UMECLIDINIUM/VILANTEROL), QVAR® REDIHALER™ (BECLOMETHASONE DIPROPIONATE), AIRDUO™ RESPICLICK® (FLUTICASONE PROPIONATE/SALMETEROL), AND FASENRA™ (BENRALIZUMAB) AND TO UPDATE NUCALA® (MEPOLIZUMAB) AND XOLAIR® (OMALIZUMAB) CRITERIA

6A: INTRODUCTION

6B: NUCALA® (MEPOLIZUMAB) FOR EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

6C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Holderread

Dr. Muchmore recommends for benralizumab that member must have history of a blood eosinophil count of 300 cell/µL or greater (can apply to either a recent level or in history prior to oral corticosteroid use)
Ms. Varalli-Claypool moved to approve; seconded by Dr. Harrell
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE EMFLAZA® (DEFLAZACORT)
7A: INTRODUCTION
7B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Preslar recommends required 6 month prednisone trial; baseline eye exam and yearly approvals with repeat eye exams
Dr. Preslar moved to approve; seconded by Dr. Anderson
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE ZILRETTA™ (TRIAMCINOLONE ACETONIDE EXTENDED-RELEASE INJECTABLE SUSPENSION)
8A: INTRODUCTION
8B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Nichols
Dr. Harrell moved to approve; seconded by Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: VOTE TO PRIOR AUTHORIZE VARUBI® IV (ROLAPITANT) AND CINVANTI™ (APREPITANT)
9A: INTRODUCTION
9B: MARKET NEWS
9C: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Adams
Dr. Harrell moved to approve; seconded by Dr. Anderson
ACTION: MOTION CARRIED

AGENDA ITEM NO. 10: ANNUAL REVIEW OF SEIZURE MEDICATIONS
10A: CURRENT PRIOR AUTHORIZATION CRITERIA
10B: UTILIZATION OF SEIZURE MEDICATIONS
10C: PRIOR AUTHORIZATION OF SEIZURE MEDICATIONS
10D: MARKET NEWS AND UPDATES
10E: COLLEGE OF PHARMACY RECOMMENDATIONS
10F: UTILIZATION DETAILS OF SEIZURE MEDICATIONS
Materials included in agenda packet; presented by Dr. Adams
Dr. Harrell moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: ANNUAL REVIEW OF OSTEOPOROSIS MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE TYMLOS™ (ABALOPARATIDE)
11A: CURRENT PRIOR AUTHORIZATION CRITERIA
11B: UTILIZATION OF OSTEOPOROSIS MEDICATIONS
11C: PRIOR AUTHORIZATION OF OSTEOPOROSIS MEDICATIONS
11D: MARKET NEWS AND UPDATES
11E: TYMLOS™ (ABALOPARATIDE) PRODUCT SUMMARY
11F: COLLEGE OF PHARMACY RECOMMENDATIONS
11G: UTILIZATION DETAILS OF OSTEOPOROSIS MEDICATIONS
Materials included in agenda packet; presented by Dr. Chandler
ACTION: NONE REQUIRED

AGENDA ITEM NO. 12: **ANNUAL REVIEW OF ANTIVIRAL MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE PREVYMIS™ (LETERMOVIR TABLETS AND INJECTION)**

12A: CURRENT PRIOR AUTHORIZATION CRITERIA
12B: UTILIZATION OF ANTIVIRAL MEDICATIONS
12C: PRIOR AUTHORIZATION OF ANTIVIRAL MEDICATIONS
12D: MARKET NEWS AND UPDATES
12E: CYTOMEGALOVIRUS PREVENTION IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS
12F: PREVYMIS™ (LETERMOVIR) PRODUCT SUMMARY
12G: COLLEGE OF PHARMACY RECOMMENDATIONS
12H: UTILIZATION DETAILS OF ANTIVIRAL MEDICATIONS

Materials included in agenda packet; presented by Dr. Nichols

ACTION: NONE REQUIRED

AGENDA ITEM NO. 13: **ANNUAL REVIEW OF GLAUCOMA MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) AND VYZULTA™ (LATANOPROSTENE BUNOD OPHTHALMIC SOLUTION)**

13A: CURRENT PRIOR AUTHORIZATION CRITERIA
13B: UTILIZATION OF GLAUCOMA MEDICATIONS
13C: PRIOR AUTHORIZATION OF GLAUCOMA MEDICATIONS
13D: MARKET NEWS AND UPDATES
13E: RHOPRESSA® (NETARSUDIL OPHTHALMIC SOLUTION) PRODUCT SUMMARY
13F: VYZULTA™ (LATANOPROSTENE BUNOD OPHTHALMIC SOLUTION) PRODUCT SUMMARY
13G: COLLEGE OF PHARMACY RECOMMENDATIONS
13H: UTILIZATION DETAILS OF GLAUCOMA MEDICATIONS

Materials included in agenda packet; presented by Dr. Nichols

ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: **ANNUAL REVIEW OF PARKINSON'S DISEASE (PD) MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE XADAGO® (SAFINAMIDE) AND GOCOVRI™ [AMANTADINE EXTENDED-RELEASE (ER)]**

14A: CURRENT PRIOR AUTHORIZATION CRITERIA
14B: UTILIZATION OF PD MEDICATIONS
14C: PRIOR AUTHORIZATION OF PD MEDICATIONS
14D: MARKET NEWS AND UPDATES
14E: XADAGO® (SAFINAMIDE) PRODUCT SUMMARY
14F: GOCOVRI™ (AMANTADINE ER) PRODUCT SUMMARY
14G: COLLEGE OF PHARMACY RECOMMENDATIONS
14H: UTILIZATION DETAILS OF PD MEDICATIONS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: **30-DAY NOTICE TO PRIOR AUTHORIZE MEPSEVII™ (VESTRONIDASE ALFA-VJBK)**

15A: INTRODUCTION
15B: MEPSEVII™ (VESTRONIDASE ALFA-VJBK) PRODUCT SUMMARY
15C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Abbott

ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: **ANNUAL REVIEW OF ANTI-MIGRAINE MEDICATIONS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ERGOMAR® (ERGOTAMINE SUBLINGUAL TABLETS)**

16A: CURRENT PRIOR AUTHORIZATION CRITERIA
16B: UTILIZATION OF ANTI-MIGRAINE MEDICATIONS
16C: PRIOR AUTHORIZATION OF ANTI-MIGRAINE MEDICATIONS

16D: MARKET NEWS AND UPDATES
16E: ERGOMAR® (ERGOTAMINE SUBLINGUAL TABLETS) PRODUCT SUMMARY
16F: COLLEGE OF PHARMACY RECOMMENDATIONS
16G: UTILIZATION DETAILS OF ANTI-MIGRAINE MEDICATIONS
Materials included in agenda packet; presented by Dr. Abbott
ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: INDUSTRY NEWS AND UPDATES
17A: INTRODUCTION
17B: NEWS AND UPDATES
Materials included in agenda packet; Non-presentation; Questions only
ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: U.S. FOOD AND DRUG ADMINISTRATION (FDA) AND DRUG ENFORCEMENT ADMINISTRATION (DEA) UPDATES
Materials included in agenda packet; presented by Dr. Cothran
ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)
19A: MULTIPLE SCLEROSIS MEDICATIONS
19B: SPINRAZA® (NUSINERSEN)
19C: LUXTURNA™ (VORETIGENE NEPARVOVEC-RZYL)
19D: ERYTHROPOIETIN STIMULATING AGENTS (ESAS)
19E: CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) MEDICATIONS
FUTURE BUSINESS SUBJECT TO CHANGE
Materials included in agenda packet; presented by Dr. Holderread
ACTION: NONE REQUIRED

AGENDA ITEM NO. 20: ADJOURNMENT
The meeting was adjourned at 5:15 pm.

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

Memorandum

Date: February 15, 2018

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 February 14, 2018

Recommendation 1: Chronic Medication Adherence Program Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Zerviate™ (Cetirizine Ophthalmic Solution)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following:

- The placement of Zerviate™ (cetirizine ophthalmic solution) into Tier-3 of the Ophthalmic Allergy Product Based Prior Authorization (PBPA) category. Current Tier-3 criteria would apply.
- Moving Elestat® (epinastine) from Tier-3 to Tier-2 based on net cost. Current Tier-2 criteria would apply.

Ophthalmic Allergy Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and
2. A trial of one Tier-1 product for a minimum of two weeks in the last 30 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. A contraindication to all lower tiered medications.

Ophthalmic Allergy Tier-3 Approval Criteria:

1. An FDA approved diagnosis; and
2. Recent trials of one Tier-1 product and all available Tier-2 medications for a minimum of two weeks each that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. A contraindication to all lower tiered medications.

Ophthalmic Allergy Medications		
Tier-1	**Tier-2**	**Tier-3**
cromolyn (Crolom®)	azelastine (Optivar®)	alcaftadine (Lastacaft®)
ketotifen (Alaway®, Zaditor® OTC)	**epinastine (Elestat®)**	bepotastine (Bepreve®)
	olopatadine (Patanol®)	**cetirizine (Zerviate™)**
	olopatadine (Pazeo®)	emedastine (Emadine®)
		lodoxamide (Alomide®)
		loteprednol (Alrex®)
		nedocromil (Alocril®)
		olopatadine (Pataday®)

OTC = over-the-counter
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendation 3: Vote to Prior Authorize ArmonAir™ RespiClick® (Fluticasone Propionate), Trelegy™ Ellipta® (Fluticasone Furoate/Umeclidinium/Vilanterol), QVAR® RediHaler™ (Beclomethasone Dipropionate), AirDuo™ RespiClick® (Fluticasone Propionate/Salmeterol), and Fasenra™ (Benralizumab) and to Update Nucala® (Mepolizumab) and Xolair® (Omalizumab) Criteria

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of ArmonAir™ RespiClick® (fluticasone propionate), Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/vilanterol), QVAR® RediHaler™ (beclomethasone dipropionate), AirDuo™ RespiClick® (fluticasone propionate/salmeterol), and Fasenra™ (benralizumab) with the following criteria:

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

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

QVAR® RediHaler™ (Beclomethasone Dipropionate HFA) Approval Criteria:

1. An FDA approved diagnosis of asthma; and
2. Member must be 4 years of age or older; and
3. A patient-specific, clinically significant reason why QVAR® (beclomethasone dipropionate HFA) is not an option for the member; and
4. A trial of all available Tier-1 inhaled corticosteroids or a patient-specific, clinically significant reason why they are not appropriate for the member.

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

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

Inhaled Corticosteroids and Combination Products	
Tier-1	**Tier-2**
beclomethasone dipropionate (QVAR®)	**beclomethasone dipropionate (QVAR® RediHaler™)**
budesonide (Pulmicort®)	budesonide/formoterol (Symbicort®)
ciclesonide (Alvesco®)	fluticasone furoate (Arnuity® Ellipta®)
flunisolide (Aerospan®)	fluticasone furoate/vilanterol (Breo® Ellipta®)
fluticasone propionate (Flovent®)	**fluticasone propionate (ArmonAir™ RespiClick®)**
fluticasone/salmeterol (Advair®)	**fluticasone propionate/salmeterol (AirDuo™ RespiClick®)**
mometasone/formoterol (Dulera® HFA)	
mometasone furoate (Asmanex®)	

Tier-1 products are covered with no prior authorization required.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

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

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

Fasenra™ (Benralizumab Injection) Approval Criteria:

1. An FDA approved indication for add-on maintenance treatment of patients with severe eosinophilic phenotype asthma; and
2. Member must be age 12 years or older; and
3. Member must have history of a blood eosinophil count of 300 cell/µL or greater (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least two asthma exacerbations requiring systemic corticosteroids within the last 12 months or require daily systemic corticosteroids despite compliant use of high-dose inhaled corticosteroid (ICS) plus at least one additional controller medication; and

5. Member must have failed a high-dose ICS (≥880mcg/day fluticasone propionate or equivalent daily dose or ≥440mcg/day in ages 12 to 17 years) used compliantly for at least the past 12 months (for ICS/LABA combination medications, the highest approved dose meets this criteria); and
6. Member must have failed at least one other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past three months; and
7. Fasenra™ must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis; and
8. Fasenra™ must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
9. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval.
10. A quantity limit of 1 prefilled syringe per 56 days will apply.

Additionally, the College of Pharmacy recommends the following criteria for Nucala® (mepolizumab) for a diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA):

Nucala® (Mepolizumab Injection) Approval Criteria [Eosinophilic Granulomatosis with Polyangiitis (EGPA) Diagnosis]:

1. An FDA approved indication for the treatment of eosinophilic granulomatosis with polyangiitis (EGPA); and
2. Member meets one of the following:
    a. Member must have a past history of at least one confirmed EGPA relapse [requiring increase in oral corticosteroid (OCS) dose, initiation/increased dose of immunosuppressive therapy, or hospitalization] with in the past twelve months; or
    b. Member must have refractory disease within the last six months following induction of standard treatment regimen administered compliantly for at least three months; and
3. Diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) will not be approved; and
4. Failure to achieve remission despite glucocorticoid therapy (oral prednisone equivalent equal to or greater than 7.5mg/day) for a minimum of 4 weeks duration; and
5. Nucala® must be prescribed by an allergist, pulmonologist, pulmonary specialist, or rheumatologist or the member must have been evaluated by an allergist, pulmonologist, pulmonary specialist, or rheumatologist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, pulmonary specialist, or rheumatologist); and
6. Nucala® must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis; and
7. A quantity limit of 3 vials per 28 days will apply.
8. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval. For continued approval, member must be compliant and prescriber must verify the member is responding to Nucala® as

demonstrated by a Birmingham Vasculitis Activity Score (BVAS) of zero, fewer EGPA relapses from baseline, or a decrease in daily OCS dose regimen from baseline.

Lastly, the College of Pharmacy recommends updating the Nucala® (mepolizumab) and Xolair® (omalizumab) asthma criteria regarding administration and anaphylaxis with criteria similar to the other medications in the class. Changes can be seen in red in the following criteria:

Nucala® (Mepolizumab Injection) Approval Criteria [Severe Eosinophilic Phenotype Asthma Diagnosis]:

1. An FDA approved indication for add-on maintenance treatment of patients with severe eosinophilic phenotype asthma; and
2. Member must be age 12 years or older; and
3. Member must have a baseline blood eosinophil count of 150 cell/mcL or greater within the last six weeks of initiation of dosing; and
4. Member must have had at least two asthma exacerbations requiring systemic corticosteroids within the last twelve months or require daily systemic corticosteroids despite compliant use of high-dose inhaled corticosteroid (ICS) plus at least one additional controller medication; and
5. Member must have failed a high-dose ICS (≥880mcg/day fluticasone propionate or equivalent daily dose or ≥440mcg/day in ages 12 to 17 years) used compliantly for at least the past twelve months (for ICS/LABA combination products, the highest approved dose meets this criteria); and
6. Member must have failed at least one other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past three months; and
7. Nucala® must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis; and
8. Nucala® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
9. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval; and
10. A quantity limit of 1 vial per 28 days will apply.

Xolair® (Omalizumab) Approval Criteria [Asthma Diagnosis]:

1. Member must have a diagnosis of severe persistent asthma [as per National Asthma Education and Prevention Program (NAEPP) guidelines]; and
2. Member must be between 6 and 75 years of age; and
3. Member must have a positive skin test to at least one perennial aeroallergen. Positive perennial aeroallergens must be listed on the prior authorization request; and
4. Member must have a pretreatment serum IgE level between 30 and 1,300 IU/mL (depending on member age); and
5. Member's weight must be between 20kg and 150kg; and
6. Member must have been on high-dose inhaled corticosteroids (ICS) (≥880mcg/day fluticasone propionate or equivalent daily dose or ≥440mcg/day in ages 12 to 17 years) for at minimum the past three months; and

7. Prescribed Xolair® dose must be an FDA approved regimen per Xolair® prescribing information; and
8. Xolair® must be administered in a healthcare setting by a healthcare professional prepared to manage anaphylaxis; and
9. Xolair® must be prescribed by an allergist, pulmonologist, or pulmonary specialist or the member must have been evaluated by an allergist, pulmonologist, or pulmonary specialist within the last twelve months (or be an advanced care practitioner with a supervising physician who is an allergist, pulmonologist, or pulmonary specialist); and
10. Member must have been in the emergency room (ER) or hospitalized, due to an asthma exacerbation, twice in the past twelve months (date of visits must be listed on the prior authorization request), or member must have been determined to be dependent on systemic corticosteroids to prevent serious exacerbations; and
11. Both the prior authorization request form and statement of medical necessity form must be submitted for processing; and
12. Initial approvals will be for the duration of six months after which time compliance will be evaluated for continued approval.

Recommendation 4: Vote to Prior Authorize Emflaza® (Deflazacort)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Emflaza® (deflazacort) with the following criteria:

Emflaza® (Deflazacort) Approval Criteria:

1. An FDA approved diagnosis of Duchenne muscular dystrophy (DMD); and
2. Member must be 5 years of age or older; and
3. Emflaza® must be prescribed by or in consultation with a prescriber who specializes in the treatment of DMD; and
4. A minimum of a six-month trial of prednisone that resulted in inadequate effects or intolerable adverse effects that are not expected to occur with Emflaza®; and
5. A patient-specific, clinically significant reason why the member cannot use prednisone even when the tablets are crushed must be provided; and
6. Patients already established on deflazacort via the ACCESS DMD Program must also document a patient-specific, clinically significant reason why the member cannot use prednisone even when the tablets are crushed; and
7. For Emflaza® suspension, a patient-specific, clinically significant reason why the member cannot use the tablet formulation in the place of oral suspension even when the tablets are crushed must be provided; and
8. Verification from the prescriber the member has had a baseline eye examination; and
9. For continued authorization, the member's recent weight must be provided in order to authorize the appropriate amount of drug required according to package labeling, and the member must have had a repeat eye exam with results that are acceptable to the prescriber; and
10. For the tablets, a quantity limit of 30 tablets per 30 days will apply and for the suspension, a quantity limit of 39mL (3 bottles) per 30 days will apply. Quantity limit requests will be based on the member's recent weight taken within the last 30 days.

Recommendation 5: Vote to Prior Authorize Zilretta™ (Triamcinolone Acetonide Extended-Release Injectable Suspension)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Zilretta™ [triamcinolone acetonide extended-release (ER) injection] with the following criteria:

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

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

Recommendation 6: Vote to Prior Authorize Varubi® IV (Rolapitant) and Cinvanti™ (Aprepitant)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Varubi® IV (rolapitant for IV use) and Cinvanti™ (aprepitant for IV use) with the following criteria:

Varubi® and Varubi® IV (Rolapitant) Approval Criteria:

1. An FDA approved indication for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy; and
2. For oral Varubi® (rolapitant oral tablets), a previously failed trial of aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why aprepitant cannot be used must be provided; and
3. For Varubi® IV [rolapitant intravenous (IV) emulsion], a previously failed trial of IV fosaprepitant (Emend® IV) that resulted in an inadequate response, or a patient-specific, clinically significant reason why IV fosaprepitant cannot be used must be provided; and
4. Approval length will be based on duration of need.
5. A quantity limit of two tablets or two vials per chemotherapy cycle will apply.

Kytril® and Sancuso® (Granisetron), Anzemet® (Dolasetron), Emend® and Cinvanti™ (Aprepitant), and Emend® IV (Fosaprepitant) Approval Criteria:

1. An FDA approved diagnosis; and
2. A recent trial of ondansetron (within the past six months) used for at least three days or one cycle that resulted in an inadequate response is required for authorization in members receiving moderately emetogenic chemotherapy; and
3. No ondansetron trial is required for authorization of Emend® (aprepitant) in members receiving highly emetogenic chemotherapy; and
4. For Emend® (aprepitant) oral suspension, an age restriction of six years and younger will apply. Members older than six years of age will require a patient-specific, clinically significant reason why the oral capsule formulation cannot be used; and

5. For Cinvanti™ [aprepitant intravenous (IV) emulsion], a previously failed trial of IV fosaprepitant (Emend® IV) that resulted in an inadequate response, or a patient-specific, clinically significant reason why IV fosaprepitant cannot be used must be provided; and
6. Approval length will be based on duration of need.

Additionally, based on the current low net cost of Akynzeo® (netupitant/palonosetron), the College of Pharmacy recommends making Akynzeo® available without a prior authorization for members with cancer; however, Akynzeo® will follow the original criteria and require a previously failed trial of aprepitant if the net cost increases compared to other available products. The changes to the current criteria are shown in red:

Akynzeo® (Netupitant/Palonosetron) Approval Criteria:

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

Recommendation 7: Annual Review of Seizure Medications

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the following changes shown in red based on new or updated U.S. Food and Drug Administration (FDA)-approved indications for Qudexy® XR [topiramate extended-release (ER)], Trokendi XR® (topiramate ER), Briviact® (brivaracetam), and Fycompa® (perampanel):

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

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

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

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

Briviact® (Brivaracetam) Approval Criteria:

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

Fycompa® (Perampanel) Approval Criteria:

1. An FDA approved indication of ~~adjunctive therapy in~~ the treatment of partial-onset seizures with or without secondarily generalized seizures or adjunctive therapy in the treatment of primary generalized tonic-clonic (PGTC) seizures; and
2. Initial prescription must be written by a neurologist; and
3. Member must have failed therapy with at least one* other medications commonly used for seizures. (*The manufacturer of Fycompa® has currently provided a supplemental rebate to require a trial with one other medication; however, Fycompa® will follow the original criteria and require trials with three other medications if the manufacturer chooses not to participate in supplemental rebates.)
4. For Fycompa® oral suspension, a patient-specific, clinically significant reason why Fycompa® oral tablets cannot be used must be provided.
5. Members currently stable on Fycompa® and who have a seizure diagnosis will be grandfathered.

Recommendation 8: Annual Review of Osteoporosis Medications and 30-Day Notice to Prior Authorize Tymlos™ (Abaloparatide)

NO ACTION REQUIRED.

Recommendation 9: Annual Review of Antiviral Medications and 30-Day Notice to Prior Authorize Prevymis™ (Letermovir Tablets and Injection)

NO ACTION REQUIRED.

Recommendation 10: Annual Review of Glaucoma Medications and 30-Day Notice to Prior Authorize Rhopressa® (Netarsudil Ophthalmic Solution) and Vyzulta™ (Latanoprostene Bunod Ophthalmic Solution)

NO ACTION REQUIRED.

Recommendation 11: Annual Review of Parkinson's Disease (PD) Medications and 30-Day Notice to Prior Authorize Xadago® (Safinamide) and Gocovri™ (Amantadine Extended-Release)

NO ACTION REQUIRED.

Recommendation 12: 30-Day Notice to Prior Authorize Mepsevii™ (Vestronidase Alfa-vjbk)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Anti-Migraine Medications and 30-Day Notice to Prior Authorize Ergomar® (Ergotamine Sublingual Tablets)

NO ACTION REQUIRED.

Recommendation 14: Industry News and Updates

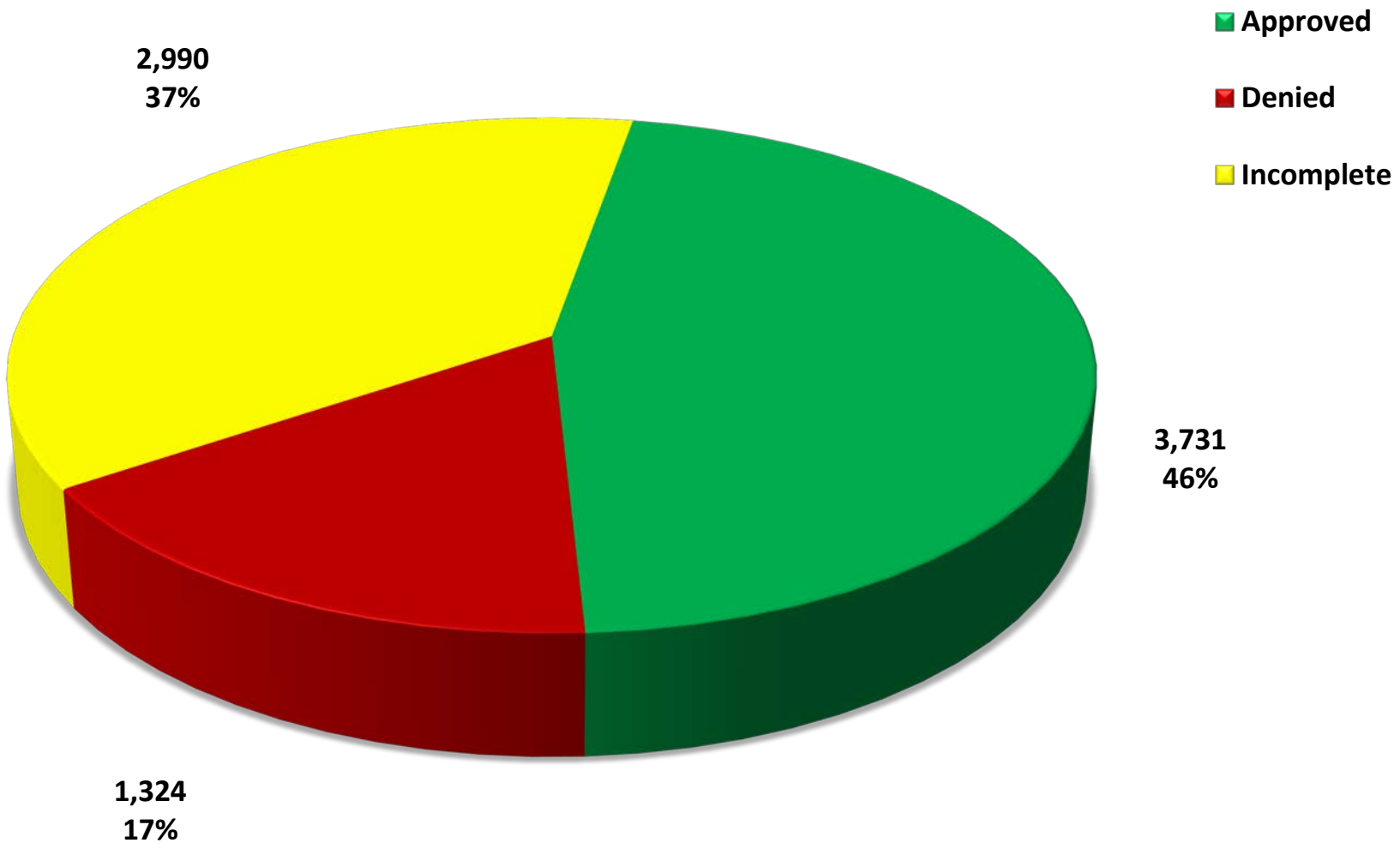
NO ACTION REQUIRED.

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

NO ACTION REQUIRED.

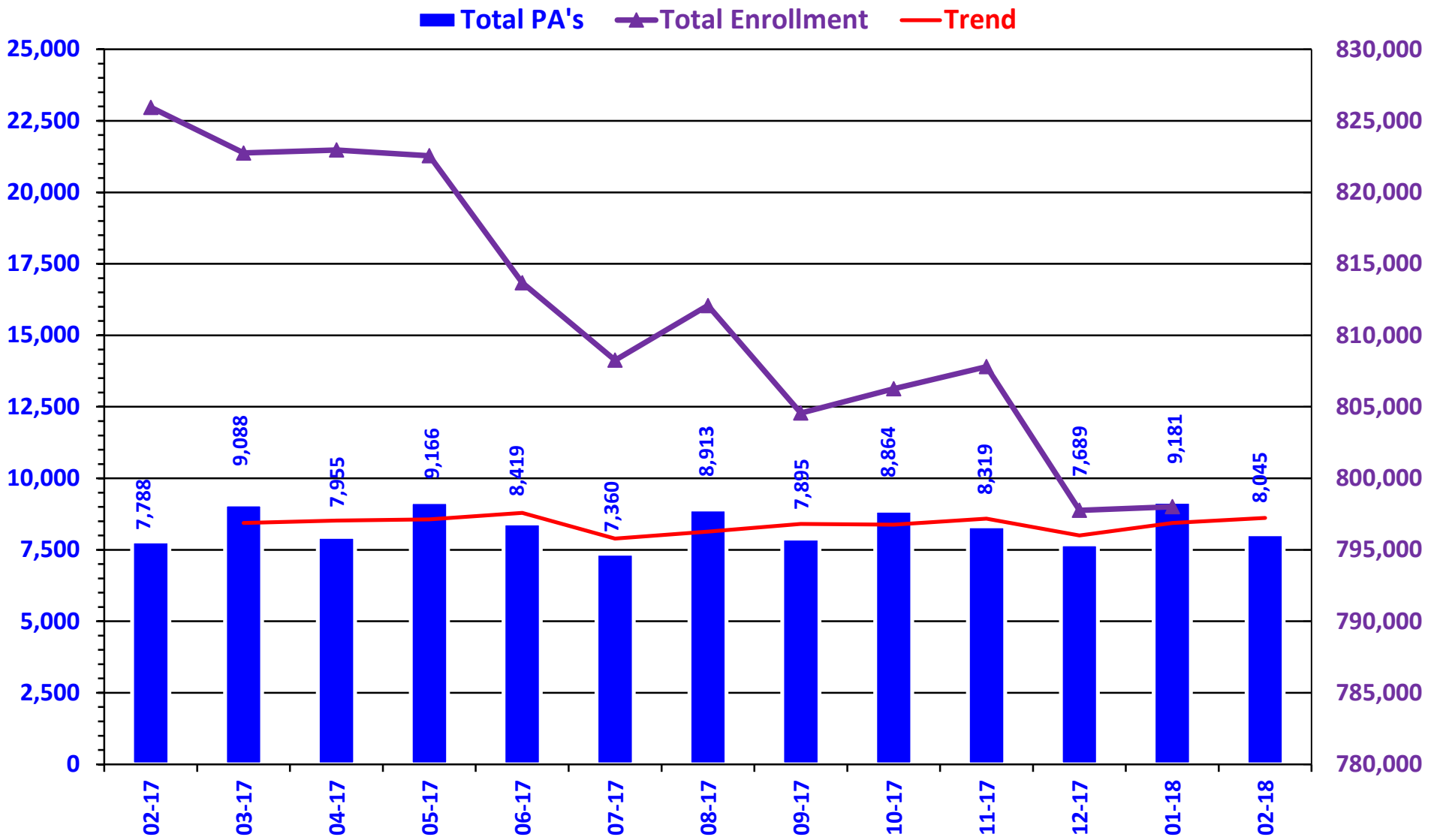
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: FEBRUARY 2018



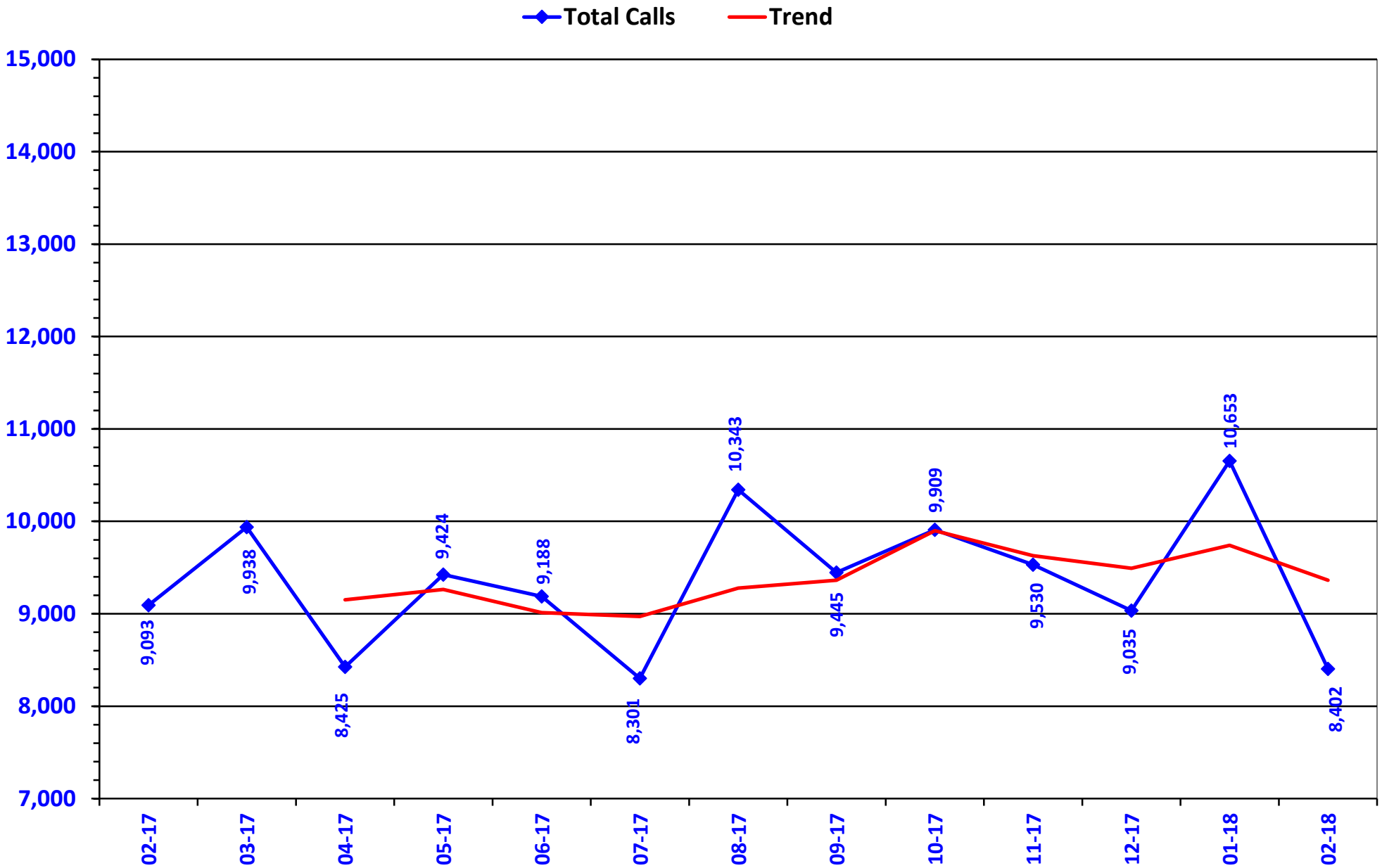
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: FEBRUARY 2017 – FEBRUARY 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
FEBRUARY 2017 – FEBRUARY 2018



Prior Authorization Activity

2/1/2018 Through 2/28/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	168	10	40	118	335
Analgesic - NonNarcotic	15	0	5	10	0
Analgesic, Narcotic	417	205	54	158	157
Angiotensin Receptor Antagonist	13	3	1	9	267
Anorectal	1	0	0	1	0
Antiasthma	54	18	9	27	326
Antibiotic	34	18	4	12	311
Anticonvulsant	115	51	14	50	335
Antidepressant	149	47	27	75	300
Antidiabetic	214	70	41	103	341
Antigout	13	9	1	3	271
Antihistamine	23	1	9	13	356
Antimigraine	41	6	13	22	301
Antineoplastic	60	36	4	20	168
Antiulcers	191	49	61	81	122
Anxiolytic	75	49	5	21	313
Atypical Antipsychotics	197	93	22	82	329
Biologics	98	54	18	26	305
Bladder Control	58	14	16	28	358
Blood Thinners	198	123	12	63	326
Botox	26	11	13	2	331
Buprenorphine Medications	321	224	17	80	75
Cardiovascular	112	56	16	40	302
Chronic Obstructive Pulmonary Disease	177	27	55	95	318
Constipation/Diarrhea Medications	162	41	49	72	283
Contraceptive	21	15	1	5	354
Dermatological	282	105	73	104	207
Diabetic Supplies	393	233	10	150	222
Endocrine & Metabolic Drugs	105	63	9	33	143
Erythropoietin Stimulating Agents	24	15	4	5	114
Fibromyalgia	212	40	97	75	331
Gastrointestinal Agents	88	24	23	41	159
Glaucoma	12	2	4	6	53
Growth Hormones	97	80	7	10	156
Hematopoietic Agents	31	17	2	12	159
Hepatitis C	211	141	24	46	9
HFA Rescue Inhalers	49	0	9	40	0
Insomnia	43	5	24	14	139
Insulin	127	35	26	66	339
Miscellaneous Antibiotics	20	4	2	14	8
Multiple Sclerosis	42	27	4	11	192
Muscle Relaxant	29	3	10	16	143
Nasal Allergy	59	8	20	31	186
Neurological Agents	98	17	42	39	219
NSAIDs	164	22	59	83	191
Ocular Allergy	38	4	12	22	83
Osteoporosis	3	1	1	1	358
Other*	332	65	93	174	232
Otic Antibiotic	20	3	6	11	8
Respiratory Agents	17	10	2	5	237

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Statins	24	4	8	12	358
Stimulant	840	385	81	374	336
Synagis	64	36	10	18	61
Testosterone	55	14	20	21	318
Topical Antifungal	29	3	8	18	17
Topical Corticosteroids	73	1	33	39	6
Vitamin	78	18	37	23	272
Pharmacotherapy	57	49	0	8	233
Emergency PAs	1	1	0	0	
Total	**6,670**	**2,665**	**1,267**	**2,738**	
Overrides					
Brand	41	21	4	16	308
Compound	12	10	0	2	20
Cumulative Early Refill	1	1	0	0	180
Diabetic Supplies	1	1	0	0	205
Dosage Change	326	299	6	21	10
High Dose	2	2	0	0	359
Ingredient Duplication	14	12	0	2	9
Lost/Broken Rx	73	69	0	4	9
NDC vs Age	247	173	14	60	247
Nursing Home Issue	30	29	1	0	15
Opioid Quantity	22	17	2	3	157
Other*	23	21	1	1	9
Prescriber Temp Unlock	1	0	0	1	0
Quantity vs. Days Supply	575	409	27	139	239
STBS/STBSM	23	15	3	5	96
Stolen	4	4	0	0	9
Temporary Unlock	3	3	0	0	12
Third Brand Request	14	9	1	4	17
Overrides Total	**1,375**	**1,066**	**57**	**252**	
Total Regular PAs + Overrides	**8,045**	**3,731**	**1,324**	**2,990**	

Denial Reasons	
Unable to verify required trials.	2,193
Does not meet established criteria.	1,356
Lack required information to process request.	751
Other PA Activity	
Duplicate Requests	578
Letters	9,975
No Process	8
Changes to existing PAs	698
Helpdesk Initiated Prior Authorizations	606
PAs Missing Information	22

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

U.S. Food and Drug Administration Safety Alerts

Oklahoma Health Care Authority
March 2018

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

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

Date	Drug	Issue
03/15/2017	**Eluxadoline (Viberzi®)**	**Risk of severe pancreatitis**
Issue Details: Patients with irritable bowel syndrome with diarrhea (IBS-D) who have had their gallbladder removed are at an increased risk of developing acute pancreatitis if taking eluxadoline. Hospitalization or death have been reported in 120 patients, 2 of whom died, since eluxadoline was introduced on the market in May 2015. The patients' gallbladder status was not reported in all cases, but among the patients who reported their gallbladder status, the majority of them, including the 2 deaths, did not have a gallbladder. **FDA Recommendation(s):** The prescribing information for eluxadoline was updated to include a *Contraindication* for patients who have had their gallbladder removed. **Pharmacy Claims Evaluation:** Since eluxadoline became available, 14 SoonerCare members have paid claims for the medication, none of whom had a diagnosis of pancreatitis in SoonerCare diagnosis claims history. **SoonerCare Action:** In November 2017, the prior authorization criteria for eluxadoline was voted to be updated by the DUR Board to include all contraindications for use, including use in those who have had their gallbladder removed.		

Date	Drug	Issue
04/20/2017	**Tramadol and Codeine**	**Increased risk of adverse effects for children and adolescents**
Issue Details: Medications containing tramadol or codeine increase the risk of slowed or difficulty breathing and death particularly in children younger than 12 years of age. The risk may also increase in children 17 years of age and younger when used for treating postoperative tonsillectomy/adenoidectomy pain. Breastfed infants are also at risk of increased sedation, respiratory issues, and death if their mothers breastfeed during treatment with tramadol or codeine. **FDA Recommendation(s):** The FDA is requiring that manufacturers of tramadol, tramadol-containing products, and single-ingredient codeine products add a *Contraindication* to drug labels for use in children younger than 12 years of age, and for children and adolescents younger than 18 years of age for the management of postoperative tonsillectomy and		

adenoidectomy pain. The FDA is also requiring that a *Warning* be added to the labels regarding use in adolescents between the ages of 12 and 18 years who are obese or who have sleep apnea or severe lung disease that might increase the risk of breathing problems. The *Warning* also applies to nursing mothers, because of the risk of serious adverse reactions in the infant. These include excessive sleepiness, difficulty breastfeeding, and serious breathing problems that could lead to death.

Pharmacy Claims Evaluation: A comparison of January 2017 to January 2018 revealed a 93% decrease in claims for tramadol- or codeine-containing products in members 12 years of age and younger.

SoonerCare Action: Based on the updated warnings from the FDA, an age restriction for all tramadol products was added in November 2017 for members younger than 12 years of age. If a member younger than 12 years of age requires tramadol or codeine products, a prior authorization request can be submitted for consideration to SoonerCare Pharmacy Services, including patient-specific, clinically significant information supporting the use of these products despite the medication being contraindicated for the member's age.

Date	Drug	Issue
05/16/2017	**Canagliflozin (Invokana®, Invokamet®)**	**Risk of leg and foot amputation**

Issue Details: Results of two large clinical trials, the CANVAS (Canagliflozin Cardiovascular Assessment Study) and CANVAS-R (A Study of the Effects of Canagliflozin on Renal Endpoints in Adult Participants with Type 2 Diabetes Mellitus), revealed that patients with type 2 diabetes who are treated with canagliflozin-containing drugs are at increased risk of leg and foot amputations. Study findings indicate that patients taking these medications had twice as many amputations as those taking placebo. The most common amputations were of toes and the middle of the foot, though leg amputations, below and above the knee, also occurred.

FDA Recommendation(s): Based on the conclusions of the two studies, a *Boxed Warning* will be added to the drug labels of canagliflozin-containing drugs. Patients taking these medications should be advised to contact their health care provider immediately if they develop pain, tenderness, sores, ulcers, or infections in their feet and/or legs. Prescribers should evaluate risk factors of patients before prescribing canagliflozin-containing drugs. Risk factors for foot amputation include neuropathy (loss of protective sensation), foot deformity, vascular disease, and history of previous foot ulceration. Other drugs in this class [sodium-glucose co-transporter 2 (SGLT2) inhibitors] have not been evaluated for this adverse effect, although the European Medicine Agency (EMA) has extended the warning to all drugs in the class.

Pharmacy Claims Evaluation: In calendar year 2017, 307 SoonerCare members had paid claims for canagliflozin-containing medications, 3 of whom had a lower limb amputation in their diagnosis claims history. Correlation to canagliflozin usage could not be determined.

SoonerCare Action: Since 2012, canagliflozin-containing drugs have required prior authorization by SoonerCare, moving between Tier-2 and Tier-3, based on rebate agreements. They are currently in Tier-3. The College of Pharmacy will monitor claims and diagnosis codes

and present data to the DUR Board where appropriate. If further information regarding a class effect is found, these details will also be presented to the DUR Board.

Date	Drug	Issue
09/06/2017	**Sodium Polystyrene Sulfonate (Kayexalate®)**	**Decreased absorption of other oral medications**

Issue Details: The FDA issued a Safety Communication regarding the co-administration of sodium polystyrene sulfonate (SPS) and other oral medications, both over-the-counter (OTC) and prescription strength. SPS is given to treat hyperkalemia and works by binding to potassium in the intestines and eliminating it from the body. A study revealed that other oral medications, when taken with oral SPS, bind to SPS, resulting in decreased absorption and reduced efficacy of the other oral medication.
FDA Recommendation(s): The FDA recommends that oral SPS and other oral medications be separated by at least 3 hours to reduce the risk of decreased efficacy of the other medications. The time should be increased to 6 hours if the patient has gastroparesis. The product label will be updated to include this recommendation. It is recommended that prescribers and pharmacists advise patients to make this change in their dosing schedules.
Pharmacy Claims Evaluation: During calendar year 2017, a total of 65 members accounted for 105 paid claims for SPS.

Date	Drug	Issue
09/21/2017	**Obeticholic Acid (Ocaliva®)**	**Risk of liver injury**

Issue Details: The FDA issued a warning regarding the incorrect dosing of obeticholic acid in some patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh class B or C hepatic impairment. The label indicates that patients with Child-Pugh class B or C hepatic impairment or patients with a prior decompensation event should be initiated at a dose of 5mg weekly rather than daily, with increases to no more than 10mg twice weekly. Excessive dosing can lead to an increased risk of serious liver injury and death. Obeticholic acid is FDA approved for PBC, and is taken with ursodeoxycholic acid (UDCA) unless UDCA is not tolerated. Since FDA approval in May 2016, 19 deaths and 11 cases of serious liver injury have been reported, most of which occurred during obeticholic acid use.
FDA Recommendation(s): The FDA required the addition of a *Boxed Warning* and clarification in the label regarding dosing. Prescribers should evaluate baseline liver function before initiating obeticholic acid. Patients should be advised to report new or worsening severe skin itching, in addition to worsening gastrointestinal (GI) complaints, fatigue, and vague behavior changes. Prescribers are encouraged to report side effects to the MedWatch program.
Pharmacy Claims Evaluation: Since obeticholic acid was approved in May 2016, only one SoonerCare member has had paid claims for this medication. The College of Pharmacy did confirm with the prescriber that this member was receiving appropriate dosing based on the member's liver status.

SoonerCare Action: All prior authorization requests will be reviewed under the clarified dosing recommendations. Requests not specifying patients' liver status will not be approved without further information.

Date	Drug	Issue
11/15/2017	**Febuxostat (Uloric®)**	**Risk of heart-related death and death from all causes**

Issue Details: Preliminary results from a clinical trial indicated a higher risk of heart-related death and death from all causes in patients treated for gout with febuxostat when compared to allopurinol. The trial, required by the FDA, studied the combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring urgent surgery. The risk for these combined events was not increased, but taken individually, the risk of heart-related death and death from all causes was increased with febuxostat.
FDA Recommendation(s): The manufacturer will continue to evaluate the study. Once the final results are reported to the FDA, a course of action will be determined. Prescribers and patients are requested to report any side effects using the MedWatch program.
Pharmacy Claims Evaluation: Febuxostat requires prior authorization for reimbursement through SoonerCare. During calendar year 2017, 29 SoonerCare members had paid claims for febuxostat. The largest number of them (12) were males from age 50 to 64.
SoonerCare Action: The College of Pharmacy will await final study results and make recommendations to the DUR Board as appropriate.

Date	Drug	Issue
12/20/2017	**LABA/ICS Combinations**	**Asthma-related side effects (follow-up)**

Issue Details: In 2011, the FDA required manufacturers to perform clinical trials to evaluate possible asthma-related side effects from the combination of long-acting beta agonists (LABAs) and inhaled corticosteroids (ICS) versus ICS alone for the treatment of asthma. Use of LABAs alone is associated with an increased risk of asthma-related death.
FDA Recommendation(s): As a result of four large clinical safety trials that showed no increase in asthma-related effects from the combination of LABA and ICS, the *Boxed Warning* on the labels of these combination medications regarding asthma-related deaths has been removed. The results of the studies are being added to the *Warnings and Precautions* section of the medication labels. The *Boxed Warning* regarding asthma-related death on the labels of LABA-only medications will remain.
Pharmacy Claims Evaluation: During state fiscal year 2017, a total of 6,635 SoonerCare members had paid claims for combination LABA/ICS products, 299 members for LABA only products, and 27,988 members for ICS only products.

Date	Drug	Issue
01/11/2018	**Opioid Cough and Cold Medicines**	**Risk of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing**

Issue Details: The risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death associated with cough and cold medicines containing hydrocodone or codeine outweigh the benefits in children younger than 18 years of age.
FDA Recommendation(s): A *Boxed Warning* will be added to the labels of all cough and cold medicines containing codeine or hydrocodone. The products will no longer be indicated for children; alternative medications such as dextromethorphan or benzonatate products are suggested for cough in the pediatric population.
Pharmacy Claims Evaluation: SoonerCare does not cover cough and cold medications.
SoonerCare Action: Details regarding this warning will be included in the provider newsletter.

Date	Drug	Issue
01/30/2018	**Loperamide (Imodium®)**	**Risk of cardiac issues and death**

Issue Details: The FDA has received reports of serious heart problems and death in patients who used higher than recommended doses of loperamide. Increasing abuse and intentional misuse of loperamide, which acts on opioid receptors to slow the movement of the intestines, has triggered health concerns. The drug is considered safe when used at appropriate doses for diarrhea, including travelers' diarrhea.
FDA Recommendation(s): Manufacturers of OTC loperamide are encouraged to change packages to blister packs or other single-use packaging, or to limit the number of doses per package. *Warnings* were added to the package labels in 2016; however, additional action is warranted because of continued abuse.
Pharmacy Claims Evaluation: SoonerCare does not cover OTC loperamide. During calendar year 2017, a total of 644 members accounted for 1,155 paid claims for prescription loperamide 2mg.
SoonerCare Action: Details regarding this warning will be included in the provider newsletter.

[1] U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: Increased Risk of Serious Pancreatitis In Patients Without A Gallbladder. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm546771.htm. Last revised 01/05/2018. Last accessed 02/12/2018.

[2] FDA. 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. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. Last revised 01/11/2018. Last accessed 02/12/2018.

[3] FDA. Canagliflozin (Invokana, Invokamet): FDA Drug Safety Communication - Increased Risk of Leg and Foot Amputations. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm558605.htm. Last revised 01/05/2018. Last accessed 02/12/2018.

[4] DeSantis A. Sodium-glucose co-transporter 2 inhibitors for the treatment of type 2 diabetes mellitus. *Up-to-Date®*. Available online at: https://www.uptodate.com/contents/sodium-glucose-co-transporter-2-inhibitors-for-the-treatment-of-type-2-diabetes-mellitus. Last revised 01/16/2018. Last accessed 02/12/2018.

[5] FDA. FDA Drug Safety Communication: FDA recommends separating dosing of potassium-lowering drug sodium polystyrene sulfonate (Kayexalate) from all other oral drugs. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm572484.htm. Last revised 09/11/2017. Last accessed 02/12/2018.

[6] FDA. FDA Drug Safety Communication: FDA warns about serious liver injury with Ocaliva (obeticholic acid) for rare chronic liver disease. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm576656.htm. Last revised 02/05/2018. Last accessed 02/12/2018.

[7] FDA. FDA Drug Safety Communication: FDA to evaluate increased risk of heart-related death and death from all causes with the gout medicine febuxostat (Uloric). Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm584702.htm. Last revised 01/22/2018. Last accessed 02/12/2018.

[8] FDA. FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS). Available online at: https://www.fda.gov/downloads/drugs/drugsafety/ucm589997.pdf. Last revised 01/22/2018. Last accessed 02/12/2018.

[9] FDA. FDA Drug Safety Communication: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older. Available online at: https://www.fda.gov/Drugs/DrugSafety/ucm590435.htm. Last revised 01/22/2018. Last accessed 02/12/2018.

[10] FDA. Imodium (loperamide) for Over-the-Counter Use: Drug Safety Communication - FDA Limits Packaging To Encourage Safe Use. Available online at: https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm594403.htm. Last revised 02/06/2018. Last accessed 02/12/2018.

Appendix C

Vote to Prior Authorize Tymlos™ (Abaloparatide)

Oklahoma Health Care Authority
March 2018

Introduction[1]

Tymlos™ (abaloparatide) is a PTHrP (1-34) analog which acts as an agonist at the PTH1 receptor (PTH1R). This results in activation of the cAMP signaling pathway in target cells. It is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy. Abaloparatide has a *Boxed Warning* for increased risk of osteosarcoma. It caused a dose-dependent increase in the incidence of osteosarcoma, a malignant bone tumor, in male and female rats. Therefore, it is not recommended in patients at increased risk for osteosarcoma. Additionally, cumulative use of abaloparatide and other parathyroid hormone analogs (e.g., teriparatide) for more than 2 years during a patient's lifetime is not recommended. Abaloparatide is supplied as a pre-assembled, single-patient-use, disposable pen containing 3,120mcg of abaloparatide in 1.56mL (2,000mcg/mL) of sterilized, clear, colorless fluid. The recommended dosage of abaloparatide is 80mcg subcutaneously (SQ) once daily. Each pen provides a 30-day supply of once daily injections.

Cost Comparison:

Medication	Cost Per Month	Cost Per Year
Tymlos™ (abaloparatide) injection	**$1,625.01**	**$19,500.12**
Forteo® (teriparatide) injection	$2,891.74	$34,700.88
Prolia® (denosumab) injection	$181.60*	$2,179.24
zoledronic acid intravenous solution	$25.00[+]	$300.00

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.
*Prolia® (denosumab) is dosed every six months; therefore, cost per month based on cost per year.
[+]Zoledronic acid is dosed yearly; therefore, cost per month based on cost per year.

Recommendations

The College of Pharmacy recommends the placement of Tymlos™ (abaloparatide) into the Special Prior Authorization (PA) Tier of the Osteoporosis Product Based Prior Authorization (PBPA) category with the following criteria:

Tymlos™ (Abaloparatide) Approval Criteria:

1. A diagnosis of postmenopausal osteoporosis confirmed by the following:
    a. History of vertebral fracture(s) or low trauma or fragility fracture(s) [e.g., prior fracture from minor trauma such as falling from standing height or less] within the past 5 years; or

   b. A Bone Mineral Density test (T-score at or below -2.5) within the last month in the spine, femoral neck, total hip, or 33% radius; or
   c. Those with a T-score between -1.0 and -2.5 in the spine, femoral neck, total hip, or 33% radius, if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3%; and
2. One of the following [if a 12-month bisphosphonate trial is inappropriate for the member, the member must have a trial of Prolia® or a selective estrogen receptor modulator (SERM) or a patient-specific, clinically significant reason why Prolia® or a SERM is not appropriate]:
   a. A minimum 12-month trial with a bisphosphonate plus adequate calcium and vitamin D; or
   b. A 12-month trial of Prolia® (denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results; or
   c. A 12-month trial of a SERM, unless contraindicated, intolerant, or allergic, that did not yield adequate results; and
3. A patient-specific, clinically significant reason why the member cannot use Forteo® (teriparatide) must be provided; and
4. Treatment duration including other parathyroid hormone analogs has not exceeded a total of 24 months during the patient's lifetime; and
5. Approval will be for a maximum of 2 years of parathyroid hormone analog therapy; and
6. A quantity limit of one pen per 30 days will apply.

The College of Pharmacy also recommends the following criteria updates noted in red based on the new U.S. Food and Drug Administration (FDA) approved indication for Xgeva® (denosumab) and net cost after rebates for Forteo® (teriparatide):

Xgeva® (Denosumab) Approval Criteria:

1. An FDA approved indication of one of the following:
   a. Prevention of skeletal-related events in patients with multiple myeloma and in patients with bone metastases from solid tumors; or
   b. Treatment of adults and skeletally mature adolescents with giant cell tumor of the bone (GCTB) that is unresectable or where surgical resection is likely to result in severe morbidity; and
      i. Prescriber must document that tumor is unresectable or that surgical resection is likely to result in severe morbidity; or
   c. Treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy; and
      ii. Member must have albumin-corrected calcium of greater than 12.5mg/dL (3.1mmol/L) despite treatment with intravenous bisphosphonate therapy in the last 30 days prior to initiation of Xgeva® therapy.

Forteo® (Teriparatide) Approval Criteria:

1. ~~A Bone Mineral Density test (T-score at or below -2.5) within the last month; and~~
2. A diagnosis of one of the following:

a. Treatment of postmenopausal women with osteoporosis at high risk for fracture; or
b. To increase bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture; or
c. Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture; or
d. Treatment of non-healing fracture; and

3. ~~One of the following (if a 12-month bisphosphonate trial is inappropriate for the member, the member must have trial of Prolia® or a patient-specific, clinically significant reason why Prolia® is not appropriate):~~
4. A minimum 12-month trial with a bisphosphonate plus adequate calcium and vitamin D or a patient-specific, clinically significant reason the member cannot use a bisphosphonate; and
   ~~a. A 12-month trial of Prolia® (denosumab), unless contraindicated, intolerant, or allergic, that did not yield adequate results; or~~
5. The diagnosis of non-healing fracture may be approved for 6 months; and
6. Treatment duration including other parathyroid hormone analogs has not exceeded a total of 24 months during the patient's lifetime; and
7. Approval will be for a maximum of 2 years of parathyroid hormone analog therapy.

Finally, the College of Pharmacy recommends moving ibandronate tablets (Boniva®) from Tier-2 to Tier-1 based on national average drug acquisition cost (NADAC).

Osteoporosis Medications		
Tier-1	**Tier-2**	**Special PA**
alendronate tabs (Fosamax®)	alendronate + vitamin D tabs (Fosamax® + D)	**abaloparatide inj (Tymlos™)**
calcium + vitamin D*	risedronate tabs (Actonel®)	alendronate effervescent tabs (Binosto®)
ibandronate tabs (Boniva®)		alendronate soln (Fosamax®)
zoledronic acid inj (Reclast®)		alendronate 40mg tabs (Fosamax®)
		denosumab inj (Prolia®)
		ibandronate inj (Boniva® IV)
		risedronate 30mg tabs (Actonel®)
		risedronate DR tabs (Atelvia®)
		teriparatide inj (Forteo®)

*Must be used in combination with a bisphosphonate to count as a Tier-1 trial.
tabs = tablets; inj = injection; soln = solution; DR = delayed-release
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

[1] Tymlos™ Prescribing Information. Radius Health, Inc. Available online at: http://radiuspharm.com/wp-content/uploads/tymlos/tymlos-prescribing-information.pdf. Last revised 04/2017. Last accessed 02/15/2018.

Appendix D

Vote to Prior Authorize Prevymis™ (Letermovir Tablets and Injection)

Oklahoma Health Care Authority
March 2018

Introduction[1]

Prevymis™ (letermovir) is a cytomegalovirus (CMV) DNA terminase complex inhibitor indicated for prophylaxis of CMV infection and disease in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). Prevymis™ is supplied as 240mg and 480mg oral tablets or 240mg/12mL and 480mg/24mL single-dose vials for intravenous (IV) injection. The recommended dosage of letermovir is 480mg administered orally or IV once daily. Letermovir should be initiated between day 0 and day 28 post-transplantation and continued through day 100 post-transplantation. If letermovir is co-administered with cyclosporine, the dosage of letermovir should be decreased to 240mg once daily. Letermovir tablet and injection formulations may be used interchangeably; no dosage adjustment is needed when switching formulations. Letermovir injection should be used only in patients unable to take oral therapy. Patients should switch to oral letermovir as soon as they are able to take oral medications.

Cost:

Medication	Cost Per Dose	Cost Per 28 Days of Therapy	Cost Per 100 Days of Therapy
Prevymis™ (letermovir tablets)	**$195.00**	**$5,460.00**	**$19,500.00**
Prevymis™ (letermovir injection)	**$270.00**	**$7,560.00**	**$27,000.00**

Costs do not reflect rebated prices or net costs. Costs based on Wholesale Acquisition Costs (WAC).

Recommendations

The College of Pharmacy recommends the prior authorization of Prevymis™ (letermovir tablets and injection) with the following criteria:

Prevymis™ (Letermovir Tablets and Injection) Approval Criteria:

1. An FDA approved indication of prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients [R+] of an allogenic hematopoietic stem cell transplant (HSCT); and
2. Member must be CMV R+; and
3. Member must have received a HSCT within the last 28 days; and
4. Members taking concomitant cyclosporine will only be approved for the 240mg dose; and
5. Members must not be taking the following medications:
    a. Pimozide; or
    b. Ergot alkaloids (e.g., ergotamine, dihydroergotamine); or

    c. Rifampin; or
    d. Atorvastatin, lovastatin, pitavastatin, simvastatin, or repaglinide when co-administered with cyclosporine; and
6. Prevymis™ must be prescribed by an oncology, hematology, infectious disease, or transplant specialist or advanced care practitioner with a supervising physician who is an oncology, hematology, infectious disease, or transplant specialist; and
7. Prescriber must verify the member will be monitored for CMV reactivation while on therapy; and
8. Approvals will be for the duration of 100 days post-transplant.
    a. For Prevymis™ vials, authorization will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation; and
    b. Approval length for vial formulation will be based on duration of need.
9. A quantity limit of one tablet or vial per day will apply.

The College of Pharmacy also recommends the following changes to current antiviral product prior authorization criteria based on low net cost of acyclovir cream.

Sitavig® (Acyclovir Buccal Tablets), Xerese® (Acyclovir/Hydrocortisone Cream), and Denavir® (Penciclovir Cream) Approval Criteria:

1. An FDA approved diagnosis of recurrent herpes labialis (cold sores); and
2. A patient-specific, clinically significant reason why the member cannot use oral acyclovir, famciclovir, or valacyclovir tablets; and
3. A patient-specific, clinically significant reason why the member cannot use acyclovir cream.

[1] Prevymis™ Prescribing Information. Merck & Co., Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939Orig1s000,209940Orig1s000lbl.pdf. Last revised 11/2017. Last accessed 02/15/2018.

Appendix E

Vote to Prior Authorize Rhopressa® (Netarsudil Ophthalmic Solution) and Vyzulta™ (Latanoprostene Bunod Ophthalmic Solution)

Oklahoma Health Care Authority
March 2018

Introduction[1,2]

- **Rhopressa® (netarsudil ophthalmic solution)** is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension (HTN). The recommended dosage is one drop in the affected eye(s) once daily in the evening. Rhopressa® cost and launch information are not available at this time.
- **Vyzulta™ (latanoprostene bunod ophthalmic solution)** is a prostaglandin analog ophthalmic solution indicated for the reduction of IOP in patients with open-angle glaucoma or ocular HTN. The recommended dosage is one drop of 0.024% solution in the conjunctival sac of the affected eye(s) once daily in the evening. The wholesale acquisition cost (WAC) of Vyzulta™ is $360.00 for a 30-day supply compared to the national average drug acquisition cost (NADAC) for a 30-day supply of latanoprost 0.005% at $4.98.

Recommendations

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

1. The creation of a Special Prior Authorization (PA) category to account for very high net cost products.
    a. Placement of brimonidine (Alphagan-P® 0.15%), dorzolamide/timolol (Cosopt® PF), timolol maleate (Timoptic Ocudose®, Timoptic-XE®), netarsudil ophthalmic solution (Rhopressa®), and latanoprostene bunod ophthalmic solution (Vyzulta™) into the Special PA category of the Glaucoma PBPA category based on net cost.
2. Move echothiophate iodide (Phospholine Iodide®) from Tier-2 to Tier-1 based on low net cost.
3. Move pilocarpine (Isopto® Carpine®, Pilopine HS®) from Tier-1 to Tier-2 based on net cost. Current Tier-2 criteria will apply.

Tier-1 products are covered with no prior authorization necessary.

Glaucoma Medications Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and

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

Glaucoma Special Prior Authorization (PA) Approval Criteria:

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

Proposed changes can be seen in red in the following Tier chart:

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
Alpha-2 Adrenergic Agonists		
brimonidine (Alphagan® 0.2%)	apraclonidine (Iopidine®)	**brimonidine (Alphagan-P® 0.15%)**
brinzolamide/brimonidine (Simbrinza®)	brimonidine (Alphagan-P® 0.1%)	
	brimonidine/timolol (Combigan®)	
Beta-Blockers		
carteolol (Ocupress® 1%)	betaxolol (Betoptic® 0.5%, Betoptic-S®)	**dorzolamide/timolol (Cosopt® PF)**
dorzolamide/timolol (Cosopt®)	brimonidine/timolol (Combigan®)	**timolol maleate (Timoptic Ocudose®, Timoptic-XE®)**
levobunolol (Betagan®)	timolol (Betimol®)	
metipranolol (OptiPranolol®)		
timolol maleate (Istalol®, Timoptic®)		
Carbonic Anhydrase Inhibitors		
acetazolamide (Diamox®)+		**dorzolamide/timolol (Cosopt® PF)**

Glaucoma Medications*		
Tier-1	**Tier-2**	**Special PA**
brinzolamide (Azopt®)		
brinzolamide/brimonidine (Simbrinza®)		
dorzolamide (Trusopt®)		
dorzolamide/timolol (Cosopt®)		
methazolamide (Neptazane®)+		
Cholinergic Agonists/Cholinesterase Inhibitors		
echothiophate iodide (Phospholine Iodide®)	carbachol (Miostat®)	
	pilocarpine (Isopto® Carpine®, Pilopine HS®)	
Prostaglandin Analogs		
latanoprost (Xalatan®)	bimatoprost (Lumigan®)	**latanoprostene bunod (Vyzulta™)**
travoprost (Travatan-Z® 0.004%)	tafluprost (Zioptan™)	
	travoprost (Travatan® 0.004%)	
Rho Kinase Inhibitors		
		netarsudil (Rhopressa®)

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

+Indicates available oral medications.

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

[1] Rhopressa® Prescribing Information. Aerie Pharmaceuticals, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208254lbl.pdf. Last revised 12/2017. Last accessed 02/05/2018.

[2] Vyzulta™ Prescribing Information. Bausch + Lomb Inc. Available online at: http://www.bausch.com/Portals/69/-/m/BL/United%20States/USFiles/Package%20Inserts/Pharma/vyzulta-prescribing-information.pdf. Last revised 11/2017. Last accessed 02/05/2018.

Appendix F

Vote to Prior Authorize Mepsevii™ (Vestronidase Alfa-vjbk)

Oklahoma Health Care Authority
March 2018

Introduction[1,2,3,4]

Mepsevii™ (vestronidase alfa-vjbk) was approved by the U.S. Food and Drug Administration (FDA) in November 2017 as an enzyme replacement therapy (ERT) for patients with Sly syndrome, also known as mucopolysaccharidosis VII or MPS VII. Sly syndrome is a rare disorder caused by mutations in the gene encoding beta-glucuronidase (GUS). The enzyme deficiency causes accumulation of heparan sulfate, dermatan sulfate, chondroitin-4-sulfate, and chondroitin-6-sulfate. Sly syndrome is inherited in an autosomal recessive pattern. The exact incidence of Sly syndrome is unknown; however, it is estimated to occur in 1 in 250,000 newborns. Sly syndrome is one of the rarest forms of MPS. Clinical presentation of Sly syndrome is variable. The most severe cases are characterized by hydrops fetalis and may account for a large proportion of patients that are unrecognized because they do not survive to be diagnosed. Other individuals with MPS VII may begin to show symptoms in early childhood. The features of MPS VII include macrocephaly, hydrocephalus, macroglossia, and distinctive-looking facial features that are described as "coarse". Individuals affected with MPS VII frequently develop hepatosplenomegaly, heart valve abnormalities, and umbilical or inguinal hernias. Patients may have developmental delay, but in some people with this condition, intelligence is unaffected. The life expectancy of MPS VII depends on the severity of symptoms. Some affected individuals do not survive infancy while others may live into adolescence or adulthood. Vestronidase alfa-vjbk is a recombinant form of human GUS and is intended to provide exogenous GUS enzyme for uptake into cellular lysosomes. Vestronidase alfa-vjbk has a *Boxed Warning* for the risk of anaphylaxis. The recommended dosage is 4mg/kg administered every two weeks as an intravenous (IV) infusion.

Cost: The wholesale acquisition cost (WAC) of Mepsevii™ is $2,115.00 per 10mg/5mL single-use vial for IV infusion.

Recommendations

The College of Pharmacy recommends the prior authorization of Mepsevii™ (vestronidase alfa-vjbk) with the following criteria:

Mepsevii™ (Vestronidase Alfa-vjbk) Approval Criteria:

1. An FDA approved diagnosis of Sly syndrome (mucopolysaccharidosis type VII; MPS VII) confirmed by:
    a. Enzyme assay demonstrating a deficiency of beta-glucuronidase (GUS) activity; or
    b. Genetic testing to confirm diagnosis of MPS VII; and

2. Mepsevii™ must be administered by a healthcare professional prepared to manage anaphylaxis; and
3. Initial approvals will be for the duration of twelve months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.
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.

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[1] Jones S, Wynn R. Mucopolysaccharidoses: Clinical features and diagnosis. *UpToDate®*. Available online at: http://www.uptodate.com/contents/mucopolysaccharidoses-clinical-features-and-diagnosis?search=sly+syndrome&sectionRank=1&anchor=H12&source=machineLearning&selectedTitle=1%7E8#H12. Last revised 09/12/2017. Last accessed 02/20/2018.

[2] National Institute of Health (NIH). U.S. National Library of Medicine. Mucopolysaccharidosis Type VII. Genetics Home Reference. Available online at: https://ghr.nlm.nih.gov/condition/mucopolysaccharidosis-type-vii. Published 02/13/2018. Last accessed 02/20/2018.

[3] Mucopolysaccharidosis Type VII. *National Organization of Rare Disorders*. Available online at: https://rarediseases.org/rare-diseases/sly-syndrome/. Last accessed 02/20/2018.

[4] Mepsevii™ Prescribing Information. Ultragenyx Pharmaceutical Inc. Available online at: http://www.ultragenyx.com/file.cfm/28/docs/FINAL%20Mepsevii%20(vestronidase%20alfa-vjbk)%20USPI.pdf. Last revised 11/2017. Last accessed 02/20/2018.

Appendix G

Vote to Prior Authorize Ergomar® (Ergotamine Sublingual Tablets)

Oklahoma Health Care Authority
March 2018

Introduction[1]

Ergomar® (ergotamine sublingual tablets) is an alpha-adrenergic blocking agent indicated as therapy to abort or prevent vascular headache (e.g., migraine, migraine variants, so-called "histaminic cephalalgia"). Ergomar® is available as sublingual tablets containing 2mg of ergotamine tartrate. They are supplied in unit-dose cartons of 20 tablets. The recommended dosage is to place one 2mg tablet under the tongue at the first sign of an attack or to relieve symptoms after onset of an attack. It is recommended that dosage start at the first sign of an attack as early administration gives maximum effectiveness. Another tablet should be taken at half hour intervals thereafter, if necessary, but dosage must not exceed three tablets in any 24-hour period. The total weekly dosage should not exceed five tablets (10mg) in any one week. Ergomar® should not be used for chronic daily administration. The wholesale acquisition cost (WAC) of Ergomar® is $56.35 per tablet.

Recommendations

The College of Pharmacy recommends the following:

1. Moving Zomig® (zolmitriptan nasal spray) from Tier-3 to Tier-2 of the Anti-Migraine Medication Product Based Prior Authorization (PBPA) category based on net cost. Current Tier-2 criteria would apply.
2. Brand name Relpax® (eletriptan) will be preferred over the generic formulation based on net cost. Approval of generic eletriptan would require a patient-specific, clinically significant reason why the member cannot use the brand formulation.
3. The placement of Ergomar® (ergotamine sublingual tablets) into the Special Prior Authorization (PA) Tier of the Anti-Migraine Medication PBPA category with the following criteria:
    a. **Ergomar® (Ergotamine Sublingual Tablets) Approval Criteria:**
        i. Use of Ergomar® (ergotamine sublingual tablets) will require a patient-specific, clinically significant reason why the member cannot use lower-tiered triptan medications; and
        ii. Member must not have any of the contraindications for use of Ergomar® (e.g., coadministration with a potent CYP 3A4 inhibitor, women who are or may become pregnant, peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, hypersensitivity to any of the components); and
        iii. A quantity limit of 20 tablets per 28 days will apply.

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

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

Anti-Migraine Medications Tier-2 Approval Criteria:

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

Anti-Migraine Medications Tier-3 Approval Criteria:

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

Anti-Migraine Medications Special Prior Authorization Approval Criteria:

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

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

[1] Ergomar® Prescribing Information. TerSera Therapeutics. Available online at: http://documents.tersera.com/ergomar/ErgomarPrescribingInformation.pdf. Last revised 11/2016. Last accessed 02/14/2018.

Appendix H

Vote to Prior Authorize Xadago® (Safinamide) and Gocovri™ (Amantadine Extended-Release)

Oklahoma Health Care Authority
March 2018

Introduction[1,2,3,4]

- **Xadago® (safinamide tablets)** is a monoamine oxidase type B (MAO-B) inhibitor indicated as adjunctive treatment for patients with Parkinson's disease (PD) who are currently taking levodopa/carbidopa and experiencing "off" episodes. An "off" episode is a time when a patient's medications are not working well, causing an increase in Parkinson's symptoms, such as tremor and difficulty walking. Safinamide has not been shown to be effective as monotherapy for the treatment of PD. Xadago® is available as 50mg and 100mg oral tablets, and the recommended dose is 50mg to 100mg once daily based on need and tolerability. The wholesale acquisition cost (WAC) per tablet of Xadago® is $24.34, resulting in a cost per month of $730.20.
- **Gocovri™ [amantadine extended-release (ER) capsules]** is indicated for the treatment of dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications. Gocovri™ is available as 68.5mg and 137mg ER oral capsules. The recommended starting dose of amantadine ER is 137mg by mouth once daily at bedtime. After one week, the dosage should be increased to 274mg (two 137mg capsules) once daily at bedtime. The dose should be reduced to a maximum of 137mg in patients with moderate renal impairment and 68.5mg in severe renal impairment. Amantadine ER is not recommended in patients with end-stage renal disease (ESRD). The WAC per capsule of Gocovri™ is $39.58, resulting in a monthly cost of $2,374.80.

Recommendations

The College of Pharmacy recommends the prior authorization of Xadago® (safinamide) and Gocovri™ (amantadine ER) with the following criteria:

Xadago® (Safinamide) Approval Criteria:

1. An FDA approved diagnosis of adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease (PD) experiencing "off" episodes; and
2. Member must be taking levodopa/carbidopa in combination with safinamide. Safinamide has not been shown to be effective as monotherapy for the treatment of PD; and
3. A patient-specific, clinically significant reason why the member cannot use rasagiline or other lower cost monoamine oxidase type B (MAO-B) inhibitors must be provided; and
4. Member must not have severe hepatic impairment; and
5. Member must not be taking any of the following medications concomitantly with safinamide:

a. Monoamine oxidase inhibitors (MAOIs); or
b. Linezolid; or
c. Opioid analgesics (including tramadol); or
d. Selective norepinephrine reuptake inhibitors (SNRIs); or
e. Tri- or tetra-cyclic or triazolopyridine antidepressants; or
f. St. John's wort; or
g. Cyclobenzaprine; or
h. Methylphenidate and its derivatives; or
i. Amphetamine and its derivatives; or
j. Dextromethorphan; and

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

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

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

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[1] U.S. Food and Drug Administration (FDA). FDA approves drug to treat Parkinson's disease. Available online at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm547852.htm. Issued 03/21/2017. Last accessed 02/26/2018.

[2] Adamas Pharmaceuticals, Inc. Adamas Announces FDA Approval of Gocovri™ as First and Only Medication for the Treatment of Dyskinesia in Parkinson's Disease Patients. *Globe Newswire*. Available online at: http://ir.adamaspharma.com/releasedetail.cfm?releaseid=1038209. Issued 08/24/2017. Last accessed 02/26/2018.

[3] Xadago® Prescribing Information. US WorldMeds. Available online at: http://www.xadago.com/XADAGO_FullPI.pdf. Last revised 05/2017. Last accessed 02/26/2018.

[4] Gocovri® Prescribing Information. Adamas Pharmaceuticals, Inc. Available online at: https://www.gocovrihcp.com/pdf/Gocovri_Prescribing_Information.pdf. Last revised 08/2017. Last accessed 02/26/2018.

Appendix I

Calendar Year 2017 Annual Review of Chronic Lymphocytic Leukemia (CLL) Medications and 30-Day Notice to Prior Authorize Arzerra® (Ofatumumab), Gazyva® (Obinutuzumab), Imbruvica® (Ibrutinib), Venclexta™ (Venetoclax), and Zydelig® (Idelalisib)

Oklahoma Health Care Authority
March 2018

Introduction[1,2,3,4]

Leukemia is an abnormal and autonomous proliferation of one or more blood-forming elements with infiltrations of the bone marrow and other organs. Leukemia is a heterogeneous group of neoplasms arising from the malignant transformation of hematopoietic cells that eventually replaces the normal marrow, leading to the signs and symptoms of leukemia. Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) is an indolent disease, patients may survive many years without therapy. The major difference between CLL and SLL is that in CLL, a significant number of abnormal lymphocytes are found in the blood in addition to bone marrow and lymphoid tissue versus SLL where there are few circulating abnormal lymphocytes and disease is mostly found in the lymph nodes, bone marrow, and other lymphoid tissues. CLL/SLL is primarily a disease of the elderly; the median age at diagnosis is 72 years. CLL/SLL is the most prevalent adult leukemia in Western countries. In 2017, there were 20,110 diagnoses and 4,660 deaths due to CLL/SLL. Treatment has evolved significantly over the past several decades. Immunotherapy and small molecule inhibitors targeting critical signaling pathways [e.g., Bruton's tyrosine kinase (BTK), phosphatidylinositol 3-kinase (PI3K)] have improved efficacy in the therapy for CLL/SLL.

Utilization of CLL Medications: Calendar Year 2017

CLL Medications Calendar Year Comparison: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	6	29	$357,664.75	$12,333.27	$411.11	3,030	870
2017	7	38	$453,509.97	$11,934.47	$397.82	3,690	1,140
% Change	**16.70%**	**31.00%**	**26.80%**	**-3.20%**	**-3.20%**	**21.80%**	**31.00%**
Change	**1**	**9**	**$95,845.22**	**-$398.80**	**-$13.29**	**660**	**270**

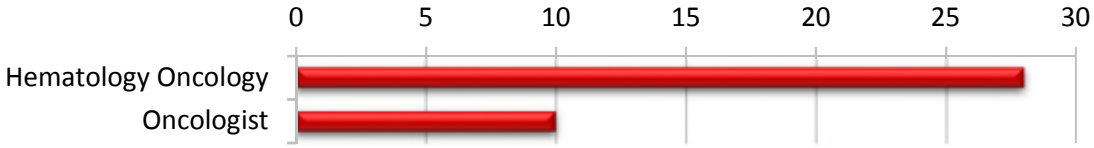
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- There were no paid medical claims for CLL medications during calendar year 2017.

Demographics of Members Utilizing CLL Medications: Pharmacy Claims

- Due to the limited number of members utilizing CLL medications detailed demographic information could not be provided.

Top Prescriber Specialties of CLL Medications By Number of Claims: Pharmacy Claims



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

Anticipated Patent Expiration(s):

- Venclexta™ (venetoclax): June 2031
- Zydelig® (idelalisib): September 2033
- Imbruvica® (ibrutinib): October 2034

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

- **August 2017:** The FDA approved Imbruvica® (ibrutinib) for the treatment of adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. This is the first FDA-approved therapy for the treatment of cGVHD.
- **November 2017:** The FDA granted regular approval to Gazyva® (obinutuzumab) in combination with chemotherapy, followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated Stage II bulky, III, or IV follicular lymphoma (FL).

Pipeline:

- Acalabrutinib, which is currently FDA approved for mantle cell lymphoma (MCL), is also being studied in CLL. The combination of venetoclax and rituximab is in Phase 3 trials showing promising results. New drugs in development that are furthest along in the pipeline are fostamatinib and entospletinib; both are oral, selective inhibitors of spleen tyrosine kinase, a mediator of B-cell receptor signaling in normal and transformed B-cells. This may have a role in patients that are resistant to ibrutinib. Also, afuresertib, a pan-protein kinase B (Akt) inhibitor, is being studied in combination with ofatumumab for the treatment of patients with CLL.

Product Summaries[9,10,11,12,13]

Arzerra® (Ofatumumab):

- **Therapeutic Class:** CD20-directed cytolytic monoclonal antibody
- **Indication(s):** The treatment of CLL in the following scenarios:
  - In combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate

- In combination with fludarabine and cyclophosphamide for the treatment of patients with relapsed CLL
- For extended treatment of patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL
- For the treatment of patients with CLL refractory to fludarabine and alemtuzumab

- **How Supplied:** 100mg/5mL or 1,000mg/50mL single-use vials for intravenous (IV) infusion
- **Dose:**
  - Previously Untreated, Relapsed: IV Cycle 1: 300mg on day 1, followed by 1,000mg on day 8; Subsequent Cycles: 1,000mg on day 1 every 28 days
    - Previously Untreated Patients: Maximum 12 cycles
    - Relapsed: In combination with fludarabine and cyclophosphamide, maximum 6 cycles
  - Refractory: IV Cycle 1: 300mg on day 1, followed by 2,000mg on day 8, continued once weekly for 7 doses, followed 4 weeks later by 200mg once every 4 weeks for 4 doses
  - Extended Treatment: IV Cycle 1: 300mg on day 1, followed by 1,000mg on day 8, followed by 1,000mg 7 weeks later and then every 8 weeks for a maximum of 2 years
- **Cost:** The state maximum allowable cost (SMAC) for ofatumumab is $564.70 per 5mL vial and $5,647.00 per 50mL vial

Gazyva® (Obinutuzumab):
- **Therapeutic Class:** CD20-directed cytolytic monoclonal antibody
- **Indication(s):**
  - In combination with chlorambucil, for the treatment of patients with previously untreated CLL
  - In combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen
  - In combination with chemotherapy followed by obinutuzumab monotherapy in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated Stage II bulky, III, or IV FL
- **How Supplied:** 1,000mg/40mL (25mg/mL) single-dose vial for IV infusion
- **Dose:**
  - Untreated CLL: Cycle 1: 100mg on day 1, followed by 900mg on day 2, followed by 1,000mg weekly for 2 doses (days 8 and 15); Cycles 2 through 6: 1,000mg on day 1 every 28 days for 5 doses
- **Cost:** The SMAC for obinutuzumab is $6,064.00 per 40mL vial

Imbruvica® (Ibrutinib):
- **Therapeutic Class:** Kinase inhibitor
- **Indication(s):**
  - Patients with MCL who have received at least one prior therapy

- CLL/SLL
- CLL/SLL with 17p deletion
- Waldenström's macroglobulinemia (WM)
- Patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy
- cGVHD after failure of one or more lines of systemic therapy

- **How Supplied:** 70mg and 140mg oral capsules
- **Dose:**
  - MCL and MZL: 560mg once daily (four 140mg capsules)
  - CLL/SLL, WM, and cGVHD: 420mg once daily (three 140mg capsules)
- **Cost:** The wholesale acquisition cost (WAC) of ibrutinib is $135.33 per 140mg capsule, resulting in a daily cost ranging from $405.99 to $541.32

Venclexta™ (Venetoclax):

- **Therapeutic Class:** B-cell lymphoma 2 (BCL-2) inhibitor
- **Indication(s):** Treatment of patients with CLL with 17p deletion, as detected by an FDA-approved test, who have received at least one prior therapy
- **How Supplied:** 10mg, 50mg, and 100mg oral tablets
- **Dose:** Initial dosing is 20mg once daily for 7 days, followed by a weekly ramp-up dosing schedule to the recommended daily dose of 400mg
- **Cost:** The WAC of venetoclax is $92.91 per 100mg tablet, resulting in a daily cost of $371.64

Zydelig® (Idelalisib):

- **Therapeutic Class:** Kinase inhibitor
- **Indication(s):**
  - Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered inappropriate therapy due to other co-morbidities
  - Relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies
  - Relapsed SLL in patients who have received at least two prior systemic therapies
- **How Supplied:** 100mg and 150mg oral tablets
- **Dose:** The recommended dose is 150mg administered twice daily
- **Cost:** The WAC of idelalisib is $170.28 per 150mg tablet, resulting in a daily cost of $340.56

Recommendations

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

1. As first-line treatment of CLL in combination with chlorambucil or bendamustine; or
2. For relapsed or refractory disease as a single-agent or in combination with fludarabine and cyclophosphamide; or
3. As maintenance therapy as second-line extended dosing following complete or partial response to relapsed or refractory therapy (maximum 2 years).

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

1. For previously treated disease that does not respond to primary therapy or for progressive or relapsed disease; and
2. As a single-agent or combination therapy; and
3. Member is rituximab-intolerant.

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

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

Gazyva® (Obinutuzumab) Approval Criteria [Follicular Lymphoma (FL) Diagnosis]:

1. Grade 1 or 2 patients with Stage I (≥7cm), contiguous Stage II (≥7cm), noncontiguous Stage II, Stage III, or Stage IV patients (first, second, or subsequent therapy); and
2. In combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), or bendamustine; and
3. When used for maintenance therapy a total of 12 doses will be approved.

Gazyva® (Obinutuzumab) Approval Criteria [Gastric or Nongastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma, Nodal or Splenic Marginal Zone Lymphoma (MZL) Diagnosis]:

1. As second-line or subsequent therapy in combination with bendamustine; or
2. Maintenance therapy as second-line consolidation or extended dosing in rituximab-refractory patients treated with obinutuzumab and bendamustine for a total of 12 doses.

Imbruvica® (Ibrutinib) Approval Criteria [Follicular Lymphoma (FL) Diagnosis]:

1. A diagnosis of Grade 1 or 2 FL; and
2. As subsequent therapy (third-line or greater) for histologic transformation to non-germinal center diffuse large B-cell lymphoma.

Imbruvica® (Ibrutinib) Approval Criteria [Gastric or Nongastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma, Nodal or Splenic Marginal Zone Lymphoma (MZL) Diagnosis]:

1. As second-line or subsequent therapy for refractory or progressive disease.

Imbruvica® (Ibrutinib) Approval Criteria [Chronic Graft-Versus-Host Disease (cGVHD) Diagnosis]:

1. A diagnosis of cGVHD after failure of one or more lines of therapy.

Imbruvica® (Ibrutinib) Approval Criteria [Histologic Transformation of Marginal Zone Lymphoma (MZL) to Diffuse Large B-Cell Lymphoma Diagnosis]:

1. As third-line or greater therapy for patients who have transformed to non-germinal center diffuse large B-cell lymphoma.

Imbruvica® (Ibrutinib) Approval Criteria [Mantle Cell Lymphoma (MCL) Diagnosis]:

1. Second-line or subsequent therapy; and
2. Used as a single-agent or in combination with rituximab or lenalidomide/rituximab.

Imbruvica® (Ibrutinib) Approval Criteria [Diffuse Large B-Cell Lymphoma Diagnosis or Acquired Immunodeficiency Syndrome (AIDS)-Related B-Cell Lymphoma Diagnosis]:

1. A diagnosis of non-germinal center diffuse large B-cell lymphoma; and
2. As second-line or subsequent therapy; and
3. Member is not a candidate for high-dose therapy.

Imbruvica® (Ibrutinib) Approval Criteria [Post-Transplant Lymphoproliferative Disorders Diagnosis]:

1. As second-line and subsequent therapy in patients with partial response, persistent, or progressive disease; and
2. Non-germinal center B-cell type.

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

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

Imbruvica® (Ibrutinib) Approval Criteria [Hairy Cell Leukemia Diagnosis]:

1. As a single-agent in patients with indication for treatment for progression.

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

1. As first or subsequent therapy; and
2. As a single-agent.

Venclexta™ (Venetoclax) Approval Criteria [Mantle Cell Lymphoma (MCL) Diagnosis]:

1. As second-line or subsequent therapy; and
2. As a single-agent only.

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

1. For relapsed/refractory disease; and
2. In combination with rituximab or as a single-agent.

Zydelig® (Idelalisib) Approval Criteria [Follicular Lymphoma (FL) Diagnosis]:

1. A diagnosis of Grade 1 to 2 FL; and
2. As second-line or subsequent therapy for refractory or progressive disease; and
3. Refractory to both alkylator and rituximab therapy.

Zydelig® (Idelalisib) Approval Criteria [Gastric or Nongastric Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma, Nodal or Splenic Marginal Zone Lymphoma (MZL) Diagnosis]:

1. As second-line or subsequent therapy for refractory or progressive disease; and
2. Refractory to both alkylator and rituximab therapy.

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

1. For relapsed or refractory disease; and
2. In combination with rituximab or rituximab/bendamustine; or
3. As a single-agent.

Utilization Details of CLL Medications: Calendar Year 2017

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
IBRUTINIB PRODUCTS					
IMBRUVICA CAP 140MG	38	7	$453,509.97	5.43	$11,934.47
TOTAL	**38**	**7***	**$453,509.97**	**5.43**	**$11,934.47**

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

[1] Chiorazzi N, Rai KR, and Ferrarini M. Chronic lymphocytic leukemia. *N Eng J Med*. 2005; 352:804-815.
[2] Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017; 67:7-30.
[3] National Comprehensive Cancer Network (NCCN) Guidelines. CLL/SLL V 3.2018. Available online at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf. Last accessed 02/05/2018.
[4] Hallek M. Chronic lymphocytic leukemia: 2015 update on diagnosis, risk stratification, and treatment. *American Journal of Hematology* 2015; 90:446-460.
[5] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 12/2017. Last accessed 01/23/2018.
[6] FDA. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Available online at: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm. Last revised 01/16/2018. Last accessed 01/23/2018.
[7] Seymour J, et al. *Blood* [ASH abstract] 2017.
[8] Starr P. The hematologic drug pipeline: exciting new treatment options looming. *Am Health Drug Benefits* 2016; 9:1-20.
[9] Arzerra® Prescribing Information. Novartis Pharmaceuticals. Available online at: https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/arzerra.pdf. Last revised 08/2016. Last accessed 01/24/2018.
[10] Gazyva® Prescribing Information. Genentech, Inc. Available online at: https://www.gene.com/download/pdf/gazyva_prescribing.pdf. Last revised 11/2017. Last accessed 01/24/2018.
[11] Imbruvica® Prescribing Information. Janssen Biotech, Inc. Available online at: https://www.imbruvica.com/docs/librariesprovider7/default-document-library/prescribing-information.pdf. Last revised 12/2017. Last accessed 01/24/2018.
[12] Venclexta™ Prescribing Information. AbbVie, Inc. Available online at: http://www.rxabbvie.com/pdf/venclexta.pdf. Last revised 12/2017. Last accessed 01/24/2018.
[13] Zydelig® Prescribing Information. Gilead Sciences, Inc. Available online at: http://www.gilead.com/~/media/Files/pdfs/medicines/oncology/zydelig/zydelig_pi.pdf. Last revised 11/2017. Last accessed 01/24/2018.

Appendix J

Calendar Year 2017 Annual Review of Erythropoietin Stimulating Agents (ESAs)

Oklahoma Health Care Authority
March 2018

Current Prior Authorization Criteria

Aranesp® (Darbepoetin Alfa) Approval Criteria:

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

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

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

Utilization of ESAs: Calendar Year 2017

ESA Calendar Year Comparison: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	41	206	$187,114.72	$908.32	$43.91	468	4,261
2017	34	209	$104,269.03	$498.89	$29.64	412	3,518
% Change	**-17.10%**	**1.50%**	**-44.30%**	**-45.10%**	**-32.50%**	**-12.00%**	**-17.40%**
Change	**-7**	**3**	**-$82,845.69**	**-$409.43**	**-$14.27**	**-56**	**-743**

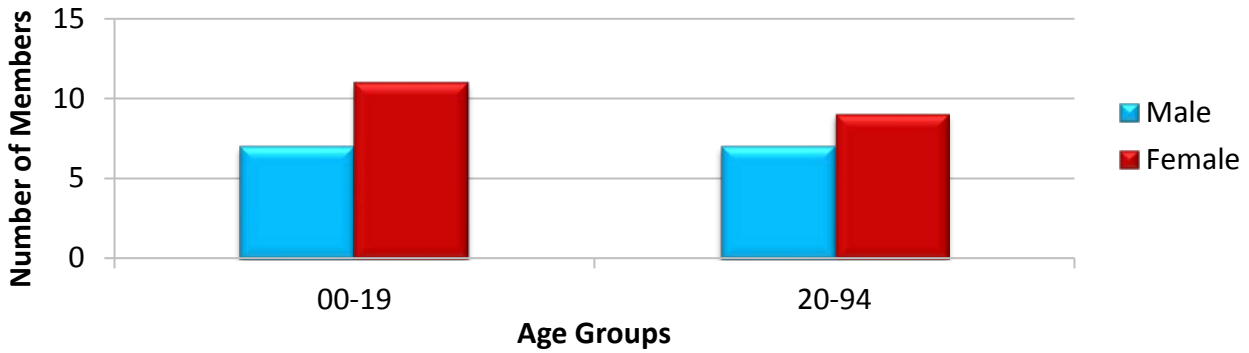
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Calendar Year 2017 Utilization of ESAs: Medical Claims

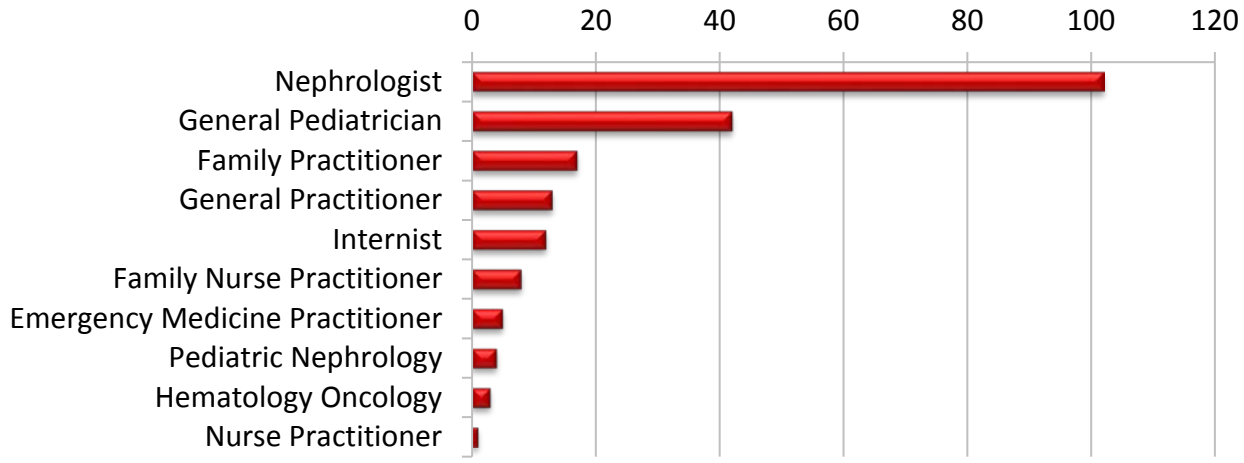
*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
34	144	$61,371.86	$426.19	6,330

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

Demographics of Members Utilizing ESAs

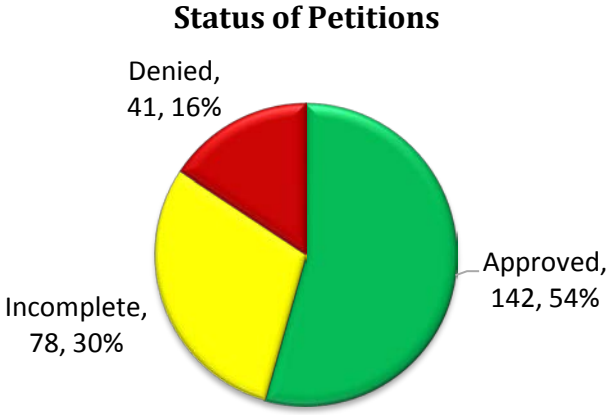


Top Prescriber Specialties of ESAs by Number of Claims



Prior Authorization of ESAs

There were 261 prior authorization requests submitted for ESAs during calendar year 2017. The following chart shows the status of the submitted petitions for calendar year 2017.



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

Anticipated Patent Expiration(s):

- Aranesp® (darbepoetin alfa): May 2024

News:

- **April 2017:** The U.S. Food and Drug Administration (FDA) announced the elimination of the Risk Evaluation and Mitigation Strategy (REMS) for epoetin alfa and darbepoetin alfa. The REMS for epoetin alfa and darbopoetin alfa was initially approved in 2010 to ensure the benefits for use as treatment for anemia associated with myelosuppressive chemotherapy outweigh its risks of shortened overall survival and/or increased risk of tumor progression or recurrence in patients with cancer.

Pipeline:

- **Epoetin Zeta:** In June 2017, one month after an FDA advisory committee recommended approval (14 to 1) of epoetin zeta, Pfizer's biosimilar to Epogen® (epoetin alfa), the FDA issued a complete response letter (CRL) citing concerns regarding the plant manufacturing the product. This is the second CRL Pfizer has received for this product.

ESA Comparison[5,6,7,8,9,10]

ESAs are a class of medications, including epoetin alfa and darbepoetin alfa, which mimic the action of erythropoietin, a hormone produced by the kidney that stimulates red blood cell (RBC) production by the bone marrow. ESAs are often used to treat anemia caused by a variety of conditions including chronic kidney disease (CKD), chemotherapy, certain treatments for Human Immunodeficiency Virus (HIV), as well as to reduce the number of blood transfusions during and after certain major surgeries. Darbepoetin alfa differs from epoetin alfa by having two additional N-linked oligosaccharide chains, resulting in a longer-half life that allows for the opportunity to administer the drug at extended intervals. The most recent Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines for treatment of anemia in CKD,

cancer, and chemotherapy-induced anemia both state neither product is superior to another in terms of patient outcomes. There are few trials that directly compare epoetin alfa to darbepoetin alfa; however, several reviews show no significant clinical or safety differences between the two products.

Table 1. Comparison of Epoetin Alfa and Darbepoetin Alfa Products

	Epoetin Alfa (Epogen®/Procrit®)	Darbepoetin Alfa (Aranesp®)
FDA-Approved Indication(s)	• Treatment of anemia due to: - CKD in pts on dialysis and not on dialysis - Zidovudine in HIV-infected pts - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy • Reduction of allogenic RBC transfusions in pts undergoing elective, noncardiac, nonvascular surgery	• Treatment of anemia due to: - CKD in pts on dialysis and not on dialysis - The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy
Dosing	• CKD Pts: - Initial dose: 50 to 100 Units/kg 3 times weekly (adults) and 50 Units/kg 3 times weekly (children on dialysis) - Maintenance dose should be individualized - IV route recommended for pts on hemodialysis • Zidovudine-Treated HIV-infected Pts: 100 Units/kg 3 times weekly • Cancer Pts on Chemotherapy: 40,000 Units weekly or 150 Units/kg 3 times weekly (adults); 600 Units/kg IV weekly (children ≥ 5 years) • Surgery Pts: 300 Units/kg per day daily for 15 days or 600 Units/kg weekly	• Pts with CKD on Dialysis: - 0.45mcg/kg IV or SQ weekly - 0.75mcg/kg IV or SQ every 2 weeks - IV route is recommended for pts on hemodialysis • Pts with CKD Not on Dialysis: 0.45mcg/kg IV or SQ at 4 week intervals • Pediatric Pts with CKD: - 0.45mcg/kg IV or SQ weekly - Pts with CKD not on dialysis may also be initiated at 0.75mcg/kg every 2 weeks • Pts with Cancer on Chemotherapy: - 2.25mcg/kg SQ weekly - 500mcg SQ every 3 weeks

CKD = chronic kidney disease; Pts = patients; HIV = human immunodeficiency virus; RBC = red blood cell; IV = intravenous; SQ = subcutaneous

Cost Comparison:

Medication	SoonerCare Average Cost/Claim For Calendar Year 2017
Aranesp® (darbepoetin alfa)	$543.25
Epogen® (epoetin alfa)	$492.32

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

Recommendations

The College of Pharmacy recommends the addition of a patient-specific, clinically significant reason why the member cannot use Epogen® or Procrit® (epoetin alfa) to the approval criteria for Aranesp® (darbepoetin alfa). The following criteria would apply based on net cost after rebates:

Aranesp® (Darbepoetin Alfa) Approval Criteria:

1. An FDA approved diagnosis of anemia due to chemotherapy in patients with non-myeloid malignancies; or
2. An FDA approved diagnosis of anemia associated with chronic renal failure; and
    a. For the diagnosis of anemia associated with chronic renal failure: member must not be receiving dialysis [erythropoietin stimulating agents (ESAs) are included in the bundled dialysis payment if member is on any form of dialysis and cannot be billed separately]; and
3. Recent hemoglobin levels must be provided; and
4. A patient-specific, clinically significant reason why the member cannot use Epogen® or Procrit® (epoetin alfa); and
5. Approvals will be for the duration of 16 weeks of therapy. Recent hemoglobin levels must be provided with continuation requests, and further approval may be granted if the member's recent hemoglobin level is less than 11g/dL.

Utilization Details of ESAs: Calendar Year 2017

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
DARBEPOETIN ALFA PRODUCTS					
ARANESP INJ 40MCG	14	1	$4,482.10	14	$320.15
ARANESP INJ 150MCG	8	1	$1,595.44	8	$199.43
ARANESP INJ 100MCG	2	1	$6,206.10	2	$3,103.05
ARANESP INJ 60MCG	2	1	$1,135.06	2	$567.53
ARANESP INJ 40MCG	1	1	$1,248.95	1	$1,248.95
SUBTOTAL	**27**	**4**	**$14,667.65**	**6.75**	**$543.25**
EPOETIN ALFA PRODUCTS					
PROCRIT INJ 20000/ML	128	12	$34,667.12	10.67	$270.84
PROCRIT INJ 10000/ML	24	8	$20,563.78	3	$856.82
PROCRIT INJ 40000/ML	9	2	$14,154.75	4.5	$1,572.75
EPOGEN INJ 10000/ML	7	2	$6,038.65	3.5	$862.66
PROCRIT INJ 3000/ML	5	2	$8,751.99	2.5	$1,750.40
PROCRIT INJ 2000/ML	4	2	$1,807.64	2	$451.91
EPOGEN INJ 20000/ML	3	2	$3,331.07	1.5	$1,110.36
EPOGEN INJ 2000/ML	2	1	$286.38	2	$143.19
SUBTOTAL	**182**	**30**	**$89,601.38**	**6.07**	**$492.32**
TOTAL	**209**	**34**	**$104,269.03**	**6.15**	**$498.89**

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

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
EPOETIN ALFA PRODUCTS					
PROCRIT INJ J0885	144	34	$61,371.86	4.2	$426.19
TOTAL	**144**	**34**	**$61,371.86**	**4.2**	**$426.19**

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

[1] Letter to Shareholders. Amgen, Inc. Available online at: http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-reportsannual. Last revised 04/03/2017. Last accessed 12/20/2017.
[2] U.S. Food and Drug Administration. Information for Aranesp® (darpepoetin alfa). Available online at: https://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm541148.htm. Last revised 04/13/2017. Last accessed 02/12/2018.
[3] U.S. Food and Drug Administration. Information for Epogen®/Procrit® (Epoetin alfa). Available online at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm541173.htm. Last revised 04/13/2017. Last accessed 02/12/2018.
[4] Palmer E. FDA Rejects Pfizer's Epogen® Biosimilar for the Second Time. *FiercePharma*. Available online at: https://www.fiercepharma.com/regulatory/fda-rejects-pfizer-s-epogen-biosimilar-for-a-second-time. Issued 06/22/2017. Last accessed 02/02/2018.
[5] Epogen® (Epoetin Alfa) Prescribing Information. Amgen, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103234s5363s5366lbl.pdf. Last revised 09/2017. Last accessed 02/12/2018.
[6] Aranesp® (Darbepoetin Alfa) Prescribing Information. Amgen, Inc. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103951s5374lbl.pdf. Last revised 10/2017. Last accessed 02/12/2018.
[7] Wilhelm-Leen ER, Winkelmayer WC. Mortality Risk of Darbepoetin Alfa versus Epoetin Alfa in Patients with Chronic Kidney Disease: Systemic Review and Meta-Analysis. *Am J Kidney Dis* 2015; 66(1):69-74.
[8] Winkelmayer WC, Chang TI, Mitani AA, Wilhelm-ER et al. Longer-term Outcomes of Darbepoetin Alfa Versus Epoetin Alfa in Patients With ESRD Initiating Hemodialysis: A Quasi-experimental Cohort Study. *Am J Kidney Dis* 2015; 66(1):106-113.
[9] KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Chapter 3: Use of ESAs and other agents to treat anemia in CKD. *Kidney International Supplements* 2012; 2:299-310.
[10] National Comprehensive Cancer Network. Cancer and Chemotherapy Induced Anemia Clinical Practice Guidelines in Oncology. Available online at: www.jnccn.org/content/10/5/628.full.pdf. Last revised 05/2012. Last accessed 02/12/2018.

Appendix K

30-Day Notice to Prior Authorize Luxturna™ (Voretigene Neparvovec-rzyl)

Oklahoma Health Care Authority
March 2018

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

Scientists have been working for decades on ways to modify genes or replace faulty genes with healthy ones to treat, cure, or prevent a disease or medical condition. In gene therapy, scientists can replace a gene that causes a medical problem with one that does not, add genes to help the body to fight or treat disease, or turn off genes that are causing problems. In order to insert new genes directly into cells, scientists use a vehicle called a "vector" which is genetically engineered to deliver the gene. Viruses have a natural ability to deliver genetic material into cells, and therefore, can be used as vectors, after being modified to remove the ability to cause an infectious disease. In gene therapy that is used to modify cells outside the body (*ex vivo*), blood, bone marrow, or another tissue can be taken from a patient, and specific types of cells can be separated out in the laboratory, where the vector containing the desired gene is then introduced into these cells. The cells are left to multiply in the laboratory and are then injected back into the patient, where they continue to multiply and eventually produce the desired effect. In gene therapy that is used to modify cells inside the body (*in vivo*), the vector carrying the desired gene is injected directly into the part of the body that has defective cells. Gene therapy holds the promise to transform medicine and create options for patients who are living with difficult, and even incurable diseases. Since August 2017, the U.S. Food and Drug Administration (FDA) has approved three gene therapy products, the first of their kind.

Luxturna™ (voretigene neparvovec-rzyl) is an adeno-associated virus vector-based gene therapy, designed to deliver a normal copy of the gene encoding the human retinal pigment epithelial 65 kDa protein (*RPE65*) to cells of the retina in patients with reduced or absent levels of biologically active *RPE65*. Luxturna™ was FDA approved in December 2017 for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy that leads to vision loss and may cause complete blindness in certain patients. *RPE65* is produced in the retinal pigment epithelial (RPE) cells and converts all-*trans*-retinol to 11-*cis*-retinol, which subsequently forms the chomophore, 11-*cis*-retinal, during the visual (retinoid) cycle. The visual cycle is critical in phototransduction, which refers to the biological conversion of a photon of light into an electrical signal in the retina. Mutations in the *RPE65* gene lead to reduced or absent levels of *RPE65* isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision. The absence of *RPE65* eventually leads to the accumulation of toxic precursors and damage to the RPE cells. Damage to the RPE cells over time, in turn, results in damage to the photoreceptors, which depend on the RPE cells for cellular metabolism. Over time, patients with untreated *RPE65*-mediated inherited retinal dystrophy lose the ability to detect light of any intensity. Independent navigation becomes severely limited, and vision-dependent activities of daily living are impaired. Injection of Luxturna™ into

the subretinal space results in transduction of some RPE cells with complementary DNA (cDNA) encoding normal human *RPE65* protein, thus providing the potential to restore the visual cycle.

Hereditary retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction and are caused by mutations in any one of more than 220 different genes. Biallelic *RPE65* mutation-associated retinal dystrophy affects approximately 1,000 to 3,000 patients in the United States, and an expected 10 to 20 new patients will be born with *RPE65* mutations in the United States each year. Patients with biallelic *RPE65* mutation-associated retinal dystrophy suffer from a severe, debilitating, and progressive retinal disease. From childhood, most patients are visually compromised, eventually progressing to near total blindness in almost all patients. The hallmark of this disease is nyctalopia, which is the inability to see or perceive in dim light, and it manifests in both reduced visual function and functional vision, accompanied by impairment in visual field and visual acuity. Retinal diseases caused by biallelic *RPE65* mutations include some forms of Leber congenital amaurosis and retinitis pigmentosa, among other disorders. Leber congenital amaurosis typically has an early onset, causing severe visual impairment beginning in infancy and is one of the most common causes of blindness in children. Retinitis pigmentosa is one of the most common inherited diseases of the retina (retinopathies), with symptoms usually beginning in childhood and progressing over years or decades, with many becoming legally blind by adulthood. Biallelic mutation carriers have a mutation (not necessarily the same mutation) in both copies of a particular gene (a paternal and a maternal mutation). The FDA granted Luxturna™ Priority Review, Breakthrough Therapy, and Orphan Drug designations for the treatment of biallelic *RPE65* mutation-associated retinal dystrophy.

Market News and Updates[6,7,8]

New FDA Approval(s):

- **December 2017:** The FDA approved Luxturna™ (voretigene neparvovec-rzyl), a one-time gene therapy product, for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy.

News:

- **January 2018:** The $850,000 list price for Luxturna™ is about four times too high for the value the drug provides, according to an analysis from the Institute for Clinical and Economic Review (ICER). ICER is an independent, non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. Luxturna™ is the first-of-its-kind gene therapy approved for the United States market and the most expensive drug by list price. In its report, ICER said a cost-effective price for Luxturna™ would be $153,000 to $217,000 and cited a lack of data that Luxturna™ causes permanent improvements in vision as a key reason that its developer, Spark Therapeutics, should not be charging so much. While Luxturna™ is a one-time therapy, long-term efficacy remains a question for this treatment. Individuals with an *RPE65* mutation have significant retinal degeneration leading to worse functional vision over time. The therapeutic effects of gene therapy may not be permanent. Visual

improvements past three years have been described by clinical experts, but no published data exist. Even if improvements persist in treated cells, it remains unclear whether long-term retinal degradation is impacted by gene therapy. Therapy with Luxturna™ involves using a viral vector to transfect cells in the RPE with a functioning copy of *RPE65*. This does not repair or eliminate the defective gene, but rather introduces a normal copy of the gene into the cell. Dr. David Rind, ICER's chief medical officer, stated, "While the evidence is clear the therapy improves vision for patients over several years, the long-term duration of this benefit remains unknown. Assuming a 10- to 20-year period of benefit, at list price the treatment does not meet standard cost-effectiveness thresholds, even after accounting for broader societal benefits improved vision has on productivity and education costs." ICER reached its suggested list price for Luxturna™ by assuming that a 15-year-old patient (the average age of the patients enrolled in the clinical trials) would experience improvements for a decade or two and taking into account the benefits to the health care system. ICER added that when it also took into account the benefits related to education, caregiver burdens, and productivity, the drug's list price should still be cut in half. ICER noted that the price of Luxturna™ is cost-effective for select patients and with certain assumptions. The drug's list price met its standards for "cost-effectiveness thresholds" when it analyzed treating 3-year-old patients, took into account both medical and societal benefits, and assumed the vision improvements would last for the patients' whole lives. Quality of life measures were collected during the Phase 3 study for Luxturna™; however, the results have not been published or presented. ICER requested quality of life data to use as part of their review, but the manufacturer was unable to provide the data to ICER.

- **January 2018:** Spark Therapeutics, the manufacturer of Luxturna™, announced three new first-of-their-kind payer programs to improve patient access to Luxturna™. The payer programs include an outcomes-based rebate agreement with a long-term durability measure, an innovative contracting model, and a proposal to the Centers for Medicare and Medicaid (CMS) under which payments for Luxturna™ would be made over time. Together, these initiatives aim to help ensure eligible patients in the United States have access to Luxturna™. Both the outcomes-based rebate agreement and the innovative contracting model are geared toward commercial insurers and payers. Spark Therapeutics is in discussions with CMS on a proposal that would enable the company to offer payers the option to spread payment over multiple years, while providing flexibility for greater outcomes-based rebates. Based on feedback from payers, Spark Therapeutics has been seeking solutions that would allow customers to pay for Luxturna™ in installments over several years rather than in a single, up-front payment. Due to current government price reporting requirements, it is not feasible for Spark Therapeutics to offer installment payments or to offer outcomes-based rebates above a certain threshold. Spark Therapeutics has submitted a proposal to CMS to conduct a demonstration project for Luxturna™ that would enable Spark Therapeutics to offer commercial and government payers an installment payment option, as well as greater rebates tied to clinical outcomes. If discussions with CMS do not result in Spark Therapeutics being able to offer an installment option, Spark Therapeutics has developed an approach that would permit its distributor to independently make

alternative payment options available to payers, which may include an installment or financing option.

Luxturna™ (Voretigene Neparvovec-rzyl) Product Summary[9,10,11,12]

Indication(s): Luxturna™ (voretigene neparvovec-rzyl) is indicated for the treatment of patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by treating physician(s).

Dosing:

- The recommended dose of Luxturna™ for each eye is 1.5×10^{11} vector genomes (vg), administered by subretinal injection in a total volume of 0.3mL.
- Luxturna™ should be administered by subretinal injection to each eye on separate days within a close interval, but no fewer than 6 days apart.
- Luxturna™ should be administered in the surgical suite under controlled aseptic conditions by a retinal surgeon experienced in performing intraocular surgery.
    - Luxturna™ is to be administered at selected treatment centers in the United States by leading retinal surgeons, who will receive surgical training provided by the pharmaceutical company on the administration procedure.
- Systemic oral corticosteroids equivalent to prednisone 1mg/kg/day (maximum of 40mg/day) are recommended for a total of 7 days (starting 3 days before administration of Luxturna™ to the first eye), and followed by tapering the dose during the following 10 days. The same corticosteroid regimen applies for the administration of Luxturna™ to the second eye.
    - If the corticosteroid taper following Luxturna™ administration to the first eye is not complete 3 days prior to the planned Luxturna™ administration to the second eye, then the corticosteroid regimen for the second eye replaces the taper for the first eye.
- Luxturna™ is an intraocular suspension for subretinal injection that must be diluted prior to use and should be prepared within 4 hours of administration using sterile technique under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (*refer to Luxturna™ prescribing information for a complete list of dilution, preparation, and administration steps*).
- Each carton of Luxturna™ contains one single-dose vial of Luxturna™ (0.5mL extractable volume) and two vials of diluent (1.7mL extractable volume in each vial). Luxturna™ contains 5×10^{12} vg/mL and requires a 1:10 dilution prior to administration. After dilution, each dose of Luxturna™ consists of 1.5×10^{11} vg in a deliverable volume of 0.3mL.
- Luxturna™ and diluent should be stored frozen at ≤ -65°C prior to dilution and administration. Luxturna™ does not contain preservatives.

Mechanism of Action: Luxturna™ is a live, non-replicating adeno-associated virus serotype 2, which has been genetically modified to express the human *RPE65* gene. Luxturna™ is derived from naturally occurring adeno-associated virus using recombinant DNA techniques. Luxturna™ is designed to deliver a normal copy of the human *RPE65* gene to cells of the retina in patients

with reduced or absent levels of biologically active *RPE65*. Mutations in the *RPE65* gene lead to reduced or absent levels of *RPE65* isomerohydrolase activity, blocking the visual cycle and resulting in impairment of vision. Injection of Luxturna™ into the subretinal space results in transduction of some RPE cells with cDNA encoding normal human *RPE65* protein, thus providing the potential to restore the visual cycle.

Contraindication(s): None.

Safety:

- Endophthalmitis: Endophthalmitis may occur following any intraocular surgical procedure or injection. Proper aseptic injection technique should be used when administering Luxturna™. Following the injection, patients should be monitored to permit early treatment of any infection. Patients should be advised to report any signs or symptoms of injection or inflammation without delay.
- Permanent Decline in Visual Acuity: Permanent decline in visual acuity may occur following subretinal injection of Luxturna™. Patients should be monitored for visual disturbances.
- Retinal Abnormalities: Retinal abnormalities may occur during or following the subretinal injection of Luxturna™, including macular holes, foveal thinning, loss of foveal function, foveal dehiscence, and retinal hemorrhage. These retinal abnormalities should be monitored for and managed appropriately. Luxturna™ should not be administered in the immediate vicinity of the fovea.
- Increased Intraocular Pressure (IOP): Increased IOP may occur after subretinal injection of Luxturna™. IOP should be monitored and managed appropriately.
- Expansion of Intraocular Air Bubbles: Patients should be instructed to avoid air travel, travel to high elevations, or scuba diving until the air bubble formed following administration of Luxturna™ has completely dissipated from the eye. It may take one week or more following injection for the air bubble to dissipate. A change in altitude while the air bubble is still present can result in irreversible vision loss. Dissipation of the air bubble should be verified through ophthalmic examination.
- Cataract: Subretinal injection of Luxturna™, especially vitrectomy surgery, is associated with an increased incidence of cataract development and/or progression.

Use in Specific Populations:

- Pregnancy: Adequate and well-controlled studies with Luxturna™ have not been conducted in pregnant women. Animal reproductive studies have not been conducted with Luxturna™.
- Lactation: There is no information regarding the presence of Luxturna™ in human milk, the effects on the breastfed infant, or the effects on milk production.
- Females and Males of Reproductive Potential: No non-clinical or clinical studies were performed to evaluate the effect of Luxturna™ on fertility.
- Pediatric Use: Treatment with Luxturna™ is not recommended in patients younger than 12 months of age because retinal cells are still undergoing cell proliferation, and Luxturna™ would potentially be diluted or lost during cell proliferation. The safety and efficacy of Luxturna™ have been established in pediatric patients. Use of Luxturna™ is

supported by two clinical studies that included 25 pediatric patients with biallelic *RPE65* mutation-associated retinal dystrophy in the following age groups: 21 children (age 4 years to younger than 12 years) and 4 adolescents (age 12 years to younger than 17 years). There were no significant differences in safety between the different age subgroups.

- Geriatric Use: The safety and effectiveness of Luxturna™ have not been established in geriatric patients. Clinical studies of Luxturna™ for this indication did not include patients ages 65 years and older.

Drug Interactions: No drug interaction studies have been performed with Luxturna™.

Adverse Reactions: The most common adverse reactions (incidence ≥ 5%) following treatment with Luxturna™ include conjunctival hyperemia, cataract, increased IOP, retinal tear, dellen (thinning of the corneal stroma), macular hole, subretinal deposits, eye inflammation, eye irritation, eye pain, and maculopathy (wrinkling on the surface of the macula).

Efficacy: The efficacy of Luxturna™ in pediatric and adult patients with biallelic *RPE65* mutation-associated retinal dystrophy was evaluated in an open-label, two-center, randomized Phase 3 clinical trial.

- Inclusion criteria for the trial included:
  - Age 3 years or older
  - Confirmed genetic diagnosis of biallelic *RPE65* gene mutation
  - Visual acuity of 20/60 or worse in both eyes and/or visual field less than 20 degrees in any meridian in both eyes
  - Sufficient viable retinal cells as determined by retinal thickness on spectral domain optical coherence tomography (>100 microns within the posterior pole), fundus photography, and clinical examination
  - Ability to perform a standardized multi-luminance mobility test (MLMT) within the luminance range evaluated, but unable to pass the MLMT at 1 lux, the lowest luminance level tested
- Exclusion criteria for the trial included:
  - Participation in a previous gene therapy or investigational drug study
  - Use of high-dose retinoid compounds (>7,500 retinol equivalent units or >3,300 IU per day of vitamin A) in the past 18 months
  - Intraocular surgery in the past 6 months
  - Known sensitivity to medications planned for use in the perioperative period
  - Ocular or systemic conditions that would interfere with study interpretation
  - Current pregnancy
  - Unwillingness to use effective contraception for 4 months after vector administration
- Patients were randomly assigned (2:1) to intervention or control using a permuted block design, stratified by age (<10 years and ≥10 years) and baseline mobility testing passing level (pass at ≥125 lux vs. <120 lux). The trial enrolled 21 patients in the intervention group and 10 patients in the control group.

- The average age of the randomized patients was 15 years (range 4 to 44 years), including 64% pediatric patients (n=20, age 4 to 17 years) and 36% adult patients (n=11).
- The 31 randomized patients included 13 males and 18 females; 68% of the patients were white, 16% were Asian, 10% were American Indian or Alaska Native, and 6% were black or African American.
- One patient from each group withdrew consent before intervention, leaving 20 intervention patients and 9 control patients. The 9 patients randomized to the control group did not receive Luxturna™, but participated in the same efficacy outcome testing as did the intervention group.
    - The control group became eligible to receive Luxturna™ 1 year after their baseline evaluations, provided they still met all eligibility criteria. At this point, they received bilateral administrations of Luxturna™ according to the same protocol as the intervention group.

- The intervention was bilateral, subretinal injections of Luxturna™, administered sequentially in two separate surgical procedures with an interval of 6 to 18 days.
- The primary efficacy endpoint was 1-year change from baseline in bilateral MLMT performance (change in lux score for the lowest passing light level), measuring functional vision at specified light levels. Baseline testing established the lowest level of illumination at which each patient could pass the MLMT. A positive change score indicates passing the MLMT at a lower light level.
    - In response to the need for a relevant, reliable, and clinically meaningful measure of functional vision in these low-vision patients with nyctalopia, members of the sponsor and study team developed the MLMT, with input from the FDA.
    - The MLMT uses a 5-foot by 10-foot course surrounded by a 1-foot border (1.52m × 3.05m × 0.3m) to evaluate an individual's ability to navigate a marked path, while avoiding obstacles in or adjacent to the path, negotiating raised steps, and identifying a door, all while relying on vision.
    - The MLMT was designed to quantify patients' ability to navigate around these obstacles in varying environmental illuminations, including very low light levels, integrating aspects of visual acuity, visual field, and light sensitivity.
    - The test has 12 configurations to reduce learning effect. After 40 minutes of dark adaptation, patients completed the course with one eye patched, then completed a new configuration with the other eye patched, then again using both eyes.
    - Passing (at any light level) is defined as completion of the course at the specified light level with fewer than 4 errors (corresponding to an accuracy score of <0.25) and within 3 minutes.
- At 1 year, mean bilateral MLMT change score was 1.8 light levels in the intervention group and 0.2 in the control group, for a difference of 1.6 [95% confidence interval (CI): 0.72 to 2.41; P=0.0013). Monocular MLMT change scores were similar to the bilateral scores.

    - The response to bilateral administration of Luxturna™ in the intervention group was rapid; mean MLMT lux score improved by the day 30 visit and remained stable throughout 1 year.
- Thirteen (65%) of the 20 intervention patients, but no control patients, passed MLMT at the lowest luminance level tested (1 lux), demonstrating maximum possible improvement.
    - A normally sighted ambulatory person would be able to complete the course at 1 lux with no or minimal errors.
- No product-related serious adverse events or deleterious immune responses occurred. Most ocular events were mild in severity.
- Patients were assessed on retinal and visual function at baseline, and 30, 90, 180, and 365 days after randomization (control group) or second injection (intervention group) using:
    - Full-field light sensitivity threshold (FST) testing, done using both white light and chromatic stimuli to probe potential differential effects on rod vs. cone photoreceptors
    - Visual field testing by Goldmann perimetry for kinetic fields
    - Humphrey computerized testing for macular static fields with foveal sensitivity thresholds
    - Contrast sensitivity testing
    - Pupillary light reflex (PLR)
- Patients (or the parents or guardians of pediatric patients) also completed a visual function questionnaire designed to assess activities of daily living relevant to visual deficits due to *RPE65* gene mutations. The questionnaire contained 25 questions with numerical answers from 0 (worst vision) to 10 (best vision) and has not been validated.
- Patients were also given in-home orientation and mobility assessments at baseline and 1 year after randomization (control group) or second injection (intervention group). These home-based assessments were designed to document the functional visual abilities of the patients in each of the following domains: self-report, functional visual field, basic visual skills, illumination, orientation, and mobility.
- Safety and efficacy will be monitored for at least 5 years through assessments at annual visits, including safety, mobility testing, and retinal and visual function testing, and for 15 years via questionnaires at annual visits or telephone visits.

Cost: Luxturna™ is expected to be available for administration late in the first quarter of 2018 and is anticipated to cost $850,000 per patient ($425,000 per single-dose vial).

Recommendations

The College of Pharmacy recommends the prior authorization of Luxturna™ (voretigene neparvovec-rzyl) with the following criteria:

Luxturna™ (Voretigene Neparvovec-rzyl) Approval Criteria:

1. An FDA approved diagnosis of biallelic *RPE65* mutation-associated retinal dystrophy; and
    a. Diagnosis must be confirmed by genetic testing; and
2. Member must have sufficient viable retinal cells in both eyes as determined by the treating physician(s); and
3. Member must have best corrected visual acuity of 20/60 or worse in both eyes and/or visual field less than 20 degrees in any meridian in both eyes; and
4. Member must be four years of age or older; and
5. Member must not have participated in a previous *RPE65* gene therapy study or have previously received treatment with Luxturna™; and
6. Member must not have used high-dose retinoid compounds (>7,500 retinal equivalent units or >3,300 IU per day of vitamin A) in the past 18 months; and
7. Member must not have had intraocular surgery in the past 6 months; and
8. Female members of child bearing age must not be pregnant and must have a negative pregnancy test immediately prior to administration of Luxturna™; and
9. Male and female members of child bearing age must be willing to use effective contraception during treatment with Luxturna™ and for at least 4 months after administration of Luxturna™; and
10. Member must take the recommended systemic oral corticosteroid regimen, starting 3 days prior to administration of Luxturna™ to each eye, and continuing after administration of Luxturna™, as per package labeling of Luxturna™; and
11. Luxturna™ must be prescribed and administered by a retinal surgeon with expertise in the treatment of biallelic *RPE65* mutation-associated retinal dystrophy and in the administration of Luxturna™ at an Ocular Gene Therapy Treatment Center; and
    a. Luxturna™ must be shipped via cold chain supply shipping and delivery to the Ocular Gene Therapy Treatment Center where the member is scheduled to receive treatment; and
    b. Luxturna™ must be stored frozen prior to preparation for administration (Luxturna™ should be administered within 4 hours of preparation); and
    c. The receiving facility must have in place a mechanism to track patient-specific Luxturna™ from receipt to storage to administration; and
12. Luxturna™ must be administered subretinally to each eye on separate days within a close interval, but no fewer than 6 days apart; and
    a. The scheduled procedure date for each eye must be provided; and
13. Only one single-dose vial per eye will be approved per member per lifetime; and
    a. Each single-dose vial of Luxturna™ is to be dispensed immediately prior to the scheduled procedure for the specific eye.

[1] U.S. Food and Drug Administration (FDA) Consumer Update: What is Gene Therapy? How Does it Work? Available online at: https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm589197.htm. Issued 12/19/2017. Last accessed 02/08/2018.
[2] U.S. FDA News Release: FDA Approves Novel Gene Therapy to Treat Patients with a Rare Form of Inherited Vision Loss. Available online at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm589467.htm. Issued 12/19/2017. Last accessed 01/31/2018.
[3] National Institutes of Health. Genetics Home Reference: RPE65 Gene. Available online at: https://ghr.nlm.nih.gov/gene/RPE65. Last accessed 02/09/2018.
[4] National Institutes of Health. Genetics Home Reference: Leber Congenital Amaurosis. Available online at: https://ghr.nlm.nih.gov/condition/leber-congenital-amaurosis#statistics. Last accessed 02/09/2018.
[5] National Institutes of Health. Genetics Home Reference: Retinitis Pigmentosa. Available online at: https://ghr.nlm.nih.gov/condition/retinitis-pigmentosa#genes. Last accessed 02/09/2018.
[6] Spark Therapeutics News Release: FDA Approves Spark Therapeutics' Luxturna™ (Voretigene Neparvovec-rzyl), a One-Time Gene Therapy for Patients with Confirmed Biallelic *RPE65* Mutation-Associated Retinal Dystrophy. *Globe Newswire*. Available online at: http://ir.sparktx.com/news-releases/news-release-details/fda-approves-spark-therapeutics-luxturnatm-voretigene-neparvovec. Issued 12/19/2017. Last accessed 01/31/2018.
[7] Banken R, Rind D, Cramer G, et al. Voretigene Neparvovec for Biallelic *RPE65*-Mediated Retinal Disease: Effectiveness and Value. *Institute for Clinical and Economic Review (ICER)*. Available online at: http://icer-review.org/wp-content/uploads/2017/06/MWCEPAC_VORETIGENE_EVIDENCE_REPORT_01122018.pdf. Issued 01/12/2018. Last accessed 01/31/2018.
[8] Spark Therapeutics News Release: Spark Therapeutics Announces First-of-their-kind Programs to Improve Patient Access to Luxturna™ (Voretigene Neparvovec-rzyl), a One-time Gene Therapy Treatment. *Globe Newswire.* Available online at: http://ir.sparktx.com/news-releases/news-release-details/spark-therapeutics-announces-first-their-kind-programs-improve. Issued 01/03/2018. Last accessed 02/08/2018.
[9] Luxturna™ Package Insert. MedLibrary.org. Available online at: https://medlibrary.org/lib/rx/meds/luxturna/. Last revised 01/02/2018. Last accessed 01/31/2018.
[10] Luxturna™ Prescribing Information. Spark Therapeutics. Available online at: http://sparktx.com/luxturna_us_prescribing_information. Last accessed 01/31/2018.
[11] Russell S, Bennett J, Wellman JA, et al. Efficacy and Safety of Voretigene Neparvovec (AAV2-hRPE65v2) in Patients with *RPE65*-Mediated Inherited Retinal Dystrophy: A Randomized, Controlled, Open-Label, Phase 3 Trial. *The Lancet* 2017; 390(10097):849-860.
[12] Sagonowsky E. Spark Sets Off Gene Therapy Debate with $850K Sticker on Luxturna™. *FiercePharma.* Available online at: https://www.fiercepharma.com/pharma/spark-prices-gene-therapy-luxturna-at-850k-grabbing-top-spot-pharma-s-costliest-drugs. Issued 01/03/2018. Last accessed 01/31/2018.

Appendix L

Calendar Year 2017 Annual Review of Spinraza® (Nusinersen)

Oklahoma Health Care Authority
March 2018

Current Prior Authorization Criteria

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 the treatment of SMA (or be an advanced care practitioner with a supervising physician who is a neurologist or specialist with expertise in the 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. HINE; or
    b. CHOP-INTEND; or
    c. ULM Test; or
    d. HFMSE; and
9. Approval quantity will be based on Spinraza® prescribing information and FDA approved dosing regimen(s).

Utilization of Spinraza® (Nusinersen): Calendar Year 2017

Calendar Year 2017 Utilization of Spinraza® (Nusinersen): Pharmacy Claims

*Total Members	Total Claims	Total Cost	Cost/Claim	Total Units
6	15	$2,623,358.25	$174,890.55	105

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

- Nusinersen was approved by the U.S. Food and Drug Administration (FDA) in December 2016, therefore there was no utilization during calendar year 2016.

Demographics of Members Utilizing Spinraza® (Nusinersen)

- Due to the small number of members utilizing nusinersen, detailed demographic information could not be provided. All paid claims were for pediatric members.

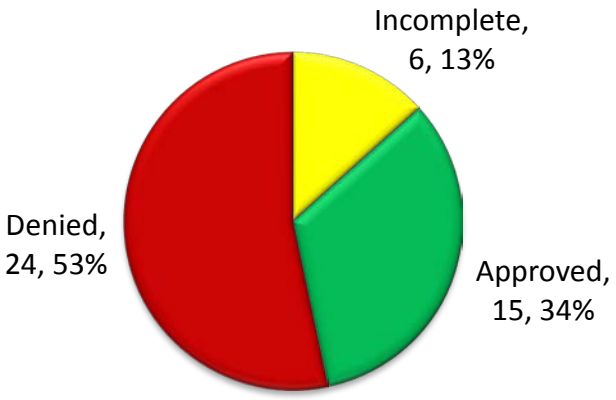
Top Prescriber Specialties of Spinraza® (Nusinersen) by Number of Claims: Pharmacy Claims

- The only prescriber specialty listed on paid nusinersen claims during calendar year 2017 was pediatric pulmonologist.

Prior Authorization of Spinraza® (Nusinersen)

There were 45 prior authorization requests (21 unique members) submitted for Spinraza® (nusinersen) during calendar year 2017. The following chart shows the status of the submitted petitions for calendar year 2017.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Spinraza® (nusinersen): November 2030

Other News:

- **July 2017:** Biogen presented final results from the ENDEAR study at the Cure SMA 2017 Annual SMA Conference. In an analysis of the study results from the Phase 3 ENDEAR study, a greater proportion of infants with spinal muscular atrophy (SMA) on permanent ventilation treated with nusinersen demonstrated clinical benefits compared to patients not treated with nusinersen. Among infants who required permanent ventilation, those treated with nusinersen achieved more motor milestones and higher CHOP-INTEND scores compared to those who received the sham control.
- **November 2017:** Biogen and Ionis Pharmaceuticals, Inc. announced that the end-of-study results from ENDEAR, the Phase 3 study of Sprinraza® (nusinersen), were published in *The New England Journal of Medicine (NEJM)*. The final analysis demonstrated that nusinersen-treated infants were motor milestone responders, compared to untreated patients (51% vs. 0%, P<0.001), including full head control, ability to roll over, and independent sitting and standing. The pre-specified primary endpoint of death or permanent ventilation was also met in the end of study analysis, demonstrating a statistically significant 47% reduction in the risk of death or use of permanent assisted ventilation (P=0.005) and 75% reduction for those with shorter disease duration. Roughly half the nusinersen-treated patients who received permanent ventilation did so within 13 weeks of receiving the first nusinersen dose indicating that a minimum treatment time is required to see the full benefits of therapy. Additionally, the likelihood of event free survival was higher among infants who had a shorter disease duration at screening compared to those who had a longer disease duration, suggesting that early initiation of treatment may maximize its efficacy. Furthermore, several of the nusinersen-treated patients died, some needed continued feeding and ventilator support, and none achieved normal motor development; these findings indicate that in symptomatic patients nusinersen is not a cure. A favorable benefit-risk profile for nusinersen was also demonstrated. Safety data was consistent with those expected in the general SMA population. Following the positive interim analysis, Biogen ended the ENDEAR study early so that all participants could have the option to receive nusinersen in the SHINE open-label extension study. SHINE is designed to assess the effects of longer treatment duration on quality of life and motor function.
- **February 2018:** Biogen and Ionis Pharmaceuticals, Inc. announced end-of-study results from CHERISH, a Phase 3 study of Spinraza® (nusinersen) in patients with later-onset SMA, were published in the *NEJM*. CHERISH was a 15-month study that investigated nusinersen in 126 non-ambulatory patients 2 to 12 years of age who experienced symptom onset at older than 6 months of age. The pre-specified primary endpoint of CHERISH was improvement in motor function, as defined by a change from baseline in the Hammersmith Functional Motor Scale-Expanded (HFMSE). HFMSE is a validated tool specifically designed to assess motor function in patients with SMA. In the final analysis, a statistically significant and clinically meaningful improvement was seen in motor function in subjects treated with nusinersen versus the sham control. A treatment difference of 4.9 points was observed in the mean change from baseline to month 15 in the HFMSE score (P=0.0000001). Subjects who were treated with nusinersen (N=84) achieved a 3.9 point mean improvement from baseline to month 15, while subjects who

did not receive treatment (N=42) experienced a mean decline of 1.0 point. The results of the end-of-study analysis were consistent with the interim analysis.

Pipeline Update(s):

- **May 2017:** Cytokinetics, Inc. announced the FDA granted Orphan Drug designation to CK-2127107 for the potential treatment of SMA. Cytokinetics, in collaboration with Astellas Pharma Inc., is developing CK-2127107, a next-generation fast skeletal muscle troponin activator as a potential treatment for SMA, chronic obstructive pulmonary disease (COPD), and certain other debilitating diseases and conditions associated with skeletal muscle weakness and/or fatigue.
- **July 2017:** Results of a Phase 2 trial to assess the safety and efficacy of olesoxime, a neuroprotectant, in patients with Type 2 or non-ambulatory Type 3 SMA were published in *The Lancet*. Of 198 patients screened, 165 patients were randomly assigned to olesoxime (N=108) or placebo (N=57). The primary outcome measure was change from baseline compared with 24 months between the two treatment groups in functional domains 1 and 2 of the Motor Function Measure assessed in the full analysis population. From the olesoxime group, five patients were not included in the primary outcome analysis because of an absence of post-baseline assessments. The change from baseline to month 24 on the primary outcome measure was 0.18 for olesoxime and -1.82 for placebo [treatment difference 2.00 points, 96% confidence interval (CI) -0.25 to 4.25; p=0.0676]. Although the primary endpoint was not met, secondary endpoints and sensitivity analyses suggest that olesoxime may maintain motor function in patients with Type 2 or 3 SMA over a period of 24 months. Olesoxime seemed to be generally well tolerated and safe at the doses studied for the duration of the trial. Based on the results, olesoxime might provide meaningful clinical benefits for patients with SMA. Due to its mechanism of action, olesoxime may be used in combination with other drugs targeting other mechanisms of the disease; however, additional evidence is needed.
- **September 2017:** Novartis announced that after a two-year pause due to safety concerns, clinical development of LMI070 (branaplam) for the treatment of SMA will resume. The ongoing Phase 1/2 clinical trial will include patients younger than six months of age with Type 1 SMA. New enrollment in the study was paused in May 2016 after simultaneous animal studies linked branaplam to unexpected nerve damage and other injuries. Patients already enrolled in the study continued treatment and were closely monitored. The company has modified its trial design and has added nerve tests to the trial as an additional safety procedure.
- **October 2017:** RG7916, an oral survival motor neuron 2 (SMN2) splicing modifier, has advanced into a second and possibly pivotal stage of a Phase 2 clinical trial to evaluate the safety and efficacy of RG7916 in patients with Type 2 or 3 SMA. The second phase of the SUNFISH trial is randomized, double-blind, and placebo-controlled. An interim analysis from its first part demonstrated an exposure-dependent increase in the SMN protein. RG7916 appears to be well-tolerated at all doses and no drug-related safety finding led to patient discontinuations in part one. The medication is also being investigated in infants with Type 1 SMA in a Phase 2 trial, known as FIREFISH.

- **January 2018:** AveXis, Inc. announced that following a review of safety data and early signals of efficacy from the first three patients dosed in its pivotal trial of AVXS-101 for SMA Type 1, the company will initiate screening of the remaining patients in the trial as per the protocol. STR1VE is an open-label, single-arm, multi-center trial designed to evaluate the safety and efficacy of a one-time intravenous (IV) infusion of AVXS-101, a gene therapy candidate for SMA Types 1 and 2. The trial will enroll a minimum of 15 patients with SMA Type 1 who are less than six months of age at the time of gene therapy and who have one or two copies of the *SMN2* backup gene.

Recommendations

The College of Pharmacy recommends the following changes shown in red to the Spinraza® (nusinersen) prior authorization criteria:

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 the treatment of SMA (or be an advanced care practitioner with a supervising physician who is a neurologist or specialist with expertise in the 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
    a. Spinraza® must be shipped to the facility where the member is scheduled to receive treatment; 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. HINE; or
    b. CHOP-INTEND; or

c. ULM Test; or
d. HFMSE; and

9. Approval quantity will be based on Spinraza® prescribing information and FDA approved dosing regimen(s).
   a. Only one 5mL vial of Spinraza® is to be dispensed prior to each scheduled procedure for administration.

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[1] U.S. Food and Drug Administration (FDA). Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Last revised 12/2017. Last accessed 02/01/2018.

[2] Biogen Press Release. New Data Reaffirm Clinically Meaningful Benefit of Spinraza® (nusinersen) in Individuals with Spinal Muscular Atrophy Across Disease Severity. Available online at: http://media.biogen.com/press-release/rare-and-genetic-diseases/new-data-reaffirm-clinically-meaningful-benefit-spinraza-nus. Issued 06/29/2017. Last accessed 02/14/2018.

[3] Finkel RS, Darras BT, Kirschner J, et al. Nusinersen Demonstrates Efficacy in Infants With and Without Permanent Ventilation: Final Results From the ENDEAR Study. 2017 Annual Spinal Muscular Atrophy Conference. Available online at: http://ir.ionispharma.com/static-files/c1e5eb6e-10a0-4626-9ce6-8f65d58b322c. Presented 07/01/2017. Last accessed 02/14/2018.

[4] Biogen Press Release. *The New England Journal of Medicine* Publishes First Phase 3 Study Results of Spinraza® for the Treatment of Spinal Muscular Atrophy. *Business Wire*. Available online at: http://media.biogen.com/press-release/neurodegenerative-diseases/new-england-journal-medicine-publishes-first-phase-3-study-. Issued 11/01/2017. Last accessed 02/01/2018.

[5] Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *The New England Journal of Medicine* 2017; 377 (18):1723-1732.

[6] Biogen. *The New England Journal of Medicine* Published Spinraza® (nusinersen) Phase 3 Study Results in Individuals with Later-Onset Spinal Muscular Atrophy. *Business Wire*. Available online at: https://www.businesswire.com/news/home/20180214006094/en/New-England-Journal-Medicine-Publishes-SPINRAZA%C2%AE-nusinersen. Issued 02/14/2018. Last accessed 02/20/2018.

[7] Cytokinetics Press Release. Cytokinetics Announces Orphan Drug Designation for CK-2127107 for the Treatment of Spinal Muscular Atrophy. Available online at: http://ir.cytokinetics.com/news-releases/news-release-details/cytokinetics-announces-orphan-drug-designation-ck-2127107. Issued 05/15/2017. Last accessed 02/01/2018.

[8] Bertini E, Dessaud E, Mercuri E, et al. Safety and Efficacy of Olesoxime in Patients with Type 2 or Non-ambulatory Type 3 Spinal Muscular Atrophy: A Randomised, Double-blind, Placebo-controlled Phase 2 Trial. *The Lancet Neurology* 2017; 16(7):513-522.

[9] Kegel M. After 2-Year Hiatus, Novartis Resumes Branaplam Clinical Trial in SMA Type 1 Infants. *SMA News Today*. Available online at: https://smanewstoday.com/2017/09/28/sma-type-1-clinical-trial-of-branaplam-resumes-after-2-year-hiatus-says-novartis/. Issued 09/28/2017. Last accessed 02/07/2018.

[10] Henriques C. Potential SMA Therapy, RG7916, for Types 2 and 3 Advancing in Clinical Trial in Europe. *SMA News Today*. Available online at: https://smanewstoday.com/2017/10/17/potential-spinal-muscular-atrophy-therapy-rg7916-advancing-in-sunfish-clinical-trial-in-europe/. Issued 10/17/2017. Last accessed 02/07/2018.

[11] AveXis, Inc. AveXis to Initiate Screening for Remaining Patients in Pivotal Trial of AVXS-101 for SMA Type 1 Following Review of Preliminary Data from First Three Patients. *Globe Newswire*. Available online at: https://globenewswire.com/news-release/2018/01/30/1314615/0/en/AveXis-to-Initiate-Screening-for-Remaining-Patients-in-Pivotal-Trial-of-AVXS-101-for-SMA-Type-1-Following-Review-of-Preliminary-Data-from-First-Three-Patients.html. Issued 01/30/2018. Last accessed 02/01/2018.

Appendix M

Calendar Year 2017 Annual Review of Multiple Sclerosis (MS) Medications and 30-Day Notice to Prior Authorize Ocrevus™ (Ocrelizumab)

Oklahoma Health Care Authority
March 2018

Current Prior Authorization Criteria

Multiple Sclerosis (MS) Interferon Medications Approval Criteria:

1. An FDA approved diagnosis of relapsing forms of MS; and
2. Authorization of Tier-2 medications requires previous failure of preferred Tier-1 medication(s) defined as:
   a. Occurrence of an exacerbation after six months; or
   b. Significant increase in magnetic resonance imaging (MRI) lesions after six months; or
   c. Adverse reactions or intolerable side effects; and
3. Approvals will not be granted for concurrent use with other disease-modifying therapies; and
4. Compliance will be checked for continued approval every six months.

Multiple Sclerosis (MS) Interferon Medications	
Tier-1	**Tier-2**
Interferon β - 1a (Avonex®)	Interferon β - 1a (Rebif®)
Interferon β - 1b (Betaseron®)	Interferon β - 1a (Plegridy®)
	Interferon β - 1b (Extavia®)

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

Ampyra® (Dalfampridine) Approval Criteria:

1. An FDA approved diagnosis of Multiple Sclerosis (MS); and
2. Kurtzke Expanded Disability Status Scale (EDSS) score between 3 and 7.5; and
3. Initial approvals will be for the duration of 90 days. If the member has responded well to treatment and the prescriber states that the member has shown improvement or the drug was effective, the member may receive authorization for one year; and
4. A quantity limit of 60 tablets for 30 days will apply.
5. Ampyra® may be used with other MS therapies.

Aubagio® (Teriflunomide) 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. All of the following will be required for initiation of treatment:
   a. Verification that female members are not pregnant and are currently using reliable contraception; and

b. Verification that the member has no active infection(s); and
c. Complete blood counts (CBC) and verification that levels are acceptable to the prescriber; and
d. Liver function tests and verification that levels are acceptable to the prescriber; and
e. Blood pressure measurement and verification that blood pressure is being monitored; and
f. Verification that the member does not have tuberculosis, or completion of standard medical treatment for patients with tuberculosis; and

4. Initial approvals of Aubagio® will be for six months, after which time all of the following will be required for further approval:
   a. Medication compliance; and
   b. Repeat CBC and verification that counts are acceptable to the prescriber; and
   c. Repeat liver function tests and verification that levels are acceptable to the prescriber; and
   d. Verification that female members are not pregnant and will continue using reliable contraception; and
   e. Verification that blood pressure and signs of renal failure are being monitored; and
5. Compliance will be checked for continued approval every six months; and
6. A quantity limit of 30 tablets per 30 days will apply.

Copaxone® (Glatiramer Acetate) 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. Approvals for the 40mg strength of Copaxone® will require a patient-specific, clinically significant reason why the member cannot use the 20mg strength; and
4. Approvals for the generic formulation of either strength of Copaxone®, including Glatopa®, will require a patient-specific, clinically significant reason why the member cannot use the brand formulation; and
5. Compliance will be checked for continued approval every six months.

Gilenya® (Fingolimod) Approval Criteria:

1. An FDA approved diagnosis of relapsing forms of Multiple Sclerosis (MS)* (*The manufacturer of Gilenya® has provided a supplemental rebate to remove the requirement of "at least one relapse in the previous 12 months, or transitioning from existing MS therapy"; however, Gilenya® will follow the original criteria if the manufacturer chooses not to participate in supplemental rebates.); 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 the 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.

Lemtrada® (Alemtuzumab) 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
    a. Lemtrada® must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. The prescriber must agree that the member will be monitored for two hours after each infusion; and
3. The prescriber must agree to monitor complete blood counts (CBC) with differential, serum creatinine levels, and urinalysis with urine counts at periodic intervals for 48 months after the last dose of Lemtrada®; and
4. The prescriber must agree that baseline and yearly skin examinations will be performed while the member is utilizing Lemtrada® therapy; and
5. Member, prescriber, pharmacy, and healthcare facility must all enroll in the Lemtrada® REMS Program and maintain enrollment throughout therapy.

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.

Tysabri® (Natalizumab) Approval Criteria:

1. An FDA approved diagnosis of Multiple Sclerosis (MS) or Crohn's disease; and
2. For a diagnosis of MS the following criteria will apply:
    a. Prescriber must be a neurologist or be an advanced care practitioner with a supervising prescriber that is a neurologist; and
    b. Approvals will not be granted for concurrent use with other disease-modifying therapies; and
3. For a diagnosis of Crohn's disease the following criteria will apply:
    a. Treatment with at least two different first-line therapeutic categories for Crohn's disease that have failed to yield an adequate clinical response, or a patient-specific, clinically significant reason why the member cannot use all available first- and second-line alternatives; and
4. Prescriber, infusion center, and member must enroll in the TOUCH Prescribing Program.
5. Compliance will be checked for continued approval every six months.

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.
6. Compliance will be checked for continued approval every six months.

Utilization of MS Medications: Calendar Year 2017

MS Medications Calendar Year Comparison: Medical Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Claims/ Member
2016	20	133	$796,979.40	$5,992.33	6.65
2017	20	114	$804,959.46	$7,061.05	5.7
% Change	**0.00%**	**-14.29%**	**1.00%**	**17.83%**	**-14.29%**
Change	**0**	**-19**	**$7,980.06**	**$1,068.72**	**-0.95**

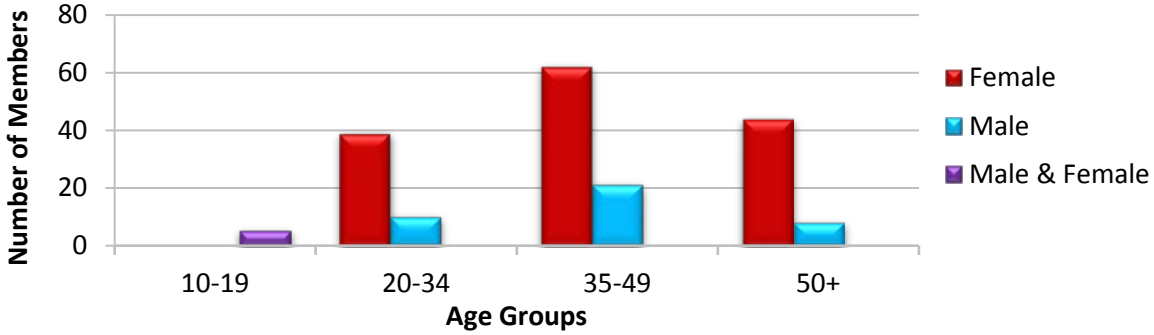
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

MS Medications Calendar Year Comparison: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	201	1,468	$8,687,150.43	$5,917.68	$203.76	43,688	42,635
2017	189	1,350	$7,911,212.78	$5,860.16	$202.97	39,773	38,978
% Change	**-6.00%**	**-8.00%**	**-8.90%**	**-1.00%**	**-0.40%**	**-9.00%**	**-8.60%**
Change	**-12**	**-118**	**-$775,937.65**	**-$57.52**	**-$0.79**	**-3,915**	**-3,657**

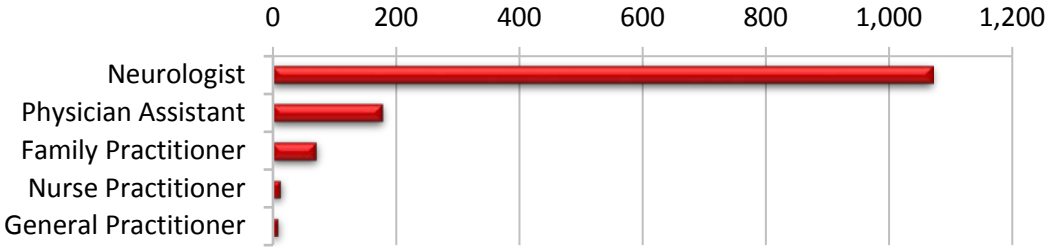
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Demographics of Members Utilizing MS Medications: Pharmacy Claims



- All members younger 21 years of age were verified to have a diagnosis of MS in their diagnosis history, and their MS therapies were prescribed by a specialist in neurology.

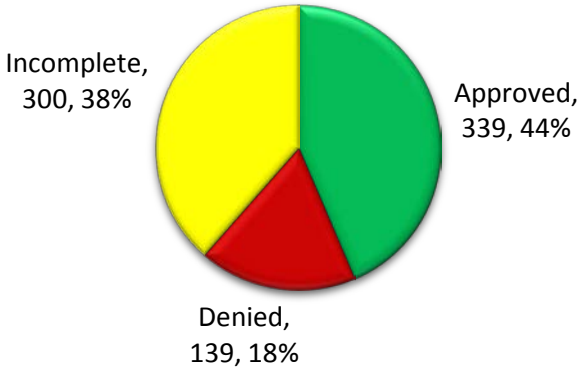
Top Prescriber Specialties of MS Medications by Number of Claims: Pharmacy Claims



Prior Authorization of MS Medications

There were 778 prior authorization requests submitted for 216 unique members for MS medications during calendar year 2017. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20]

Anticipated Patent Expiration(s):

- Gilenya® (fingolimod): June 2027
- Tecfidera® (dimethyl fumarate): February 2028
- Aubagio® (teriflunomide): February 2034

Generic Formulation Update(s):

- **April 2017:** A United States district court invalidated four of the five patents for Ampyra® (dalfampridine). The remaining patent is set to expire in mid-2018, paving the way for generic products in late 2018.
- **October 2017:** Mylan announced U.S. Food and Drug Administration (FDA) approval of generic formulations of Copaxone® (glatiramer acetate) 40mg and 20mg. Mylan is the first to receive FDA approval for the 40mg strength.
- **February 2018:** Momenta Pharmaceuticals announced the FDA approval and launch of a generic formulation of Copaxone® (glatiramer acetate) 40mg to be marketed as

Glatopa® 40mg. Glatopa® 20mg was previously approved as a generic to Copaxone® 20mg in April 2015.

Safety Update(s):

- **May 2017:** Roche is investigating one case of progressive multifocal leukoencephalopathy (PML) in a patient with MS after one treatment with Ocrevus™ (ocrelizumab). The patient, who was JC virus (JCV) positive, had been treated with Tysabri® (natalizumab) for 3 years prior to treatment with ocrelizumab.
- **March 2018:** AbbVie and Biogen announced they are voluntarily taking Zinbryta® (daclizumab) off the market worldwide because of reports of severe liver damage and serious inflammatory brain disorders, including encephalitis and meningoencephalitis.

New FDA Approval(s):

- **March 2017:** The FDA approved Ocrevus™ (ocrelizumab) for the treatment of adults with relapsing (RMS) or primary progressive (PPMS) forms of MS. Ocrelizumab is the first drug approved by the FDA for PPMS. After initial loading doses, ocrelizumab is administered every six months via an intravenous (IV) infusion by a health care professional.

Pipeline Update(s):

- **CHS-131:** In April 2017, *Neurology* published results of a Phase 2b study of CHS-131, an investigational, once daily, oral therapy in patients with RMS. New gadolinium contrasting lesions were significantly lower (52%) than placebo (P=0.003) after six months of treatment with 3mg of CHS-131. Treatment with CHS-131 was generally well-tolerated.
- **Cladribine:** In May 2017, researchers reported that patients with RMS saw continued benefits in new lesion development with long-term use of cladribine tablets, a chemotherapy agent. Approximately 73% of 98 patients were free of new lesions after starting treatment with 3.5mg/kg cladribine and then switching to placebo (P=0.001 vs patients always on cladribine; P=0.012 vs those switched to cladribine); the rate of infections was similar among treatment groups. Researchers acknowledged a depletion of immune cells for longer than a year after discontinuation of cladribine. Cladribine was rejected for an MS indication by the FDA in March 2011. As a result, Merck halted its development program in June 2011, but in July 2016 submitted a marketing authorization package with the European Medicines Agency.
- **Ibudilast:** In October 2017, results were released of a Phase 2b trial of ibudilast, an oral, phosphodiesterase-4 and -10 inhibitor and macrophage migration inhibitory factor inhibitor. Secondary progressive MS (SPMS) and PPMS patients treated with ibudilast had a 48% reduction in whole brain atrophy by 96 weeks. This reduction was significantly greater than that seen in patients receiving matching placebo.
- **Laquinimod:** Laquinimod, an oral small molecule being developed by Teva Pharmaceuticals to treat MS and Huntington's Disease (HD) failed to show benefit in the CONERTO trial for RMS. In December 2017, Teva announced laquinimod failed to meet primary and secondary endpoints in the treatment of PPMS. The drug did, however, reduce new T2 lesions. Laquinimod is currently in a Phase 2 trial in patients with HD with results expected mid-2018.

- **Opicinumab:** In October 2017, Biogen announced opicinumab, an anti-LINGO antibody being developed to promote re-myelination in patients with MS, will be tested in a Phase 2b clinical trial as an add-on therapy in patients with RMS. Opicinumab failed to reach its primary goal of improving disability in the Phase 2 SYNERGY trial in 2016. SYNERGY included patients with SPMS and several different doses of opicinumab; Biogen believes information obtained from SYNERGY will help determine the most effective dose and which patients will benefit from opicinumab therapy.
- **Ozanimod:** In October 2017, Celgene Corporation announced detailed results from a Phase 3 trial of ozanimod, an oral sphingosine 1-phosphate 1 (S1PR1) and 5 (S1PR5) receptor modulator, versus Avonex® (interferon beta-1a) in patients with RMS. A significant reduction in annualized relapse rate (ARR) was demonstrated for ozanimod 1mg (ARR=0.18, P<0.0001) and for ozanimod 0.5mg (ARR=0.24, P=0.0013) compared with Avonex® (ARR=0.35) over an average of 13.6 months of treatment. In February 2018, Celgene received a "Refusal to File" letter from the FDA regarding a New Drug Application (NDA) for onzanimod for the treatment of patients with RMS. In its initial review, the FDA found the nonclinical and clinical pharmacology sections in the NDA deficient to permit a complete review.
- **Siponimod:** In October 2017, results of the Phase 3 EXPAND study were presented evaluating the efficacy of siponimod in SPMS. Siponimod reduced the number of gadolinium enhancing lesions by 86.6% after one year. Additionally, siponimod-treated patients experienced 39% less brain volume loss compared to placebo.
- **Ublituximab:** In October 2017, TG Therapeutics announced positive interim trial results of a Phase 2 trial of ublituximab in RMS patients. Researchers indicated that six months of treatment with ublituximab nearly eradicated a type of immune B-cell believed to be involved in MS.

Other News:

- **October 2017:** The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) presented a summary of guidelines regarding the use of disease-modifying therapies in MS. The American Academy of Neurology (AAN) is also formulating guidelines on the same topic; no timeline for release of those guidelines is currently available. The ECTRIMS/EAN guidelines cover the treatment of adults with MS or clinically isolated syndrome (CIS), the monitoring of treatment response, the stopping and switching of treatment strategies, and treatment in special situations, such as pregnancy.
- **December 2017:** IQuity released a blood test that detects serum neurofilament light chain (NF-L), a protein that is released following damage to cell axons. Serum NF-L may offer an alternative to magnetic resonance imaging (MRI) scans in helping diagnose and track MS progression. A study of NF-L in cerebral spinal fluid (CSF) revealed that levels correlated with disease activity in 85% of participants over two years.
- **January 2018:** The FDA denied a request for use of a qualified health claim that taking vitamin D may reduce the risk for MS in healthy people. The FDA reviewed 85 publications submitted in addition to an independent literature review and determined that scientific conclusions could not be drawn regarding the relationship between vitamin D intake and MS risk.

- **January 2018:** A Swedish registry study of 494 patients found that use of Rituxan® (rituximab) for first-line treatment of RMS showed significantly less drug discontinuation (0.03 vs. 0.29 to 0.53), fewer clinical relapses, and less neuroradiologic disease activity than injectable interferon, Copaxone® (glatiramer acetate), or Tecfidera® (dimethyl fumarate) and showed borderline significance over Gilenya® (fingolimod) and Tysabri® (natalizumab). Rituximab, used off-label for MS, has a similar mechanism of action to Ocrevus™ (ocrelizumab); both target CD20 immune B-cells instead of T-cells.

Institute for Clinical Effectiveness and Economic Review (ICER): Disease-Modifying Therapies for MS[21]

In March 2017, the Institute for Clinical Effectiveness and Economic Review (ICER) released a final evidence report regarding the effectiveness and value of disease modifying therapies (DMTs) for RMS and PPMS. ICER is an independent, non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. The following is a table representation of net cost per relapse avoided for DMTs compared to supportive care for RMS. DMTs are divided into tiers based on net cost in order to be viewed easily and do not reflect specific net costs or ratios. It is important to note that while a product may have a low net cost per relapse avoided; disability progression, MRI lesion data, safety information, and guideline recommendations are not included. Products are listed alphabetically by brand name; order within a tier does not reflect net costs.

Lowest Net Cost Per Relapse Avoided	→	→	→	Highest Net Cost Per Relapse Avoided
• Avonex® (interferon beta 1a) • Copaxone® 20mg (glatiramer)	• Betaseron® (interferon beta 1b) • Lemtrada® (alemtuzumab) • Rebif® 44mcg (interferon beta 1a)	• Gilenya® (fingolimod) • Tysabri® (natalizumab)	• Aubagio® 14mg (teriflunomide) • Glatopa® 20mg (glatiramer) • Plegridy® (interferon beta 1a) • Tecfidera® (dimethyl fumarate)	• Extavia® (interferon beta 1b) • Zinbryta® (daclizumab)

After review of the evidence, a panel of independent medical evidence experts with a mix of practicing clinicians deliberated and voted on key questions related to the systematic review of the clinical evidence and economic analysis. The panel was split (7 vs. 7) when asked if the evidence was adequate to determine that the net health benefit of Gileyna® (fingolimod) is greater than that of Aubagio® (teriflunomide 14mg). The panel did not find evidence (12 vs. 2) to determine a superior health benefit of Tecfidera® (dimethyl fumarate) to teriflunomide 14mg or to distinguish the net health benefit between dimethyl fumarate and fingolimod.

Ocrevus™ (Ocrelizumab) Product Summary[22]

Indication(s): Ocrevus™ (ocrelizumab) is a CD20-directed cytolytic antibody indicated for the treatment of patients with RMS or PPMS.

Dosing:

- Ocrevus™ is supplied as 300mg/10mL single-dose vials intended for IV infusion.
- The recommended initial dosage is 300mg via IV infusion over a minimum period of 2.5 hours, followed two weeks later by a second 300mg IV infusion. Recommended maintenance dosing is a single 600mg IV infusion over a minimum period of 3.5 hours every six months.
- Ocrelizumab should be administered under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions. Patients should be observed for at least one hour after the completion of the infusion.
- Patients should be pre-medicated with 100mg of methylprednisolone (or an equivalent corticosteroid) and an antihistamine (e.g., diphenhydramine) approximately 30 minutes prior to each ocrelizumab infusion to reduce the frequency and severity of infusion reactions.
- Prior to every infusion, patients should be assessed for active infection. In the case of active infection, infusion of ocrelizumab should be delayed until the infection resolves.
- Prior to initiating ocrelizumab, hepatitis B virus (HBV) screening should be performed. Ocrelizumab is contraindicated in patients with active HBV.
- Because vaccination with live-attenuated or live vaccines is not recommended during treatment and after discontinuation until B-cell repletion, all necessary immunizations should be administered according to immunization guidelines at least six weeks prior to initiation of ocrelizumab.

Contraindication(s):

- Active HBV infection
- A history of life-threatening infusion reaction to ocrelizumab

Warnings and Precautions:

- Infusion Reactions: Ocrelizumab can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia. In clinical trials, the incidence of infusion reactions in patients who received pre-medication to reduce the risk of infusion reactions prior to each infusion was 34% to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of patients experienced infusion reactions that were serious, some requiring hospitalization.
- Infections: A higher proportion of ocrelizumab-treated patients experienced infections (e.g., respiratory tract infections, herpes infections), compared to patients taking interferon β-1a or placebo. In RMS trials, 58% of ocrelizumab-treated patients experienced one or more infections compared to 52% of interferon β-1a-treated patients.

- Malignancies: An increased risk of malignancy with ocrelizumab may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in ocrelizumab-treated patients. Breast cancer occurred in 6 of 781 females treated with ocrelizumab and none of 668 females treated with interferon β-1a or placebo. Patients should follow standard breast cancer screening guidelines.

Adverse Reactions: The most common adverse reactions reported with ocrelizumab treatment (incidence ≥10%) during clinical trials included the following: upper respiratory tract infection, infusion reactions, skin infections, and lower respiratory tract infection.

Drug Interactions:

- Immunosuppressive or Immune-Modulating Therapies: The concomitant use of ocrelizumab and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression.

Use in Special Populations:

- Pregnancy: There are no adequate data on the developmental risk associated with the use of ocrelizumab in pregnant women. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other anti-CD20 antibodies during pregnancy. IV administration of ocrelizumab to pregnant monkeys at doses 2 and 10 times the maximum recommended human dose led to increased perinatal deaths, renal toxicity, lymphoid follicle formation in the bone marrow, and severe decreases in circulating B-lymphocytes in neonates.
- Lactation: There are no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys.
- Females of Reproductive Potential: Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
- Pediatric Use: The safety and effectiveness of ocrelizumab in patients younger than 18 years of age have not been established.
- Geriatric Use: Clinical studies did not include a sufficient number of patients 65 years of age and older to determine whether they respond differently from younger patients.

Efficacy: The efficacy of ocrelizumab was demonstrated in two randomized, double-blind, active comparator-controlled clinical trials in patients with RMS treated for 96 weeks (Study 1 and Study 2). Patients were randomized to ocrelizumab 600mg or interferon β-1a 44mcg. Both studies included patients who had experienced at least one relapse within the prior year, or two relapses within the prior two years, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Patients with PPMS were excluded. Neurological evaluations were performed every 12 weeks and at the time of a suspected relapse. The primary outcome of both Study 1 and Study 2 was the annualized relapse rate (ARR). An additional outcome measure included the proportion of patients with confirmed disability progression. Progression of disability was defined as an increase of 1 point or more from the baseline EDSS score attributable to MS when the baseline EDSS score was 5.5 or less, or 0.5 points or more when

the baseline EDSS score was above 5.5. Results of Study 1 and 2 are presented in the following table:

Endpoints	Study 1		Study 2	
	Ocrelizumab (N=410)	Interferon β-1a (N=411)	Ocrelizumab (N=417)	Interferon β-1a (N=418)
ARR	0.156	0.292	0.155	0.290
ARR Relative Reduction	46%; P<0.0001		47%; P<0.0001	
Proportion Relapse-Free	83%	71%	82%	72%
Proportion of Pts w/ Disability Progression (Risk Reduction)*	9.8% ocrelizumab vs. 15.2% interferon β-1a (40%; P=0.0006)			

ARR = annualized relapse rate; Pts = patients; w/ = with
*Pooled analysis (data prospectively pooled from Study 1 and Study 2).

The safety and efficacy of ocrelizumab were also evaluated in a randomized, double-blind, placebo-controlled clinical trial in patients with PPMS (Study 3). Patients were randomized 2:1 to receive either ocrelizumab (N=488) or placebo (N=244). Selection criteria required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity findings. Neurological assessments were conducted every 12 weeks. The primary outcome was the time to onset of disability progression attributable to MS confirmed to be present at the next neurological assessment at least 12 weeks later. Disability progression was defined similar to Study 1 and 2. In Study 3, confirmed disability progression also was deemed to have occurred if patients who had onset of disability progression discontinued participation in the study before the next assessment. The time to onset of disability progression confirmed at 12 weeks after onset was significantly longer for ocrelizumab-treated patients than for placebo-treated patients [proportion of patients with 12-week disability progression: ocrelizumab 32.9% vs placebo 39.3%; risk reduction: 24% (P=0.0321)].

Cost:

Medication	Cost Per Dose*	Cost Per Year+
Ocrevus™ (ocrelizumab)	**$32,500.00**	**$65,000.00**

*Cost based on Wholesale Acquisition Cost (WAC) and does not reflect rebated price or net cost.
+Cost per year based on maintenance dosing after loading dosing complete.

Recommendations

The College of Pharmacy recommends the prior authorization of Ocrevus™ (ocrelizumab) with the following criteria:

Ocrevus™ (Ocrelizumab) Approval Criteria:

1. An FDA approved diagnosis of relapsing or primary progressive forms of Multiple Sclerosis (MS); and
2. Approvals will not be granted for concurrent use with other disease modifying therapies; and
3. Ocrevus™ must be administered in a setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. The prescriber must agree that the member will be monitored for one hour after each infusion; and

4. Prescriber must verify hepatitis B virus (HBV) testing has been performed prior to initiating Ocrevus™ therapy and member does not have active HBV; and
5. Verification from the prescriber that member has no active infection(s); and
6. Verification from the prescriber that female members are not currently pregnant and will use contraception while receiving Ocrevus™ therapy and for six months after the last infusion of Ocrevus™; and
7. Compliance will be checked for continued approval.

Utilization Details of MS Medications: Calendar Year 2017

Pharmacy Claims: Calendar Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
INTERFERON BETA-1A PRODUCTS					
AVONEX PEN KIT 30MCG/0.5ML	48	8	$290,035.05	6	$6,042.40
REBIF REBIDO INJ 44MCG/0.5ML	43	6	$290,253.56	7.17	$6,750.08
REBIF INJ 22MCG/0.5ML	35	3	$163,749.99	11.67	$4,678.57
AVONEX SYR KIT 30MCG/0.5ML	34	6	$204,674.35	5.67	$6,019.83
REBIF SYR INJ 44MCG/0.5ML	21	4	$134,818.69	5.25	$6,419.94
REBIF REBIDO INJ TITRATN	3	3	$20,152.44	1	$6,717.48
REBIF REBIDO INJ 22MCG/0.5ML	1	1	$6,635.72	1	$6,635.72
REBIF TITRTN INJ PACK	1	1	$6,639.72	1	$6,639.72
SUBTOTAL	**186**	**25**	**$1,116,959.52**	**7.44**	**$6,005.16**
INTERFERON BETA-1B PRODUCTS					
BETASERON INJ 0.3MG	97	18	$619,110.72	5.39	$6,382.58
SUBTOTAL	**97**	**18**	**$619,110.72**	**5.39**	**$6,382.58**
PEGINTERFERON BETA-1A PRODUCTS					
PLEGRIDY INJ 125MCG/0.5ML	23	5	$144,286.65	4.6	$6,273.33
PLEGRIDY INJ STARTER	2	2	$12,587.10	1	$6,293.55
SUBTOTAL	**25**	**5**	**$156,873.75**	**5**	**$6,274.95**
DALFAMPRIDINE PRODUCTS					
AMPYRA TAB 10MG	142	24	$313,532.32	5.92	$2,207.97
SUBTOTAL	**142**	**24**	**$313,532.32**	**5.92**	**$2,207.97**
TERIFLUNOMIDE PRODUCTS					
AUBAGIO TAB 14MG	102	21	$606,724.86	4.86	$5,948.28
AUBAGIO TAB 7MG	25	3	$148,866.35	8.33	$5,954.65
SUBTOTAL	**127**	**22**	**$755,591.21**	**5.77**	**$5,949.54**
GLATIRAMER ACETATE PRODUCTS					
COPAXONE INJ 40MG/ML	220	38	$1,211,581.13	5.79	$5,507.19
COPAXONE INJ 20MG/ML	134	27	$915,626.34	4.96	$6,833.03
GLATIRAMER INJ 40MG/ML	13	7	$65,538.90	1.86	$5,041.45
SUBTOTAL	**367**	**64**	**$2,192,746.37**	**5.73**	**$5,974.79**

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
FINGOLIMOD PRODUCTS					
GILENYA CAP 0.5MG	149	19	$1,033,392.87	7.84	$6,935.52
SUBTOTAL	**149**	**19**	**$1,033,392.87**	**7.84**	**$6,935.52**
DIMETHYL FUMARATE PRODUCTS					
TECFIDERA CAP 240MG	188	36	$1,280,309.83	5.22	$6,810.16
TECFIDERA MIS STARTER	18	18	$122,894.90	1	$6,827.49
TECFIDERA CAP 120MG	2	1	$12,752.30	2	$6,376.15
SUBTOTAL	**208**	**44**	**$1,415,957.03**	**4.73**	**$6,807.49**
NATALIZUMAB PRODUCTS					
TYSABRI INJ 300/15ML	26	4	$142,040.52	6.5	$5,463.10
SUBTOTAL	**26**	**4**	**$142,040.52**	**6.5**	**$5,463.10**
DACLIZUMAB PRODUCTS					
ZINBRYTA INJ 150MG/ML	23	4	$165,008.47	5.75	$7,174.28
SUBTOTAL	**23**	**4**	**$165,008.47**	**5.75**	**$7,174.28**
TOTAL	**1,350**	**189***	**$7,911,212.78**	**7.14**	**$5,860.16**

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

Medical Claims: Calendar Year 2017

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
ALEMTUZUMAB PRODUCTS					
LEMTRADA 10MG/1ML (J0202)	10	2	$210,334.68	5	$21,033.47
NATALIZUMAB PRODUCTS					
TYSABRI INJ 300MG/15ML (J2323)	104	18	$594,624.78	5.78	$5,717.55
TOTAL	**114**	**20***	**$804,959.46**	**5.7**	**$7,061.05**

*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 12/2017. Last accessed 01/26/2018.
[2] Helfand C. Court nixes Acorda patents, teeing up Ampyra generics—and potential cost cuts, analyst says. *FiercePharma*. Available online at: https://www.fiercepharma.com/pharma/court-nixes-4-acorda-patents-teeing-up-amprya-generics-for-2018. Issued 04/03/2017. Last accessed 01/26/2018.
[3] Hughes S. PML Reported in Patient Receiving Ocrelizumab. *Medscape*. Available online at: https://www.medscape.com/viewarticle/880654. Issued 05/25/2017. Last accessed 01/30/2018.
[4] Brooks M. MS Drug Daclizumab (Zinbryta) Pulled From the Market. *Medscape*. Available online at: https://www.medscape.com/viewarticle/893352. Issued 03/02/2018. Last accessed 03/05/2018.
[5] Momenta Pharmaceuticals, Inc. Momenta Pharmaceuticals Announces FDA Approval and Launch of Glatopa® (glatiramer acetate injection) 40 mg/mL. *Globe Newswire*. Available online at: http://ir.momentapharma.com/news-releases/news-release-details/momenta-pharmaceuticals-announces-fda-approval-and-launch. Issued 02/13/2018. Last accessed 02/19/2018.
[6] FDA. FDA approves new drug to treat multiple sclerosis. Available online at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm549325.htm. Issued 03/29/2017. Last accessed 01/30/2018.
[7] Mylan. Mylan Announces U.S. FDA Approval of First Generic for Copaxone® 40 mg/mL 3-Times-a-Week and May Be Eligible for 180-Day Exclusivity. Available online at: http://newsroom.mylan.com/2017-10-03-Mylan-Announces-U-S-FDA-Approval-of-First-Generic-for-Copaxone-R-40-mg-mL-3-Times-a-Week-and-May-Be-Eligible-for-180-Day-Exclusivity. Issued 10/03/2017. Last accessed 01/31/2018.
[8] Weinstein D, Boyko A, Pugliese L, et al. CHS-131, A Novel Once Daily Oral Treatment, Decreased Lesion Burden of Patients with Relapsing-Remitting Course of Multiple Sclerosis (RRMS) in a Randomized, Double-blind, Phase 2b, Multicenter Study (S50.002). *Neurology* 2017; 88(16):S50-002.
[9] Susman E. CMSC: Chemo Drug Offers Durable Effects in MS. *Medpage Today*. Available online at: https://www.medpagetoday.com/mastery-of-medicine/neurology-mastery-in-ms/65646. Issued 05/28/2017. Last accessed 01/31/2018.
[10] Brauser D. Ibudilast 'Impressive' for Progressive MS in Phase 2 Trial. *Medscape*. Available online at: https://www.medscape.com/viewarticle/887774. Issued 10/30/2017. Last accessed 02/08/2018.
[11] Taylor P. Active Bio and Teva's laquinimod strikes out again, this time in progressive MS. *FierceBiotech*. Available online at: https://www.fiercebiotech.com/biotech/active-bio-and-teva-s-laquinimod-strikes-out-again-time-progressive-ms. Issued 12/01/2017. Last accessed 01/30/2018.
[12] Silva P. #MSParis2017 – New Trial of Opicinumab, an Anti-LINGO Antibody, in MS Builds on Lessons Learned, Biogen Says. *Multiple Sclerosis News Today*. Available online at: https://multiplesclerosisnewstoday.com/2017/10/25/msparis2017-interview-with-biogen-focused-on-opicinumab-an-anti-lingo-antibody/. Issued 10/25/2017. Last accessed 02/08/2018.
[13] Celegene Corporation. Efficacy and Safety Results from First Phase III Trial of Oral Ozanimod (SUNBEAM™) Versus an Active Comparator in Relapsing Multiple Sclerosis Presented at MSParis2017 - 7th Joint ECTRIMS - ACTRIMS Meeting. *Business Wire*. Available online at: http://ir.celgene.com/releasedetail.cfm?releaseid=1045797. Issued 10/27/2017. Last accessed 02/08/2018.
[14] Brooks M. FDA Rejects Celgene's NDA for Ozanimod in MS. *Medscape*. Available online at: https://www.medscape.com/viewarticle/893269. Issued 02/28/2018. Last accessed 03/05/2018.
[15] Kegel M. Siponimod Leads to Dramatic Drop in MS Lesions, Phase 3 Trial Shows. *Multiple Sclerosis News Today*. Available online at: https://multiplesclerosisnewstoday.com/2017/10/26/msparis2017-trial-shows-siponimod-leads-to-major-drop-in-ms-brain-and-spinal-cord-lesions/. Issued 10/26/2017. Last accessed 02/01/2018.
[16] Kegel M. #MSParis2017 – TG Therapeutics' Ublituximab Depletes Harmful B-cells and Lowers MRI Lesions, Trial Shows. *Multiple Sclerosis News Today*. Available online at: https://multiplesclerosisnewstoday.com/2017/10/19/phase-2-trial-shows-that-ublituximab-depletes-b-cells-and-lowers-mri-lesions/. Issued 10/19/2017. Last accessed 02/08/2018.
[17] Hughes S. European MS Treatment Guidelines Released. *Medscape*. Available online at: https://www.medscape.com/viewarticle/887730. Issued 10/27/2017. Last accessed 02/01/2018.
[18] Craven C. New Blood Test Could Help with MS Prognosis. *Healthline®*. Available online at: https://www.healthline.com/health-news/new-blood-test-help-with-ms-prognosis#1. Issued 12/09/2017. Last accessed 02/01/2018.
[19] George J, Wilson FP. First-Line Rituximab Bests Other MS Drugs In Sweden. *Medpage Today*. Available online at: https://www.medpagetoday.com/neurology/multiplesclerosis/70393. Issued 01/09/2018. Last accessed 02/01/2018.
[20] Jeffrey S. FDA Denies Health Claim for Vitamin D to Prevent MS. *Medscape*. Available online at: https://www.medscape.com/viewarticle/891307. Issued 01/15/2018. Last accessed 01/29/2018.
[21] Institute for Clinical and Economic Review (ICER). Disease-Modifying Therapies for Relapsing-Remitting and Primary-Progressive Multiple Sclerosis: Effectiveness and Value. Available online at: https://icer-review.org/wp-content/uploads/2016/08/CTAF_MS_Final_Report_030617.pdf. Issued 03/06/2017. Last accessed 01/29/2018.
[22] Ocrevus™ Prescribing Information. Genentech, Inc. Available online at: https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Last revised 03/2017. Last accessed 01/29/2018.

Appendix N

Calendar Year 2017 Annual Review of Alpha$_1$-Proteinase Inhibitors and 30-Day Notice to Prior Authorize Prolastin®-C Liquid [Alpha$_1$-Proteinase Inhibitor (Human)]

Oklahoma Health Care Authority
March 2018

Alpha$_1$-Antitrypsin Deficiency[1,2,3]

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 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. AAT is a protease inhibitor of the proteolytic enzyme elastase. 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.

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 of AATD, though many patients initially have symptoms of cough, sputum production, or wheezing. Treatment involves smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen when indicated, physical rehabilitation, and intravenous (IV) augmentation therapy with AAT. The goal of AAT augmentation is to slow the progression of emphysema. There are currently five pooled human plasma AAT products available: Aralast NP™, Glassia®, Prolastin®-C, Zemaira®, and most recently approved by the U.S. Food and Drug Administration (FDA), Prolastin®-C Liquid. These products work by restoring serum and alveolar AAT concentrations to protective levels, thereby restoring the balance between neutrophil elastase in the lung, which destroys elastin, and the elastase inhibitor AAT, which protects against proteolytic degradation of elastin.

Current Prior Authorization Criteria

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 of Alpha$_1$-Proteinase Inhibitors: Calendar Year 2017

Alpha$_1$-Proteinase Inhibitors Calendar Year Comparison: Pharmacy Claims

Calendar Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2016	10	76	$623,160.05	$8,199.47	$292.84	1,330,836	2,128
2017	11	84	$789,544.87	$9,399.34	$338.72	1,625,763	2,331
% Change	**10.00%**	**10.50%**	**26.70%**	**14.60%**	**15.70%**	**22.20%**	**9.50%**
Change	**1**	**8**	**$166,384.82**	**$1,199.87**	**$45.88**	**294,927**	**203**

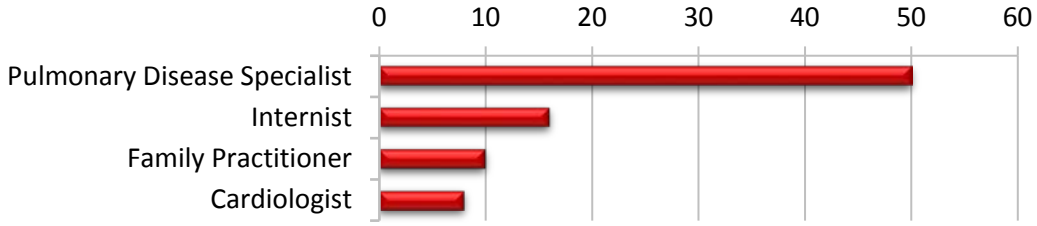
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- There were no paid medical claims for alpha$_1$-proteinase inhibitors during calendar year 2017.

Demographics of Members Utilizing Alpha$_1$-Proteinase Inhibitors

- Due to the small number of members utilizing alpha$_1$-proteinase inhibitors, detailed demographic information could not be provided.

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



Prior Authorization of Alpha$_1$-Proteinase Inhibitors

There were 11 prior authorization requests submitted for alpha$_1$-proteinase inhibitors during calendar year 2017, all of which were approved. Prior authorization for the alpha$_1$-proteinase inhibitors was implemented on September 1, 2017. Members that were on these medications at the time of implementation were grandfathered and given pre-emptive approvals as reflected, in part, in the 100% approval rating.

Market News and Updates[4,5,6]

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

- **September 2017:** Prolastin®-C Liquid [alpha$_1$-proteinase inhibitor (human)]

News:

- **June 2017:** Kamada Ltd., a plasma-derived protein therapeutics company focused on orphan indications, announced the receipt of an undisclosed additional milestone payment under the supply and distribution agreement with Shire for Glassia®, Kamada's IV AAT. The milestone payment was triggered by Shire achieving a sales milestone for Glassia® in the United States. Shire is Kamada's strategic partner for the exclusive supply and distribution of Glassia® for all IV indications in the United States, Canada, Australia, and New Zealand. Under their current agreement, Kamada's minimum revenue for Glassia® for the years 2017 to 2020 will reach approximately $237 million, and may be expanded to up to $288 million during that period.
- **July 2017:** Kamada Ltd. announced it has submitted to the FDA for review a proposed pivotal Phase 3 protocol for its proprietary inhaled AAT therapy for the treatment of AATD. The study is intended to treat AATD subjects with inhaled AAT at a dose of 80mg once daily for a period of two years, with a placebo arm at a 2:1 ratio and cross over to the treatment arm following a period of 12 months. In parallel, a concurrent AAT IV arm will be evaluated for two years. The study is planned to include approximately 200 to 300 patients, and is expected to measure lung function as a primary endpoint and lung density as a secondary endpoint.
- **September 2017:** Grifols announced the approval from the FDA for a liquid formulation of its AAT (Prolastin®-C Liquid) as a replacement therapy to treat AATD. As a ready-to-infuse liquid formulation, Prolastin®-C Liquid provides several advantages for both patients and healthcare professionals since it requires less preparation time as compared to the lyophilized product and less volume for infusion (1g in 20mL) as compared to the liquid product of a competitor. Previously, Prolastin®-C had only been offered in a lyophilized formulation.

Prolastin®-C Liquid [Alpha$_1$-Proteinase Inhibitor (Human)] Product Summary[7]

Indication(s): Prolastin®-C Liquid is an alpha$_1$-proteinase inhibitor (human) (alpha$_1$-PI) indicated for chronic augmentation and maintenance therapy in adults with clinical evidence of emphysema due to severe AATD.

- Limitations of Use:
  - The effect of augmentation therapy with any alpha$_1$-PI, including Prolastin®-C Liquid, on pulmonary exacerbations and on the progression of emphysema in alpha$_1$-PI deficiency has not been conclusively demonstrated in randomized, controlled clinical trials.
  - Clinical data demonstrating the long-term effects of chronic augmentation or maintenance therapy with Prolastin®-C Liquid are not available.
  - Prolastin®-C Liquid is not indicated as therapy for lung disease in patients in whom severe alpha$_1$-PI deficiency has not been established.

Dosing:

- Prolastin®-C Liquid is supplied in a 1,000mg (approximate) single-use vial containing 20mL of solution for IV infusion. The actual amount of functionally active alpha$_1$-PI in milligrams is printed on the vial label and carton.
- Prolastin®-C Liquid should be refrigerated at 2 to 8°C (36 to 46°F) for the period indicated by the expiration date on its label. It may be stored at room temperatures not

exceeding 25°C (77°F) for up to one month, after which the product must be used or immediately discarded.

- The solution is clear, colorless or pale yellow, or pale green, and may contain a few protein particles.
- The recommended dosage of Prolastin®-C Liquid is 60mg/kg given IV once per week. It is recommended to infuse at 0.08mL/kg/min as determined by patient response and comfort. Each infusion takes approximately 15 minutes.
- Prior to administration, the required amount of Prolastin®-C Liquid is pooled from several vials into an empty, sterile IV solution container using aseptic technique. It should be administered with a sterile 15 micron in-line filter.

Contraindication(s):

- IgA deficient patients with antibodies against IgA, due to the risk of severe hypersensitivity
- Patients with a history of anaphylaxis or other severe systemic reaction(s) to $alpha_1$-PI

Warnings and Precautions:

- Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, may occur. Patients should be carefully monitored throughout the infusion. Early signs and symptoms of hypersensitivity reactions may include: pruritus; generalized urticaria; flushing; swollen lips, tongue, or uvula; wheezing; tightness of the chest; dyspnea; hypotension; and syncope. If these symptoms occur, it is recommended to stop the infusion and begin appropriate treatment.
- Transmissible Infectious Agents: Prolastin®-C Liquid is made from human plasma, and may carry a risk of transmitting infectious agents including viruses, and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent. This also applies to unknown or emerging viruses and other pathogens. The risk of transmission of infectious agents has been reduced by screening plasma donors for prior exposure to certain infectious agents, by testing for the presence of certain viral infections, and by including steps in the manufacturing process with the demonstrated capacity to inactivate and/or remove certain infectious agents. Despite these measures, this product may still potentially transmit disease.

Adverse Reactions: The most common adverse reactions observed at a rate of >5% in subjects receiving Prolastin®-C Liquid were diarrhea and fatigue.

Use in Specific Populations:

- Pregnancy: There are no data with Prolastin®-C Liquid use in pregnant women to inform a drug-associated risk. Animal reproduction studies have not been conducted. It is not known whether it can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Prolastin®-C Liquid should be given to a pregnant woman only if clearly needed.
- Lactation: There is no information regarding the presence of Prolastin®-C Liquid in human milk, the effects on the breastfed infant, or the effects on milk production.
- Pediatric Use: The safety and effectiveness of Prolastin®-C Liquid in the pediatric population have not been established.

- Geriatric Use: Clinical studies of Prolastin®-C Liquid did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

Efficacy: The clinical efficacy of Prolastin®-C Liquid in influencing the course of pulmonary emphysema or pulmonary exacerbations has not been demonstrated in adequately powered, randomized, controlled clinical trials.

- The efficacy data for Prolastin®-C Liquid is based on the predecessor product Prolastin®-C.
- A pharmacokinetic (PK) study was performed to determine bioequivalence between the two products. The PK study was a randomized, double-blind, crossover trial comparing Prolastin®-C Liquid to Prolastin®-C and was conducted in 32 adult subjects 44 to 71 years of age with severe AATD. Sixteen subjects were randomized to each treatment sequence. All but one subject had the PiZZ genotype and the remaining subject was PiSZ. Twenty-eight subjects had received prior Alpha$_1$-PI augmentation therapy and 4 subjects were naïve to Alpha$_1$-PI augmentation therapy. Study subjects were randomly assigned to receive either 60mg/kg of Prolastin®-C Liquid or Prolastin®-C weekly by IV infusion during the first 8-week treatment period. Following the last dose in the first 8-week treatment period, subjects underwent serial blood sampling for PK analysis and then crossed over to the alternate treatment for the second 8-week treatment period. Following the last treatment in the second 8-week treatment period, subjects underwent serial blood sampling for PK analysis. In addition, blood samples were drawn for trough levels before infusion at weeks 6, 7, 8, and 9, as well as before infusion at weeks 14, 15, 16, and 17. A final PK sample was drawn at week 20 (4 weeks after the last dose) to correct for endogenous alpha$_1$-PI levels. The PK parameters of alpha$_1$-PI in plasma showed bioequivalence between Prolastin®-C Liquid treatment and Prolastin®-C treatment.

Cost Comparison:

Medication	Cost Per mg	Cost Per Month$^{\Delta}$	Cost Per Year$^{\Delta}$
Prolastin®-C Liquid	**$0.50**	**$9,000.00**	**$108,000.00**
Prolastin®-C	$0.50	$9,000.00	$108,000.00
Aralast NP™	$0.53	$9,540.00	$114,480.00
Glassia®	$0.53	$9,540.00	$114,480.00
Zemaira®	$0.52	$9,360.00	$112,320.00

Costs do 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 weekly dosing of 60mg/kg for a 75kg patient.

Recommendations

The College of Pharmacy recommends the prior authorization of Prolastin®-C Liquid [alpha$_1$-proteinase inhibitor (human)] with the following criteria:

Prolastin®-C Liquid [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™, Glassia®, and Zemaira®; 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.

The College of Pharmacy also recommends adding Zemaira® to the current Aralast NP™ and Glassia® criteria based on net cost after rebates.

Aralast NP™, ~~and~~ Glassia®, and 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; 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 2017

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	PERCENT COST
PROLASTIN-C INJ 1000MG	81	10	$768,700.81	$342.10	$9,490.13	97.36%
ARALAST NP INJ 1000MG	2	1	$14,651.98	$261.64	$7,325.99	1.86%
ARALAST NP INJ 500MG	1	1	$6,192.08	$221.15	$6,192.08	0.78%
TOTAL	**84**	**11***	**$789,544.87**	**$338.72**	**$9,399.34**	**100.00%**

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

[1] Stoller JK. Clinical manifestations, diagnosis, and natural history of alpha$_1$-antitrypsin deficiency. *Up-To-Date®*. 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 01/16/2018. Last accessed 02/17/2018.

[2] Izaguirre-Anariba DE. Alpha$_1$-Antitrypsin Deficiency Clinical Presentation. *Medscape*. Available online at: http://emedicine.medscape.com/article/295686-clinical#b5. Last revised 02/10/2017. Last accessed 02/17/2018.

[3] Stoller JK. Treatment of alpha-1 antitrypsin deficiency. *Up-To-Date®*. Available online at: http://www.uptodate.com/contents/treatment-of-alpha-1-antitrypsin-deficiency?search=alpha+1+antitrypsin+deficiency+treatment&sectionRank=1&anchor=H2&source=machineLearning&selectedTitle=1%7E95#H2. Last revised 01/12/2018. Last accessed 02/19/2018.

[4] Grifols Therapeutics Inc. FDA approves Grifols Prolastin®-C Liquid [alpha-1 proteinase inhibitor, liquid] for the treatment of alpha-1 antitrypsin deficiency. Available online at: http://www.grifols.mx/documents/10192/22522080/np-20170922-en/4e3f4d5e-4a4d-44ac-9a4a-18e355cbe4ff. Issued 09/22/2017. Last accessed 02/19/2018.

[5] Kamada Ltd. Kamada Receives Additional Milestone Payment Under GLASSIA® Exclusive Supply and Distribution Agreement with Shire. Available online at: http://www.kamada.com/news_item.php?ID=280. Issued 06/12/2017. Last accessed 02/19/2018.

[6] Kamada Ltd. Kamada Submits Proposed Phase 3 Protocol to FDA for Inhaled Alpha-1-Antitrypsin for Treatment of Alpha-1 Antitrypsin Deficiency Disease. Available online at: http://www.kamada.com/news_item.php?ID=285. Issued 07/20/2017. Last accessed 02/19/2018.

[7] Prolastin®-C Liquid Prescribing Information. Grifols Therapeutics Inc. Available online at: https://www.fda.gov/downloads/BiologicsBloodVaccines/UCM209676.pdf. Last revised 09/2017. Last accessed 02/19/2018.

Appendix O

Industry News and Updates

Oklahoma Health Care Authority
March 2018

Introduction

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

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

News:

- **Compounding Policy:** In January 2018, the U.S. Food and Drug Administration (FDA) issued its 2018 Compounding Policy Priorities Plan. The plan outlines how the FDA will implement certain aspects of the Drug Quality and Security Act (DQSA) and other provisions of the law relevant to compounders. DQSA enabled closer federal and state collaboration, more robust oversight of compounders, and established a clear legal framework that provides for compounding to meet patients' medical needs. The law also created a new category of compounders, known as outsourcing facilities, which may engage in nationwide distribution under additional FDA oversight. The 2018 Compounding Policy Priorities Plan addresses how the FDA will handle manufacturing standards for outsourcing facilities, regulate compounding from bulk drug substances, restrict compounding of drugs that are essentially copies of FDA-approved medications, solidify the FDA's collaboration with state regulatory authorities, and provide guidance on additional activities that compounders undertake.
- **Medication-Assisted Treatment:** The U.S. Drug Enforcement Administration (DEA) announced in January 2018 that it changed a regulation to allow more health care professionals to prescribe medications used to treat opioid addiction. The change is part of a 2016 law that added categories of practitioners who may prescribe buprenorphine for maintenance or detoxification treatment. This change will open up access in rural America where there are fewer doctors to prescribe medication to those addicted to opioids. A study published in 2017 by the National Rural Health Association found that 53% of rural counties had no physician available to prescribe such medications and about 90% of physicians allowed to prescribe medications for opioid addiction live in urban counties.
- **Miniaturized Neural Drug Delivery System:** Scientists at the Massachusetts Institute of Technology have created a hair-thin implant that can deliver medications into the brain by remote control and with pinpoint accuracy. The device, which has currently only been tested in animals, could be a new approach to treating diseases of the brain. The plan is for the miniaturized neural drug delivery system (MiNDS) to be a fully implantable system that will contain programmable pumps, which can be refilled with an injection. While additional research is needed before the system could be tested on

humans, the researchers noted that these kinds of tools are important for research as it provides feedback on how neurons react to different compounds.

- **Smart Watch:** In February 2018, the FDA approved Embrace, a smart watch that helps epilepsy patients and caregivers monitor seizures. Embrace is a prescription-only device that uses a seizure detection algorithm to recognize electrodermal activity patterns that are likely to accompany epileptic seizures. The device monitors for grand mal or generalized tonic-clonic seizures and alerts caregivers through text and phone. A clinical study of 135 epilepsy patients who were admitted to multiple epilepsy monitoring units for continuous video electroencephalography was conducted to test the device. Researchers collected data over 272 days and the device detected 100% of the seizures, which were confirmed by independent epileptologists who made assessments without seeing the Embrace data.
- **Asthma Attacks:** According to a report from the U.S. Centers for Disease Control and Prevention (CDC), children with asthma are having fewer asthma attacks. The report, released in February 2018, shows that the percentage of children with asthma who experienced one or more asthma attacks in the preceding 12 months decreased from 61.7% in 2001 to 53.7% in 2016. The report shows that some children are more likely than others to have asthma, including boys, non-Hispanic black children, children of Puerto Rican descent, children from low income families, and children between the ages of 5 to 17 years. Asthma hospitalizations and asthma-related missed school days also declined from 2003 to 2013. The study findings show that despite the progress, 1 in 6 children with asthma still end up in the emergency department and approximately 1 in 20 are hospitalized each year.
- **Influenza Medication:** Shionogi, a Japanese drugmaker, states it has developed a medication that can kill the influenza virus within a day. A late-stage trial on Japanese and American patients with the flu found that for the patients who took the experimental medication the median time to kill the virus was 24 hours. The trial showed this was much faster than any other flu medication on the market, including oseltamivir, which took three times longer to achieve the same result during the trial. The experimental medication requires only a single dose, compared to oseltamivir, which requires two doses a day, for five days.

[1] U.S. Food and Drug Administration (FDA): Guidance, Compliance & Regulatory Information. 2018 Compounding Policy Priorities Plan. Available online at: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm592795.htm?utm_campaign=2018%20Compounding%20Policy%20Priorities%20Plan-%20Drug%20Information%20Update&utm_medium=email&utm_source=Eloqua. Issued 01/2018. Last accessed 01/22/2018.

[2] Abutaleb Y. U.S. Lets More Healthcare Workers Prescribe Opioid Addiction Treatment. *Reuters*. Available online at: https://www.reuters.com/article/us-usa-healthcare-opioids/u-s-lets-more-healthcare-workers-prescribe-opioid-addiction-treatment-idUSKBN1FC2NB. Issued 01/23/2018. Last accessed 01/29/2018.

[3] Neergaard L: *Associated Press*. Scientists Create Hair-Thin Implant That Can Drip Medication into Brain by Remote Control. *STAT*. Available online at: https://www.statnews.com/2018/01/24/implant-brain-remote-control/. Issued 01/24/2018. Last accessed 01/29/2018.

[4] George J. FDA OKs Smart Watch for Epilepsy Patients. *Medpage Today.* Available online at: https://www.medpagetoday.com/neurology/seizures/70996?xid=nl_mpt_DHE_2018-02-07&eun=g720351d0r&pos=7&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily%20Headlines%202018-02-07&utm_term=Daily%20Headlines%20-%20Active%20User%20-%20180%20days. Issued 02/06/2018. Last accessed 02/07/2018.

[5] Centers for Disease Control and Prevention (CDC). Asthma attacks declining among U.S. children. *PR Newswire*. Available online at: https://www.prnewswire.com/news-releases/asthma-attacks-declining-among-us-children-300594650.html. Issued 02/06/2018. Last accessed 02/07/2018.

[6] Rana P. Experimental Drug Promises to Kill the Flu Virus in a Day. *The Wall Street Journal*. Available online at: https://www.wsj.com/articles/experimental-drug-promises-to-kill-the-flu-virus-in-a-day-1518264004. Issued 02/10/2018. Last accessed 02/12/2018.

Appendix P

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

FDA NEWS RELEASE

For Immediate Release: February 14th, 2018

FDA approves new treatment for a certain type of prostate cancer using novel clinical trial endpoint

The FDA approved Erleada™ (apalutamide) for the treatment of patients with prostate cancer that has not spread (non-metastatic), but that continues to grow despite treatment with hormone therapy (castration-resistant). This is the first FDA-approved treatment for non-metastatic, castration-resistant prostate cancer.
According to the National Cancer Institute (NCI) at the National Institutes of Health, prostate cancer is the second most common form of cancer in men in the United States. The NCI estimates approximately 161,360 men were diagnosed with prostate cancer in 2017, and 26,730 were expected to die of the disease. Approximately 10 to 20% of prostate cancer cases are castration-resistant, and up to 16% of these patients show no evidence that the cancer has spread at the time of the castration-resistant diagnosis.
Erleada™ works by blocking the effect of androgens on the tumor. These androgens, such as testosterone, can promote tumor growth.
The safety and efficacy of Erleada™ were based on a randomized clinical trial of 1,207 patients with non-metastatic, castration-resistant prostate cancer. Patients in the trial either received Erleada™ or placebo. All patients were also treated with hormone therapy, either with gonadotropin-releasing hormone (GnRH) analog therapy or with surgery to lower the amount of testosterone in their body (surgical castration). The median metastasis-free survival for patients taking Erleada™ was 40.5 months compared to 16.2 months for patients taking placebo.
Common side effects of Erleada™ include fatigue, hypertension, rash, diarrhea, nausea, weight loss, joint pain (arthralgia), falls, hot flush, decreased appetite, fractures, and swelling in the limbs (peripheral edema). Severe side effects of Erleada™ include falls, fractures, and seizures.
This application was granted Priority Review, under which the FDA's goal is to take action on an application within 6 months where the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing or preventing a serious condition.
The sponsor for Erleada™ is the first participant in the FDA's recently-announced Clinical Data Summary Pilot Program, an effort to provide stakeholders with more usable information on the clinical evidence supporting drug product approvals and more transparency into the FDA's decision-making process. Soon after approval, certain information from the clinical summary report will post with the Erleada™ entry on Drugs@FDA and on the new pilot program landing page.
The FDA granted the approval of Erleada™ to Janssen Pharmaceutical Companies.

FDA NEWS RELEASE

For Immediate Release: February 16th, 2018

FDA expands approval of Imfinzi® to reduce the risk of non-small cell lung cancer progressing

The FDA approved Imfinzi® (durvalumab) for the treatment of patients with Stage III non-small cell lung cancer (NSCLC) whose tumors are not able to be surgically removed (unresectable) and whose cancer has not progressed after treatment with chemotherapy and radiation (chemoradiation).
Lung cancer is the leading cause of cancer death in the United States, with an estimated 222,500 new diagnoses and 155,870 deaths in 2017, according to the National Cancer Institute at the National Institutes of Health. The most common type of lung cancer, NSCLC occurs when cancer cells form in the tissues of the lung. Stage III NSCLC means tumors have spread to nearby lymph nodes or into other parts of the body near the lungs.
Imfinzi® targets the PD-1/PD-L1 pathway (proteins found on the body's immune cells and some cancer cells). By blocking these interactions, Imfinzi® may help the body's immune system attack cancer cells. Imfinzi® was previously granted accelerated approval in 2017 for the treatment of certain patients with locally advanced or metastatic bladder cancer.

The approval of Imfinzi® for the treatment of Stage III, unresectable NSCLC was based on a randomized trial of 713 patients whose cancer had not progressed after completing chemotherapy and radiation. The trial measured the length of time the tumors did not have significant growth after starting treatment with Imfinzi® or placebo (progression-free survival). The median progression-free survival for patients taking Imfinzi® was 16.8 months compared to 5.6 months for patients receiving placebo. In addition, the sponsor has agreed to a post-marketing commitment to provide additional information from their study to the FDA about how long patients lived following treatment with Imfinzi® after chemotherapy and radiation (overall survival).
Common side effects of Imfinzi® in patients with Stage III unresectable NSCLC include cough, fatigue, inflammation in the lungs (pneumonitis/radiation pneumonitis), upper respiratory tract infections, difficulty breathing (dyspnea), and rash.
Serious risks of Imfinzi® include immune-mediated side effects, where the body's immune system attacks healthy cells or organs, such as the lungs (pneumonitis), liver (hepatitis), colon (colitis), hormone-producing glands (endocrinopathies), and kidneys (nephritis). Other serious side effects of Imfinzi® include infection and infusion-related reactions. Imfinzi® can cause harm to a developing fetus; women should be advised of the potential risk to the fetus and to use effective contraception.
The FDA granted this application Priority Review and Breakthrough Therapy designations.
The FDA granted the approval of Imfinzi® to AstraZeneca.

FDA NEWS RELEASE

For Immediate Release: February 26th, 2018
FDA approves Verzenio™ (abemaciclib) as initial therapy for HR-positive, HER2-negative metastatic breast cancer

The FDA approved Verzenio™ (abemaciclib, Eli Lilly and Company) in combination with an aromatase inhibitor as initial endocrine-based therapy for postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.
Approval was based on MONARCH 3, a randomized (2:1), double-blinded, placebo-controlled, multicenter clinical trial in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. A total of 493 patients were randomized to receive either Verzenio™ 150mg or placebo orally twice daily, plus physician's choice of letrozole or anastrozole. The estimated median progression-free survival (PFS) was 28.2 months for patients receiving Verzenio™ and 14.8 months for those receiving placebo.
The most common adverse reactions in at least 20% of patients receiving Verzenio™ in MONARCH 3 and more than 2% higher than the placebo arm were diarrhea, neutropenia, fatigue, infections, nausea, abdominal pain, anemia, vomiting, alopecia, decreased appetite, and leukopenia.
The recommended starting dose of Verzenio™ in combination with an aromatase inhibitor is 150mg twice daily orally with or without food.
FDA granted this application priority review.
Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's MedWatch Reporting System.

FDA NEWS RELEASE

For Immediate Release: March 6th, 2018
FDA approves new HIV treatment for patients who have limited treatment options

The FDA approved Trogarzo™ (ibalizumab-uiyk), a new type of antiretroviral medication for adult patients living with HIV who have tried multiple HIV medications in the past (heavily treatment-experienced) and whose HIV infections cannot be successfully treated with other currently available therapies (multidrug resistant HIV, or MDR HIV).Trogarzo™ is administered intravenously (IV) once every 14 days by a trained medical professional and used in combination with other antiretroviral medications.
The safety and efficacy of Trogarzo™ were evaluated in a clinical trial of 40 heavily treatment-experienced patients with MDR HIV-1 who continued to have high levels of virus (HIV-RNA) in their blood despite being on antiretroviral drugs. Many of the participants had previously been treated with 10 or more antiretroviral drugs. The majority of participants experienced a significant decrease in their HIV-RNA levels one week after Trogarzo™ was added to their failing antiretroviral regimens. After 24 weeks of Trogarzo™ plus other antiretroviral drugs, 43% of the trial's participants achieved HIV RNA suppression.

The clinical trial focused on the small patient population with limited treatment options and demonstrated the benefit of Trogarzo™ in achieving reduction of HIV RNA. The seriousness of the disease, the need to individualize other drugs in the treatment regimen, and safety data from other trials were considered in evaluating the Trogarzo™ development program.
A total of 292 patients with HIV-1 infection have been exposed to Trogarzo™ IV infusion. The most common adverse reactions to Trogarzo™ were diarrhea, dizziness, nausea, and rash. Severe side effects included rash and changes in the immune system (immune reconstitution syndrome).
The FDA granted this application Fast Track, Priority Review, and Breakthrough Therapy designations. Trogarzo™ also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted approval of Trogarzo™ to TaiMed Biologics USA Corp.

Safety Announcements

FDA Drug Safety Communication: FDA review finds additional data supports the potential for increased long-term risks with antibiotic clarithromycin (Biaxin®) in patients with heart disease

[02/22/2018] The FDA is advising caution before prescribing the antibiotic clarithromycin (Biaxin®) to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later. The FDA's recommendation is based on their review of the results of a 10-year follow-up study of patients with coronary heart disease from a large clinical trial that first observed this safety issue.
As a result, the FDA has added a new warning about this increased risk of death in patients with heart disease, and advised prescribers to consider using other antibiotics in such patients. The FDA has also added the study results to the clarithromycin drug labels. As part of FDA's usual ongoing safety monitoring of drugs, the FDA is continuing to monitor safety reports in patients taking clarithromycin.
Health care professionals should be aware of these significant risks and weigh the benefits and risks of clarithromycin before prescribing it to any patient, particularly in patients with heart disease and even for short periods, and consider using other available antibiotics. Patients with heart disease should be advised of the signs and symptoms of cardiovascular problems, regardless of the medical condition for which they are being treated with clarithromycin.
Patients should tell their health care professionals if they have heart disease, especially when they are being prescribed an antibiotic to treat an infection. Patients should talk to them about the benefits and risks of clarithromycin and any alternative treatments. Patients should not stop taking their heart disease medicine or antibiotic without first talking to their health care professionals. Doing so could be harmful without their health care professionals' direct supervision. Patients should seek medical attention immediately if they experience symptoms of a heart attack or stroke, such as chest pain, shortness of breath or trouble breathing, pain or weakness in one part or side of your body, or slurred speech.
Like other antibiotics, clarithromycin is used to treat many types of infections affecting the skin, ears, sinuses, lungs, and other parts of the body, including Mycobacterium avium complex (MAC) infection, a type of lung infection that often affects people with human immunodeficiency virus (HIV). Clarithromycin is not approved to treat heart disease. The drug has been used for more than 25 years, and is sold under the brand name Biaxin® and as generics by many different drug companies. It works by stopping the growth of bacteria. Without treatment, some infections can spread and lead to serious health problems.
The large clinical trial, called the CLARICOR trial, observed an unexpected increase in deaths among patients with coronary heart disease who received a 2-week course of clarithromycin that became apparent after patients had been followed for one year or longer. There is no clear explanation for how clarithromycin would lead to more deaths than placebo. Some observational studies also found an increase in deaths or other serious heart-related problems, while others did not. All the studies had limitations in how they were designed. Of the six observational studies published to date in patients with or without coronary artery disease, two found evidence of long-term risks from clarithromycin, and four did not. Overall, results from the prospective, placebo-controlled CLARICOR trial provide the strongest evidence of the increase in risk compared to the observational study results. Based on these studies, the FDA was unable to determine why the risk of death is greater for patients with heart disease.
Furthermore, there are no prospective, randomized, and controlled trials with prespecified long-term safety outcome measures following clarithromycin treatment in patients who do not have heart disease. Because the

FDA currently does not have study information in these patients, and observational studies have shown different results, the FDA cannot determine whether results of the CLARICOR trial can be applied to patients who do not have heart disease.
The FDA previously communicated about this safety issue in December 2005, before the 10-year follow-up results were available for CLARICOR.
The FDA urges health care professionals and patients to report side effects involving clarithromycin and other drugs to the FDA MedWatch program.

Current Drug Shortages Index (as of March 6th, 2018):

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

Amino Acids	***Currently in Shortage***
Aminocaproic Acid Injection, USP	***Currently in Shortage***
Amoxapine Tablets	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atenolol Tablets	***Currently in Shortage***
Atropine Sulfate Injection	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Betaine Hydrochloride (Cystadane) for Oral Solution	***Currently in Shortage***
Bumetanide Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride and Epinephrine Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride Injection, USP	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Carbidopa and Levodopa Extended Release Tablets	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Cromolyn Sodium Inhalation Solution, USP	***Currently in Shortage***
Deferoxamine Mesylate for Injection, USP	***Currently in Shortage***
Dexrazoxane Injection	***Currently in Shortage***
Dextrose 5% Injection Bags	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Diazepam Injection, USP	***Currently in Shortage***
Dihydroergotamine Mesylate Injection	***Currently in Shortage***
Diltiazem Hydrochloride	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Dobutamine Hydrochloride Injection	***Currently in Shortage***
Dopamine Hydrochloride Injection	***Currently in Shortage***
Dorzolamide Hydrochloride and Timolol Maleate (Cosopt) Ophthalmic Solution	***Currently in Shortage***
Dorzolamide Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fluorescein Strips	***Currently in Shortage***
Folic Acid Injection	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Guanfacine Hydrochloride Tablets	***Currently in Shortage***
Heparin Sodium and Sodium Chloride 0.9% Injection	***Currently in Shortage***
Hydromorphone Hydrochloride Injection, USP	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***

Ketamine 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) and Dextrose Injection Solution-Premix Bags	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methylphenidate Hydrochloride (Quillichew ER) Extended-Release Chewable Tabs	***Currently in Shortage***
Methylphenidate Hydrochloride (Quillivant XR) for Extended-Release Oral Susp	***Currently in Shortage***
Metoclopramide Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Molindone Hydrochloride Tablets	***Currently in Shortage***
Morphine Sulfate Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nitrous Oxide, Gas	***Currently in Shortage***
Pantoprazole (Protonix) Powder for Injection	***Currently in Shortage***
Penicillamine (Depen) Titratable Tablets	***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***
Phosphate Injection Products	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Progesterone Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	***Currently in Shortage***
Rocuronium Bromide Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***
Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Sterile Water	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Theophylline Extended Release Tablets and Capsules	***Currently in Shortage***
Thioridazine Hydrochloride Tablets	***Currently in Shortage***