Oklahoma Health Care Authority

Drug Utilization Review Board

Wednesday,
December 12, 2018
4:00pm

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

The University of Oklahoma

Health Sciences Center

COLLEGE OF PHARMACY

PHARMACY MANAGEMENT CONSULTANTS

MEMORANDUM

TO: Drug Utilization Review (DUR) Board Members

FROM: Bethany Holderread, Pharm.D.

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

DATE: December 3, 2018

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

Enclosed are the following items related to the December 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/Chronic Medication Adherence Program Update – Appendix B

Action Item – Vote to Prior Authorize Hemlibra® (Emicizumab-kxwh), Feiba® (Anti-Inhibitor Coagulant Complex), NovoSeven® RT [Coagulation Factor VIIa (Recombinant)], and Jivi® [Antihemophilic Factor (Recombinant), PEGylated-aucl] – Appendix C

Action Item – Vote to Prior Authorize Onpattro™ (Patisiran) and Tegsedi™ (Inotersen) – Appendix D

Action Item – Vote to Prior Authorize Zemdri™ (Plazomicin), Xerava™ (Eravacycline), Nuzyra™ (Omadacycline), Seysara™ (Sarecycline), and Ximino™ (Minocycline Extended-Release) – Appendix E

Action Item – Vote to Prior Authorize Signifor® LAR (Pasireotide) – Appendix F

Action Item – Vote to Prior Authorize Symdeko® (Tezacaftor/Ivacaftor) and Orkambi® (Lumacaftor/Ivacaftor Oral Granules) and to Update the Kalydeco® (Ivacaftor) Prior Authorization Criteria – Appendix G

Annual Review of Maintenance Asthma and Chronic Obstructive Pulmonary Disease (COPD) Medications and 30-Day Notice to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab Injection) – Appendix H

Annual Review of Thrombocytopenia Medications and 30-Day Notice to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag) – Appendix I

Annual Review of Inhaled Anti-Infective Medications and 30-Day Notice to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension) – Appendix J

Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Akynzeo® IV (Fosnetupitant/ Palonosetron Injection for Intravenous Use) – Appendix K

30-Day Notice to Prior Authorize Carbaglu® (Carglumic Acid) – Appendix L

Annual Review of Muscular Dystrophy Medications – Appendix M

Industry News and Updates – Appendix N

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

Future Business

Adjournment

Oklahoma Health Care Authority

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

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

AGENDA

Discussion and Action on the Following Items:

Items to be presented by Dr. Muchmore, Chairman:

1. Call to Order

A. Roll Call – Dr. Cothran

Items to be presented by Dr. Muchmore, Chairman:

2. Public Comment Forum

A. Acknowledgment of Speakers for Public Comment

Items to be presented by Dr. Muchmore, Chairman:

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

A. November 14, 2018 DUR Minutes – Vote
B. November 14, 2018 DUR Recommendations Memorandum
C. Correspondence

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

4. Update on Medication Coverage Authorization Unit/Chronic Medication Adherence Program Update – See Appendix B

A. Medication Coverage Activity for November 2018
B. Pharmacy Helpdesk Activity for November 2018
C. Chronic Medication Adherence Program Update

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

5. Action Item – Vote to Prior Authorize Hemlibra® (Emicizumab-kxwh), Feiba® (Anti-Inhibitor Coagulant Complex), NovoSeven® RT [Coagulation Factor VIIa (Recombinant)], and Jivi® [Antihemophilic Factor (Recombinant), PEGylated-aucl] – See Appendix C

A. Introduction
B. Recommendations

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

6. Action Item – Vote to Prior Authorize Onpattro™ (Patisiran) and Tegsedi™ (Inotersen) – See Appendix D

A. Introduction
B. College of Pharmacy Recommendations

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

7. Action Item – Vote to Prior Authorize Zemdri™ (Plazomicin), Xerava™ (Eravacycline), Nuzyra™ (Omadacycline), Seysara™ (Sarecycline), and Ximino™ (Minocycline Extended-Release) – See Appendix E

A. Introduction
B. Cost Comparison: Minocycline Products
C. College of Pharmacy Recommendations

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

8. Action Item – Vote to Prior Authorize Signifor® LAR (Pasireotide) – See Appendix F

A. Introduction
B. College of Pharmacy Recommendations

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

9. Action Item – Vote to Prior Authorize Symdeko® (Tezacaftor/Ivacaftor) and Orkambi® (Lumacaftor/Ivacaftor Oral Granules) and to Update the Kalydeco® (Ivacaftor) Prior Authorization Criteria – See Appendix G

A. Introduction
B. College of Pharmacy Recommendations

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

10. Annual Review of Maintenance Asthma and Chronic Obstructive Pulmonary Disease (COPD) Medications and 30-Day Notice to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab Injection) – See Appendix H

A. Current Prior Authorization Criteria
B. Utilization of Maintenance Asthma and COPD Medications
C. Prior Authorization of Maintenance Asthma and COPD Medications
D. Market News and Updates
E. Lonhala® Magnair® (Glycopyrrolate Inhalation Solution) Product Summary
F. Yupelri™ (Revefenacin Inhalation Solution) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Maintenance Asthma and COPD Medications
I. Utilization Details of Inhaled Corticosteroids

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

11. Annual Review of Thrombocytopenia Medications and 30-Day Notice to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag) – See Appendix I

A. Current Prior Authorization Criteria
B. Utilization of Thrombocytopenia Medications
C. Prior Authorization of Thrombocytopenia Medications
D. Market News and Updates
E. Tavalisse™ (Fostamatinib) Product Summary
F. Doptelet® (Avatrombopag) Product Summary
G. Mulpleta® (Lusutrombopag) Product Summary
H. College of Pharmacy Recommendations
I. Utilization Details of Thrombocytopenia Medications

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

12. Annual Review of Inhaled Anti-Infective Medications and 30-Day Notice to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension) – See Appendix J

A. Introduction
B. Current Prior Authorization Criteria
C. Utilization of Inhaled Anti-Infective Medications
D. Prior Authorization of Inhaled Anti-Infective Medications
E. Market News and Updates
F. Arikayce® (Amikacin Liposome Inhalation Suspension) Product Summary
G. College of Pharmacy Recommendations
H. Utilization Details of Inhaled Anti-Infective Medications

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

13. Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Akynzeo® IV (Fosnetupitant/Palonosetron Injection for Intravenous Use) – See Appendix K

A. Current Prior Authorization Criteria
B. Utilization of Anti-Emetic Medications
C. Prior Authorization Anti-Emetic Medications
D. Market News and Updates
E. Cost Comparison
F. College of Pharmacy Recommendations

G. Utilization Details of Anti-Emetic Medications

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

14. 30-Day Notice to Prior Authorize Carbaglu® (Carglumic Acid) – See Appendix L

A. Introduction
B. Carbaglu® (Carglumic Acid) Product Summary
C. College of Pharmacy Recommendations

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

15. Annual Review of Muscular Dystrophy Medications – See Appendix M

A. Current Prior Authorization Criteria
B. Utilization of Muscular Dystrophy Medications
C. Prior Authorization of Muscular Dystrophy Medications
D. Market News and Updates
E. Cost Changes
F. College of Pharmacy Recommendations

Non-Presentation; Questions Only:

16. Industry News and Updates – See Appendix N

A. Introduction
B. News and Updates

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

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

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

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

No live meeting scheduled for January. January 2019 will be a packet only meeting.

A. Glaucoma Medications
B. Revcovi™ (Elapegademase-lvlr)
C. Injectable and Vaginal Progesterone Products
D. Hyperkalemia Medications
E. Zilretta® (Triamcinolone Extended-Release Injectable Suspension)

**Future business subject to change.*

19. Adjournment

Appendix A

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

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

COLLEGE OF PHARMACY STAFF:	PRESENT	ABSENT
Terry Cothran, D.Ph.; Pharmacy Director	x	
Melissa Abbott, Pharm.D.; Clinical Pharmacist		x
Michyla Adams, Pharm.D.; Clinical Pharmacist	x	
Wendi Chandler, Pharm.D.; Clinical Pharmacist	x	
Sarai Connell, Pharm.D.; MBA; Resident	x	
Karen Egesdal, D.Ph.; SMAC-ProDUR Coordinator/OHCA Liaison	x	
Thomas Ha, Pharm.D.; Clinical Pharmacist		x
Bethany Holderread, Pharm.D.; Clinical Coordinator	x	
Shellie Keast, Ph.D.; Assistant Professor	x	
Brandy Nawaz, Pharm.D.; Clinical Pharmacist	x	
Timothy Pham, Ph.D.; Postdoctoral Research Fellow		x
Regan Smith, Pharm.D.; Clinical Pharmacist		x
Ashley Teel, Pharm.D.; Clinical Pharmacist	x	
Jacquelyn Travers, Pharm.D.; Practice Facilitating Pharmacist		x
Graduate Students: Michael Nguyen, Pharm.D.	x	x
Philip Looper, Pharm.D.		x
Laura Tidmore, Pharm.D.		x
Corby Thompson, Pharm.D.		x
Reagan Williams, Pharm.D.	x	
Visiting Pharmacy Student(s): Sean Monroe	x	

OKLAHOMA HEALTH CARE AUTHORITY STAFF:	PRESENT	ABSENT
Melody Anthony, Deputy State Medicaid Director	x	
Marlene Asmussen, R.N.; Population Care Management Director	x	
Burl Beasley, D.Ph.; M.P.H.; M.S. Pharm.; Sr. Director of Pharmacy	x	
Kelli Brodersen, Marketing Coordinator		x
Susan Eads, J.D.; Director of Litigation	x	
Robert Evans, M.D.; Sr. Medical Director		x
Michael Herndon, D.O.; Chief Medical Officer		x
Maria Maule, J.D.; Senior Director Legal Services	x	
Nancy Nesser, Pharm.D.; J.D.; Pharmacy Director	x	
Thomas Nunn, D.O.; Medical Director		x
Rebecca Pasternik-Ikard, J.D.; M.S.; R.N.; State Medicaid Director; CEO		x
Jill Ratterman, D.Ph.; Clinical Pharmacist	x	
Kerri Wade, Pharmacy Operations Manager	x	

OTHERS PRESENT:		
Rick Dabner, Alnylam	Andrew Kucharski, Alnylam	Kristin Crouch, Vertex
Trina Ballard, Bayer	Chris Holtzer, AbbVie	Folger Tuggle, Bioverativ
Jason Russell, Bioverativ	Gregg Rasmussen, Vertex	John Kim, Vertex
Georg Lunday, Integris	Michele Puyear, Gilead	Amber Schrantz, Lilly
Brent Hildebrand, Gilead	Marc Parker, Sunovion	Doug Wood, ViiV
Bob Goodley, OHF	Brian Maves, Pfizer	Roger Grotzinger, Bristol-Myers Squibb
Eric Gardner, Vertex	Matt Forney, Merck	Clint Roberson, OHF
Evie Knisely, Novartis	Lori Howarth, Bayer	Sharon Cahoon-Metzger, Bioverativ
Frances Bauman, Novo Nordisk	Joel Turner, Array	Gwendolyn Caldwell, PhRMA
Susan Conway, OU COP		

PRESENT FOR PUBLIC COMMENT:	
Andrew Kucharski	Alnylam
Chris Holtzer	AbbVie
Kristin Crouch	Vertex
Trina Ballard	Bayer
Sharon Cahoon-Metzger	Bioverativ
Clint Roberson	Oklahoma Hemophilia Foundation

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 CHRIS HOLTZER
2B: AGENDA ITEM NO. 9 TRINA BALLARD
2C: AGENDA ITEM NO. 9 SHARON CAHOON-METZGER
2D: AGENDA ITEM NO. 9 CLINT ROBERSON
2E: AGENDA ITEM NO. 13 KRISTIN CROUCH
2F: AGENDA ITEM NO. 14 ANDREW KUCHARSKI
2G: AGENDA ITEM NO. 16 CHRIS HOLTZER

ACTION: NONE REQUIRED

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

3A: OCTOBER 10, 2018 DUR MINUTES – VOTE
3B: OCTOBER 10, 2018 DUR RECOMMENDATIONS MEMORANDUM

Materials included in agenda packet; presented by Dr. Cothran
Dr. Broyles moved to approve; seconded by Dr. Munoz

ACTION: MOTION CARRIED

AGENDA ITEM NO. 4: **UPDATE ON MEDICATION COVERAGE AUTHORIZATION UNIT/2018 FALL PIPELINE UPDATE**

4A: MEDICATION COVERAGE ACTIVITY FOR OCTOBER 2018
4B: PHARMACY HELPDESK ACTIVITY FOR OCTOBER 2018
4C: 2018 FALL PIPELINE UPDATE

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 5: **VOTE TO PRIOR AUTHORIZE ILUMYA™ (TILDRAKIZUMAB-ASMN) AND OLUMIANT® (BARICITINIB)**

5A: INTRODUCTION

5B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Anderson moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 6: VOTE TO PRIOR AUTHORIZE TRIPTODUR® (TRIPTORELIN) AND ORILISSA™ (ELAGOLIX)
6A: INTRODUCTION
6B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Holderread
Dr. Garton moved to approve; seconded by Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 7: VOTE TO PRIOR AUTHORIZE YESCARTA® (AXICABTAGENE) AND TO UPDATE THE ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) AND CHRONIC MYELOID LEUKEMIA (CML) MEDICATIONS APPROVAL CRITERIA
7A: INTRODUCTION
7B: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Borders
Dr. Huddleston moved to approve; seconded by Dr. Broyles
ACTION: MOTION CARRIED

AGENDA ITEM NO. 8: VOTE TO PRIOR AUTHORIZE BRAFTOVI™ (ENCORAFENIB), MEKTOVI® (BINIMETINIB), AND LIBTAYO® (CEMIPLIMAB-RWLC)
8A: INTRODUCTION
8B: RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Borders
Dr. Anderson moved to approve; seconded by Dr. Huddleston
ACTION: MOTION CARRIED

AGENDA ITEM NO. 9: ANNUAL REVIEW OF FACTOR REPLACEMENT PRODUCTS AND 30-DAY NOTICE TO PRIOR AUTHORIZE HEMLIBRA® (EMICIZUMAB-KXWH), FEIBA® (ANTI-INHIBITOR COAGULANT COMPLEX), NOVOSEVEN® RT [COAGULATION FACTOR VIIA (RECOMBINANT)], AND JIVI® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), PEGYLATED-AUCL]
9A: CURRENT PRIOR AUTHORIZATION CRITERIA
9B: UTILIZATION OF FACTOR REPLACEMENT PRODUCTS
9C: PRIOR AUTHORIZATION OF FACTOR REPLACEMENT PRODUCTS
9D: MARKET NEWS AND UPDATES
9E: INHIBITORS AND TREATMENT
9F: HEMLIBRA® (EMICIZUMAB-KXWH) PRODUCT SUMMARY
9G: JIVI® [ANTIHEMOPHILIC FACTOR (RECOMBINANT), PEGYLATED-AUCL] PRODUCT SUMMARY
9H: RECOMMENDATIONS
9I: UTILIZATION DETAILS OF FACTOR REPLACEMENT PRODUCTS
Materials included in agenda packet; presented by Dr. Ratterman
ACTION: NONE REQUIRED

AGENDA ITEM NO. 10: VOTE TO PRIOR AUTHORIZE NOCDURNA® (DESMOPRESSIN ACETATE SUBLINGUAL TABLET)
10A: INTRODUCTION
10B: COLLEGE OF PHARMACY RECOMMENDATIONS
Materials included in agenda packet; presented by Dr. Chandler
Dr. Broyles moved to approve; seconded by Dr. Garton
ACTION: MOTION CARRIED

AGENDA ITEM NO. 11: VOTE TO PRIOR AUTHORIZE KRYSTEXXA® (PEGLOTICASE)

11A: INTRODUCTION

11B: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Connell

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 12: VOTE TO PRIOR AUTHORIZE IMPOYZ™ (CLOBETASOL PROPIONATE 0.025% CREAM)

12A: INTRODUCTION

12B: MARKET NEWS AND UPDATES

12C: COLLEGE OF PHARMACY RECOMMENDATIONS

Materials included in agenda packet; presented by Dr. Nawaz

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

ACTION: MOTION CARRIED

AGENDA ITEM NO. 13: ANNUAL REVIEW OF CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR) MODULATORS AND 30-DAY NOTICE TO PRIOR AUTHORIZE SYMDEKO® (TEZACAFTOR/IVACAFTOR) AND ORKAMBI® (LUMACAFTOR/IVACAFTOR ORAL GRANULES)

13A: CURRENT PRIOR AUTHORIZATION CRITERIA

13B: UTILIZATION OF CFTR MODULATORS

13C: PRIOR AUTHORIZATION OF CFTR MODULATORS

13D: MARKET NEWS AND UPDATES

13E: SYMDEKO® (TEZACAFTOR/IVACAFTOR) PRODUCT SUMMARY

13F: COLLEGE OF PHARMACY RECOMMENDATIONS

13G: UTILIZATION DETAILS OF CFTR MODULATORS

Materials included in agenda packet; presented by Dr. Nawaz

ACTION: NONE REQUIRED

AGENDA ITEM NO. 14: 30-DAY NOTICE TO PRIOR AUTHORIZE ONPATTRO™ (PATISIRAN) AND TEGSEDI™ (INOTERSEN)

14A: INTRODUCTION

14B: ONPATTRO™ (PATISIRAN) PRODUCT SUMMARY

14C: TEGSEDI™ (INOTERSEN) PRODUCT SUMMARY

14D: MARKET NEWS AND UPDATES

14E: COLLEGE OF PHARMACY RECOMMENDATIONS

Dr. Muchmore recommends amending the criteria to state “tissue biopsy (fat pad biopsy)” to confirm amyloid deposits.

Materials included in agenda packet; presented by Dr. Chandler

ACTION: NONE REQUIRED

AGENDA ITEM NO. 15: ANNUAL REVIEW OF VARIOUS SYSTEMIC ANTIBIOTICS AND 30-DAY NOTICE TO PRIOR AUTHORIZE ZEMDRI™ (PLAZOMICIN), XERAVA™ (ERAVACYCLINE), NUZYRA™ (OMADACYCLINE), SEYSARA™ (SARECYCLINE), AND XIMINO™ (MINOCYCLINE EXTENDED-RELEASE)

15A: CURRENT PRIOR AUTHORIZATION CRITERIA

15B: UTILIZATION OF VARIOUS SYSTEMIC ANTIBIOTICS

15C: PRIOR AUTHORIZATION OF VARIOUS SYSTEMIC ANTIBIOTICS

15D: MARKET NEWS AND UPDATES

15E: PRODUCT SUMMARIES

15F: COST COMPARISON

15G: COLLEGE OF PHARMACY RECOMMENDATIONS

15H: UTILIZATION DETAILS OF VARIOUS SYSTEMIC ANTIBIOTICS

Materials included in agenda packet; presented by Dr. Adams

ACTION: NONE REQUIRED

AGENDA ITEM NO. 16: **ANNUAL REVIEW OF HEPATITIS C MEDICATIONS**

16A: INTRODUCTION
16B: CURRENT PRIOR AUTHORIZATION CRITERIA
16C: HEPATITIS C SUMMARY STATISTICS FOR TREATED MEMBERS
16D: TRENDS OF HEPATITIS C MEDICATION UTILIZATION
16E: UTILIZATION OF HEPATITIS C MEDICATIONS
16F: PRIOR AUTHORIZATION OF HEPATITIS C MEDICATIONS
16G: MARKET NEWS AND UPDATES
16H: REGIMEN COMPARISON
16I: COLLEGE OF PHARMACY RECOMMENDATIONS
16J: UTILIZATION DETAILS OF HEPATITIS C MEDICATIONS

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 17: **30-DAY NOTICE TO PRIOR AUTHORIZE SIGNIFOR® LAR (PASIREOTIDE)**

17A: ACROMEGALY SUMMARY
17B: CUSHING'S DISEASE SUMMARY
17C: MARKET NEWS AND UPDATES
17D: SIGNIFOR® LAR (PASIREOTIDE) PRODUCT SUMMARY
17E: COLLEGE OF PHARMACY RECOMMENDATIONS

Dr. Muchmore recommends amending the criteria to read members with "Cushing's disease due to pituitary tumor for whom pituitary surgery is not an option or has not been curative."

Materials included in agenda packet; presented by Dr. Connell

ACTION: NONE REQUIRED

AGENDA ITEM NO. 18: **INDUSTRY NEWS AND UPDATES**

18A: INTRODUCTION
18B: NEWS AND UPDATES

Materials included in agenda packet; non-presentation; questions only

ACTION: NONE REQUIRED

AGENDA ITEM NO. 19: **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. 20: **FUTURE BUSINESS* (UPCOMING PRODUCT AND CLASS REVIEWS)**

20A: MAINTENANCE ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) MEDICATIONS
20B: THROMBOCYTOPENIA MEDICATIONS
20C: INHALED ANTI-INFECTIVE MEDICATIONS
20D: MUSCULAR DYSTROPHY MEDICATIONS

**Future business subject to change.*

Materials included in agenda packet; presented by Dr. Holderread

ACTION: NONE REQUIRED

AGENDA ITEM NO. 21: **ADJOURNMENT**

The meeting was adjourned at 5:40pm.

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

Memorandum

Date: November 15, 2018

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

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

Subject: Drug Utilization Review (DUR) Board Recommendations from Meeting of November 14, 2018

Recommendation 1: 2018 Fall Pipeline Update

NO ACTION REQUIRED.

Recommendation 2: Vote to Prior Authorize Ilumya™ (Tildrakizumab-asmn) and Olumiant® (Baricitinib)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the addition of Ilumya™ (tildrakizumab-asmn) and Olumiant® (baricitinib) to Tier-3 of the Targeted Immunomodulator Agents Product Based Prior Authorization (PBPA) category. Current Tier-3 approval criteria for this category will apply. Additionally, the College of Pharmacy recommends the following criteria for Rituxan® (rituximab) for the treatment of adults with moderate-to-severe pemphigus vulgaris (PV):

Rituxan® (Rituximab) Approval Criteria [Pemphigus Vulgaris (PV) Diagnosis]:

1. An FDA approved diagnosis of moderate-to-severe PV; and
2. Rituxan® must be used in combination with a tapering course of glucocorticoids; and
3. Initial approvals will be for two 1,000mg intravenous (IV) infusions separated by 2 weeks and a 500mg infusion at month 12. Subsequent approvals may be authorized based on

6-month evaluations or upon relapse. Subsequent infusions may be no sooner than 16 weeks after the previous infusion.

Targeted Immunomodulator Agents*±		
Tier-1 (DMARDs appropriate to disease state)	**Tier-2***	**Tier-3**
6-mercaptopurine	adalimumab (Humira®)+	abatacept (Orencia® & Orencia® ClickJect™)Δ
azathioprine	etanercept (Enbrel®)	adalimumab-adbm (Cyltezo™)
hydroxychloroquine		adalimumab-atto (Amjevita™)
leflunomide		alefacept (Amevive®)
mesalamine		anakinra (Kineret®)
methotrexate		apremilast (Otezla®)
minocycline		**baricitinib (Olumiant®)**
NSAIDs		brodalumab (Siliq™)
oral corticosteroids		canakinumab (Ilaris®)¥
		certolizumab pegol (Cimzia®)
		etanercept-szzs (Erelzi™)
		golimumab (Simponi® & Simponi® Aria™)
		guselkumab (Tremfya™)
		infliximab (Remicade®)
		infliximab-abda (Renflexis™)
		infliximab-dyyb (Inflectra™)
		ixekizumab (Taltz®)
		rituximab (Rituxan®)~
		sarilumab (Kevzara®)
		secukinumab (Cosentyx®)Ω
		tildrakizumab-asmn (Ilumya™)
		tocilizumab (Actemra®)π
		tofacitinib (Xeljanz® & Xeljanz® XR)Δ
		ustekinumab (Stelara®)
		vedolizumab (Entyvio™)

DMARDs = Disease modifying antirheumatic drugs; NSAIDs = Nonsteroidal anti-inflammatory drugs

*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. Tier-2 drugs subject to move to Tier-3. Appropriate laboratory monitoring must be verified by the prescriber prior to approval. ±Biosimilars or reference products preferred based on lowest net cost product. Authorization of higher net cost biosimilars or reference products requires a patient-specific, clinically significant reason why the member could not use the preferred formulation.

+Unique criteria applies for a diagnosis of hidradentitis suppurativa (HS) or noninfectious intermediate and posterior uveitis and panuveitis.

ΔIf the net cost of Xeljanz® XR (tofacitinib extended-release) and Orencia® ClickJect™ (abatacept autoinjector) is > the net cost of the immediate-release formulation of Xeljanz® or the prefilled syringe formulation of Orencia® authorization would also require a patient-specific, clinically significant reason why the member could not use the immediate-release formulation of Xeljanz® or the prefilled syringe formulation of Orencia®.

¥Unique criteria applies for a diagnosis of Cryopyrin-Associated Periodic Syndromes (CAPS), Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), or Familial Mediterranean Fever (FMF).

~Unique criteria applies for a diagnosis of pemphigus vulgaris (PV).

ΩFor Cosentyx™ (secukinumab), only a trial of Humira® from the available Tier-2 medications will be required (based on supplemental rebate participation).

πUnique criteria applies for a diagnosis of giant cell arteritis (GCA) or chimeric antigen receptor T (CAR T) cell-induced cytokine release syndrome (CRS).

Targeted Immunomodulator Tier-2 Approval Criteria:

1. An FDA approved diagnosis; and
2. A trial of at least one Tier-1 medication in the last 90 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. For a diagnosis of Crohn's disease (CD) or ulcerative colitis (UC), authorization of a Tier-2 medication requires history of failure of a mesalamine medication (does not have to be within the last 90 days) and a trial of 1 Tier-1 medication in the last 90 days that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
4. Prior stabilization on the Tier-2 medication documented within the last 100 days.

Targeted Immunomodulator Tier-3 Approval Criteria:

1. An FDA approved diagnosis; and
2. Recent trials of one Tier-1 medication and all available Tier-2 medications that did not yield adequate relief of symptoms or resulted in intolerable adverse effects; or
3. Prior stabilization on the Tier-3 medication documented within the last 100 days; or
4. A unique FDA-approved indication not covered by Tier-2 medications.

Recommendation 3: Vote to Prior Authorize Triptodur® (Triptorelin) and Orilissa™ (Elagolix)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Orilissa™ (elagolix) with the following criteria:

Orilissa™ (Elagolix) Approval Criteria:

1. An FDA approved diagnosis of moderate-to-severe pain associated with endometriosis; and
2. Member must be 18 years of age or older; and
3. Member must not have known osteoporosis; and
4. Female members must not be pregnant and must have a negative pregnancy test prior to initiation of therapy; and
5. Female members of reproductive potential must be willing to use effective non-hormonal contraception during treatment with Orilissa™ and for at least one week after discontinuing treatment; and
6. Member must not have severe hepatic impairment (Child-Pugh C); and
7. Member must not be taking a strong organic anion transporting polypeptide (OATP) 1B1 inhibitor (e.g., cyclosporine, gemfibrozil); and
8. Orilissa™ must be prescribed by, or in consultation with, an obstetrician/gynecologist or a specialist with expertise in the treatment of endometriosis; and
9. A failed trial at least one month in duration with nonsteroidal anti-inflammatory drugs (NSAIDs) or a patient-specific, clinically significant reason why the member cannot use NSAIDs; and
10. A failed trial at least three months in duration of hormonal contraceptives or a patient-specific, clinically significant reason why the member cannot use hormonal contraceptives; and

11. A patient-specific, clinically significant reason why the member cannot use leuprolide depot formulations which are available without prior authorization; and
12. Dosing and lifetime approval duration will be limited based on the following:
    a. Coexisting condition of moderate hepatic impairment (Child-Pugh B):
        i. 150mg once daily for a maximum of 6 months; or
    b. Normal liver function or mild hepatic impairment (Child-Pugh A):
        i. 150mg once daily for a maximum of 24 months; or
        ii. 200mg twice daily for a maximum of 6 months.

Additionally, the College of Pharmacy recommends the placement of Triptodur® (triptorelin) into Tier-3 of the Gonadotropin-Releasing Hormone (GnRH) Medications Product Based Prior Authorization (PBPA) category as shown in red:

Supprelin® LA (Histrelin), Synarel® (Nafarelin), and Triptodur® (Triptorelin) Approval Criteria:

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

Gonadotropin-Releasing Hormone (GnRH) Medications		
Tier-1	**Tier-2**	**Tier-3**
leuprolide (Lupron Depot®)	histrelin (Supprelin® LA)	nafarelin (Synarel®)
leuprolide (Lupron Depot-Ped®)		**triptorelin (Triptodur®)**

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

Recommendation 4: Vote to Prior Authorize Yescarta® (Axicabtagene) and to Update the Acute Lymphoblastic Leukemia (ALL) and Chronic Myeloid Leukemia (CML) Medications Approval Criteria

MOTION CARRIED by unanimous approval.

Recommendations:

- Update the prior authorization criteria to reflect new FDA approved indications and guideline recommendations. Changes can be seen in the following criteria listed in red (only criteria with updates listed).
- The prior authorization of Yescarta® (axicabtagene) with the following criteria listed in red:

Yescarta® (Axicabtagene) Approval Criteria [Lymphoma Diagnosis]:

1. Large B-cell lymphoma [including diffuse large B cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)]; and
2. Member must be 18 years of age or older; and
3. Relapsed or refractory disease; and
4. Member must not have primary central nervous system lymphoma; and
5. Member must have had two or more lines of therapy; and
6. Health care facilities must be on the certified list to administer chimeric antigen receptor (CAR) T-cells and must be trained in the management of cytokine release syndrome (CRS), neurologic toxicities, and comply with the REMS requirements.

Bosulif® (Bosutinib) Approval Criteria [Chronic Myeloid Leukemia (CML) Diagnosis]:

1. Members with chronic, accelerated, or blast phase CML; and ~~with resistance or intolerance after primary treatment with either: dasatinib, imatinib, or nilotinib with the following BCR-ABL1 transcript levels:~~
   ~~a. 0.01% to 1% at >12 months; or~~
   ~~b. >1% to 10% at ≥12 months; or~~
   ~~c. >10% at any milestone.~~
2. Newly diagnosed or resistant/intolerant to other tyrosine kinase inhibitors (TKIs).

Kymriah® (Tisagenlecleucel) Approval Criteria [Lymphoma Diagnosis]:

1. Large B-cell lymphoma [including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL)]; and
2. Relapsed or refractory disease; and
3. Member must be 18 years of age or older; and
4. Member must not have primary central nervous system lymphoma; and
5. Member must have had two or more lines of therapy; and
6. Health care facilities must be on the certified list to administer chimeric antigen receptor (CAR) T-cells and must be trained in the management of cytokine release syndrome (CRS), neurologic toxicities, and comply with the REMS requirements.

Recommendation 5: Vote to Prior Authorize Braftovi™ (Encorafenib), Mektovi® (Binimetinib), and Libtayo® (Cemiplimab-rwlc)

MOTION CARRIED by unanimous approval.

Recommendations:

- Update the prior authorization criteria to reflect new FDA approved indications and guideline recommendations. Changes can be seen in the following criteria listed in red (only criteria with updates listed).
- The prior authorization of Braftovi™ (encorafenib), Mektovi® (binimetinib), and Libtayo® (cemiplimab-rwlc) with the following criteria listed in red:

Braftovi™ (Encorafenib) Approval Criteria [Melanoma Diagnosis]:

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
3. Used in combination with binimetinib.

Mektovi® (Binimetinib) Approval Criteria [Melanoma Diagnosis]:

1. Diagnosis of unresectable or metastatic melanoma; and
2. BRAF V600E or V600K mutation; and
3. Used in combination with encorafenib.

Libtayo® (Cemiplimab-rwlc) Approval Criteria [Cutaneous Squamous Cell Carcinoma (CSCC) Diagnosis]:

1. Diagnosis of metastatic or locally advanced CSCC; and
2. Member is not eligible for curative surgery or radiation; and
3. Member has not received prior immunotherapy agent(s) [e.g., Keytruda® (pembrolizumab), Opdivo® (nivolumab), Yervoy® (ipilimumab)].

Opdivo® (Nivolumab) Approval Criteria [Metastatic Colorectal Cancer (mCRC) Diagnosis]:

1. Diagnosis of mCRC; and
2. Disease has progressed on treatment with 5-FU, oxaliplatin, and irinotecan; and
3. Tumor possesses high microsatellite-instability or mismatch repair deficiency; and
4. Used as a single-agent or in combination with ipilimumab.

Yervoy® (Ipilimumab) Approval Criteria [Metastatic Colorectal Cancer (mCRC) Diagnosis]:

1. Diagnosis of mCRC; and
2. Disease has progressed on treatment with 5-FU, oxaliplatin, and irinotecan; and
3. Tumor possesses microsatellite instability-high or mismatch repair deficiency; and
4. Used in combination with nivolumab.

Mekinist® (Trametinib) Approval Criteria [Anaplastic Thyroid Cancer (ATC) Diagnosis]:

1. Diagnosis of ATC; and
2. Locally advanced or metastatic disease; and
3. BRAF V600E mutation; and
4. No satisfactory locoregional treatment options.

Tafinlar® (Dabrafenib) Approval Criteria [Anaplastic Thyroid Cancer (ATC) Diagnosis]:

1. Diagnosis of ATC; and
2. Locally advanced or metastatic disease; and
3. BRAF V600E mutation; and
4. No satisfactory locoregional treatment options.

Zelboraf® (Vemurafenib) Approval Criteria [Erdheim-Chester Disease (ECD) Diagnosis]:

1. Diagnosis of ECD; and
2. BRAF V600E or V600K mutation; and
3. Vemurafenib must be used as a single-agent.

Recommendation 6: Annual Review of Factor Replacement Products and 30-Day Notice to Prior Authorize Hemlibra® (Emicizumab-kxwh), Feiba® (Anti-Inhibitor Coagulant Complex), NovoSeven® RT [Coagulation Factor VIIa (Recombinant)], and Jivi® [Antihemophilic Factor (Recombinant), PEGylated-aucl]

NO ACTION REQUIRED.

Recommendation 7: Vote to Prior Authorize Nocdurna® [Desmopressin Acetate Sublingual (SL) Tablet]

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends placement of Nocdurna® (desmopressin acetate SL tablets) into the Special Prior Authorization (PA) Tier of the Bladder Control Medications Product Based Prior Authorization (PBPA) category with criteria similar to Noctiva™ (desmopressin acetate nasal spray):

Nocdurna® (Desmopressin Acetate Sublingual Tablets) Approval Criteria:

1. An FDA approved diagnosis of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void; and
2. All other causes of nocturia have been ruled out or adequately treated [e.g., benign prostatic hyperplasia (BPH), overactive bladder (OAB), obstructive sleep apnea (OSA)]; and
3. The prescriber must confirm the member has a 6-month history of at least two nocturic episodes per night; and
4. Member has failed behavior modifications including reducing caffeine intake, alcohol intake, and nighttime fluid intake; and
5. Member must have failed a trial of DDAVP® (desmopressin acetate tablets) or have a patient-specific, clinically significant reason why the standard tablet formulation cannot be used; and
6. The prescriber must be willing to measure serum sodium levels prior to starting treatment and document levels are acceptable; and
7. The prescriber must agree to monitor serum sodium levels within the first week and approximately one month after starting treatment, and periodically during treatment; and
8. The prescriber must confirm the member is not taking loop diuretics; and
9. The prescriber must confirm the member does not have renal impairment with an estimated glomerular filtration rate (eGFR) <50mL/min/1.73m^2; and
10. Initial approvals will be for the duration of 3 months; for continued authorization the prescriber must provide the following:
    a. Documentation that serum sodium levels are acceptable to the prescriber; and
    b. Documentation that the member is responding to treatment; and
11. Approvals will be limited to the 27.7mcg dose for female members; and
12. A quantity limit of 30 tablets per 30 days will apply.

The College of Pharmacy also recommends updating the Noctiva™ (desmopressin acetate nasal spray) criteria as shown in red to be consistent with Nocdurna® (desmopressin acetate SL tablets) criteria and clarify the quantity limit to ensure appropriate use:

Noctiva™ (Desmopressin Acetate Nasal Spray) Approval Criteria:

1. An FDA approved diagnosis of nocturia due to nocturnal polyuria in adults ~~50 years of age and older~~; and

2. All other causes of nocturia have been ruled out or adequately treated [e.g., benign prostatic hyperplasia (BPH), overactive bladder (OAB), obstructive sleep apnea (OSA)]; and
3. The prescriber must confirm the member has a 6-month history of at least two nocturic episodes per night; and
4. Member has failed behavior modifications including reducing caffeine intake, alcohol intake, and nighttime fluid intake; and
5. Member must have failed a trial of DDAVP® (desmopressin tablets) or have a patient-specific, clinically significant reason why the tablet formulation cannot be used; and
6. The prescriber must be willing to measure serum sodium levels within seven days of anticipated start of treatment and document levels are acceptable; and
7. The prescriber must agree to monitor serum sodium levels within one month of starting treatment or increasing the dose; and
8. The prescriber must confirm the member is not taking any of the following:
    a. Other medications via the nasal route; or
    b. Loop diuretics; and
9. The prescriber must confirm the member does not have renal impairment with an estimated glomerular filtration rate (eGFR) below 50mL/min/1.73m^2; and
10. Initial approvals will be for the duration of 3 months; for continued authorization the prescriber must provide the following:
    a. Documentation that serum sodium levels are acceptable to the prescriber; and
    b. Documentation that the member is responding to treatment; and
11. A quantity limit of one bottle (3.8g) per 30 days will apply.

Additionally, the College of Pharmacy recommends updating the Bladder Control Medications PBPA Tier-3 criteria to include the use of Myrbetriq® in combination with VESIcare® (changes noted in red):

Bladder Control Medications Tier-3 Approval Criteria:

1. A trial of all Tier-1 and Tier-2 medications that yielded inadequate clinical response or adverse effects; or
2. A unique indication which the Tier-1 and Tier-2 medications lack.
3. For use of Myrbetriq® (mirabegron) in combination with VESIcare® (solifenacin), the member must have failed monotherapy with either mirabegron or solifenacin (minimum 4-week trial) defined by continued symptoms of urge urinary incontinence, urgency, and urinary frequency. Current tier structure rules will also apply.

Finally, the College of Pharmacy recommends the following:

1. Move trospium (Sanctura®) from Tier-2 to Tier-1 based on National Average Drug Acquisition Cost (NADAC).
2. Move tolterodine extended-release (ER) (Detrol LA®) from Tier-3 to Tier-2 based on NADAC. Current Tier-2 criteria will apply.

Bladder Control Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
fesoterodine (Toviaz®)	tolterodine (Detrol®)	darifenacin (Enablex®)	desmopressin acetate nasal spray (Noctiva™)+

Bladder Control Medications			
Tier-1	**Tier-2**	**Tier-3**	**Special PA**
oxybutynin (Ditropan®)	**tolterodine ER (Detrol LA®)**	mirabegron (Myrbetriq®)[Δ]	**desmopressin acetate SL tablets (Nocdurna®)[+]**
oxybutynin ER (Ditropan XL®)		oxybutynin gel (Gelnique®)	oxybutynin patch (Oxytrol®)[+]
trospium (Sanctura®)		solifenacin (VESIcare®)[Δ]	
		trospium ER (Sanctura XR®)	

Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
ER = extended release; PA = prior authorization; SL = sublingual
[+]Unique criteria specific to Oxytrol® (oxybutynin patch), Noctiva™ (desmopressin acetate nasal spray), and Nocdurna® (desmopressin acetate sublingual tablet) applies.
[Δ]Unique criteria specific to use of Myrbetriq® (mirabegron) in combination with VESIcare® (solifenacin) applies.

Recommendation 8: Vote to Prior Authorize Krystexxa® (Pegloticase)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the prior authorization of Krystexxa® (pegloticase) with the following criteria:

Krystexxa® (Pegloticase) Approval Criteria:

1. An FDA approved diagnosis of gout; and
2. Member must have symptomatic gout with:
   a. ≥3 gout flares in the previous 18 months; or
   b. ≥1 gout tophus; or
   c. Gouty arthritis; and
3. Failure of the following urate lowering therapies: allopurinol, febuxostat, lesinurad, and probenecid titrated to the maximum tolerable dose for at least 3 months; and
4. Pegloticase must be administered in a health care setting by a health care provider prepared to manage anaphylaxis; and
5. Prescriber must attest that the member will be pre-medicated with antihistamines and corticosteroids to reduce the risk of anaphylaxis; and
6. Prescriber must document that member does not have glucose-6-phosphate dehydrogenase (G6PD) deficiency prior to starting pegloticase; and
7. Member must discontinue oral urate-lowering agents prior to starting pegloticase; and
8. Member must receive gout flare prophylaxis with non-steroidal anti-inflammatory drug(s) (NSAIDs) or colchicine at least 1 week before initiation of pegloticase therapy and continue for at least 6 months unless medically contraindicated or member is unable to tolerate therapy.
9. Approvals will be for the duration of 6 months. Reauthorizations may be granted if the prescriber documents the member is responding well to treatment, and member has not exceeded >4 consecutive weeks without therapy.

Recommendation 9: Vote to Prior Authorize Impoyz™ (Clobetasol Propionate 0.025% Cream)

MOTION CARRIED by unanimous approval.

The College of Pharmacy recommends the placement of Impoyz™ (clobetasol propionate 0.025% cream) into Tier-3 of the Ultra-High to High Potency category of the Topical Corticosteroids Product Based Prior Authorization (PBPA) Tier Chart. Current Tier-3 criteria would apply. Additionally, the College of Pharmacy recommends the following changes to the Topical Corticosteroids PBPA category:

1. Move Synalar® (fluocinolone acetonide 0.01% cream) from Tier-1 to Tier-2 of the Low Potency category of the Topical Corticosteroid PBPA Tier Chart based on net cost.
2. Move desonide 0.05% lotion and desonide emollient 0.05% cream and ointment from Tier-2 to Tier-3 of the Low Potency category of the Topical Corticosteroid PBPA Tier Chart based on net cost.
3. Move mometasone furoate 0.1% ointment from Tier-2 to Tier-1 of the Medium/High to Medium Potency category of the Topical Corticosteroid PBPA Tier Chart based on net cost.

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

Tier-2 Topical Corticosteroid Approval Criteria:

1. Documented trials of all Tier-1 topical corticosteroids of similar potency in the past 30 days that did not yield adequate relief; and
2. If Tier-1 trials are completed and do not yield adequate relief, a patient-specific, clinically significant reason for requesting a Tier-2 in the same potency instead of trying a higher potency medication must be provided; and
3. When the same medication is available in Tier-1, a patient-specific, clinically significant reason must be provided for use of a special dosage formulation of the requested medication in Tier-2 (e.g., foams, shampoos, sprays, kits); and
4. Topical corticosteroid kits require tier trials and a patient-specific, clinically significant reason for use of the kit over other standard formulations.

Tier-3 Topical Corticosteroid Approval Criteria:

1. Documented trials of all Tier-1 and Tier-2 topical corticosteroids of similar potency in the past 90 days that did not yield adequate relief; and
2. If Tier-1 and Tier-2 trials are completed and do not yield adequate relief, a patient-specific, clinically significant reason for requesting a Tier-3 in the same potency instead of trying a higher potency medication must be provided; and
3. When the same medication is available in Tier-1 or Tier-2, a patient-specific, clinically significant reason must be provided for use of a special dosage form of the requested medication in Tier-3 (e.g., foams, shampoos, sprays, kits); and
4. Topical corticosteroid kits require tier trials and a patient-specific, clinically significant reason for use of the kit over other standard formulations.

Topical Corticosteroids					
Tier-1		**Tier-2**		**Tier-3**	
Ultra-High to High Potency					
augmented betamethasone dipropionate 0.05% (**Diprolene AF®**)	**C,G**	amcinonide 0.1%	**C,O,L**	**clobetasol propionate 0.025% (Impoyz™)**	**C**
betamethasone dipropionate 0.05% (**Diprosone®**)	**O**	augmented betamethasone dipropionate 0.05% (**Diprolene®**)	**O,L**	clobetasol propionate 0.05% (**Clobex®**)	**Sh,Spr**
clobetasol propionate 0.05% (**Temovate®**)	**C,So**	betamethasone dipropionate 0.05% (**Diprosone®**)	**C**	clobetasol propionate 0.05% (**Olux®, Olux-E®**)	**F**
fluocinonide 0.05%	**C,O, So**	clobetasol propionate 0.05% (**Clobex®**)	**L**	clobetasol propionate 0.05% (**Temovate®**)	**O**
halobetasol propionate 0.05% (**Ultravate®**)	**C**	clobetasol propionate 0.05% (**Temovate®**)	**G**	desoximetasone 0.25% (**Topicort®**)	**C,O,Spr**
		desoximetasone 0.05% (**Topicort®**)	**G**		
		diflorasone diacetate 0.05% (**Apexicon®**)	**C**		
		diflorasone diacetate 0.05% (**Apexicon E®**)	**C,O**		
		fluocinonide 0.05%	**G**		
		fluocinonide 0.1% (**Vanos®**)	**C**		
		flurandrenolide tape 0.05% (**Cordran®**)	**Tape**		
		halcinonide 0.1% (**Halog®**)	**C,O**		
		halobetasol propionate 0.05% (**Ultravate®**)	**L,O**		
		halobetasol propionate/lactic acid 0.05%/10% (**Ultravate X®**)	**C**		
Medium/High to Medium Potency					
betamethasone dipropionate 0.05%	**L**	betamethasone dipropionate/calcipotriene 0.064%/0.005% (**Taclonex®**)	**O,Sus, Spr**	betamethasone dipropionate 0.05% (**Sernivo®**)	**Spr**
betamethasone valerate 0.1% (**Beta-Val®**)	**C,O, L**	betamethasone valerate 0.12% (**Luxiq®**)	**F**	hydrocortisone valerate 0.2% (**Westcort®**)	**C,O**
fluticasone propionate 0.05% (**Cutivate®**)	**C,O**	calcipotriene/betamethasone dipropionate 0.064%/0.005% (**Enstilar®**)	**F**		
mometasone furoate 0.1% (**Elocon®**)	**C,L, S,O**	clocortolone pivalate 0.1% (**Cloderm®**)	**C**		
triamcinolone acetonide 0.025%	**O**	desoximetasone 0.05% (**Topicort LP®**)	**C,O**		
triamcinolone acetonide 0.1%	**C,O, L**	fluocinolone acetonide 0.025% (**Synalar®**)	**C,O**		
triamcinolone acetonide 0.5%	**C,O**	fluocinonide emollient 0.05% (**Lidex E®**)	**C**		
		flurandrenolide 0.05%	**C,L,O**		
		fluticasone propionate 0.05% (**Cutivate®**)	**L**		

Topical Corticosteroids					
Tier-1		**Tier-2**		**Tier-3**	
		hydrocortisone butyrate 0.1%	**C,O,L,S**		
		hydrocortisone probutate 0.1% (**Pandel®**)	**C**		
		prednicarbate 0.1% (**Dermatop®**)	**O,C**		
		triamcinolone acetonide 0.147mg/g (**Kenalog®**)	**Spr**		
Low Potency					
desonide 0.05% (**Desonate®**)	**G**	alclometasone dipropionate 0.05% (**Aclovate®**)	**C,O**	fluocinolone acetonide 0.01% (**Derma-Smoothe®; Derma-Smoothe FS®**)	**Oil**
fluocinolone acetonide 0.01% (**Capex®**)	**Sh**	desonide 0.05% (**Verdeso®**)	**F**	**desonide 0.05%**	**L**
hydrocortisone acetate 1%	**C,O,**	fluocinolone acetonide 0.01% (**Synalar®**)	**So,C**	**desonide emollient 0.05%**	**C,O**
hydrocortisone acetate 2.5%	**C,O, L**	hydrocortisone 2.5% (**Texacort®**)	**So**		
hydrocortisone/urea 1%/10% (**U-Cort®**)	**C**	hydrocortisone/pramoxine 1%/1% (**Pramosone®**)	**C,L**		
triamcinolone acetonide 0.025%	**C,L**				

C= Cream; O = Ointment; L = Lotion; G = Gel, Sh = Shampoo; So = Solution; Spr = Spray; Sus = Suspension; F = Foam
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.

Recommendation 10: Annual Review of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Modulators and 30-Day Notice to Prior Authorize Symdeko® (Tezacaftor/Ivacaftor) and Orkambi® (Lumacaftor/Ivacaftor Oral Granules)

NO ACTION REQUIRED.

Recommendation 11: 30-Day Notice to Prior Authorize Onpattro™ (Patisiran) and Tegsedi™ (Inotersen)

NO ACTION REQUIRED.

Recommendation 12: Annual Review of Various Systemic Antibiotics and 30-Day Notice to Prior Authorize Zemdri™ (Plazomicin), Xerava™ (Eravacycline), Nuzyra™ (Omadacycline), Seysara™ (Sarecycline), and Ximino™ (Minocycline Extended-Release)

NO ACTION REQUIRED.

Recommendation 13: Annual Review of Hepatitis C Medications

NO ACTION REQUIRED.

Recommendation 14: 30-Day Notice to Prior Authorize Signifor® LAR (Pasireotide)

NO ACTION REQUIRED.

Recommendation 15: Industry News and Updates

NO ACTION REQUIRED.

Recommendation 16: U.S. Food and Drug Administration (FDA) and Drug Enforcement Administration (DEA) Updates

NO ACTION REQUIRED.

Recommendation 17: Future Business

NO ACTION REQUIRED.

November 12, 2018

Oklahoma Drug Utilization Board
c/o: Oklahoma Healthcare Authority
4345 N. Lincoln Blvd.
Oklahoma City, OK 73105

Re: Review of Hemophilia Agents

Dear DUR Board:

We are writing today on behalf of the National Hemophilia Foundation (NHF) and the Oklahoma Hemophilia Foundation (OHF) to comment on the upcoming November 14th Drug Utilization Review Board's review of Hemophilia agents. NHF is the nation's leading advocacy organization for individuals with bleeding disorders. Our mission is to ensure that individuals affected by hemophilia and other inherited bleeding disorders have timely access to quality medical care, therapies and services, regardless of financial circumstances or place of residence. OHF is the chapter based in the state of Oklahoma and is dedicated to service, education, and advocacy for Oklahomans with bleeding disorders.

NHF and OHF recognize the complexities involved in treating hemophilia and related bleeding disorders can result in high medical expenses for patients and their health insurance plans. While the need to identify cost containment strategies is necessary, it is critical that such strategies not compromise care for those with complex medical conditions. Hemophilia and related bleeding disorders are rare, complex genetic conditions for which there are no known cures. Individuals often experience spontaneous and prolonged internal bleeding into the joints and soft tissues. To effectively manage these disorders, patients often require life-long infusions of clotting factor therapies that replace the missing or deficient blood proteins, thus preventing debilitating and life-threatening internal bleeding.

While today's therapies are safer and more effective than ever, they are also more costly than other types of medication. For example, cost of treatment for a person with severe hemophilia can reach $350,000 per year or more.

Developing an inhibitor (i.e., an immune response to treatment) or other complications such as HIV/AIDS, hepatitis, chronic joint disease, or bleeding as a direct result of trauma or surgery can increase those costs to over $1 million.

Clotting factor and non-factor replacement therapies are biological products derived from human blood plasma or by using recombinant technology for which there are no generic equivalents. Moreover, because of the nature of bleeding disorders, an individual's response and tolerability for a specific product is unique. For these reasons, NHF's Medical and Scientific Advisory Council (MASAC) recommends that individuals retain access to the full range of FDA-approved clotting factor products.[1] Limiting access through the use of restrictive drug formularies such as those requiring prior authorization, preferred drug lists (PDLs), and fail first/step therapy, could have a negative impact on patient care and ultimately result in higher drug spends. Therefore, drug benefit designs employing these methods should be avoided, and the choice of product used by an individual should remain a decision between patient and physician.[2]

On behalf of individuals in the State of Oklahoma affected by bleeding disorders, we urge you to prioritize the practice of allowing patient access to all FDA-approved therapies available to treat hemophilia and related bleeding disorders. In the event the state decides to manage clotting factor products, we want to be a resource to help mitigate any potential excess costs associated with our patients not having access to the medication they need.

Thank you for the opportunity to share our concerns. If you would like additional information or have questions, please feel free to me at 317-517-3032 or mrice@hemophilia.org.

Thank you,

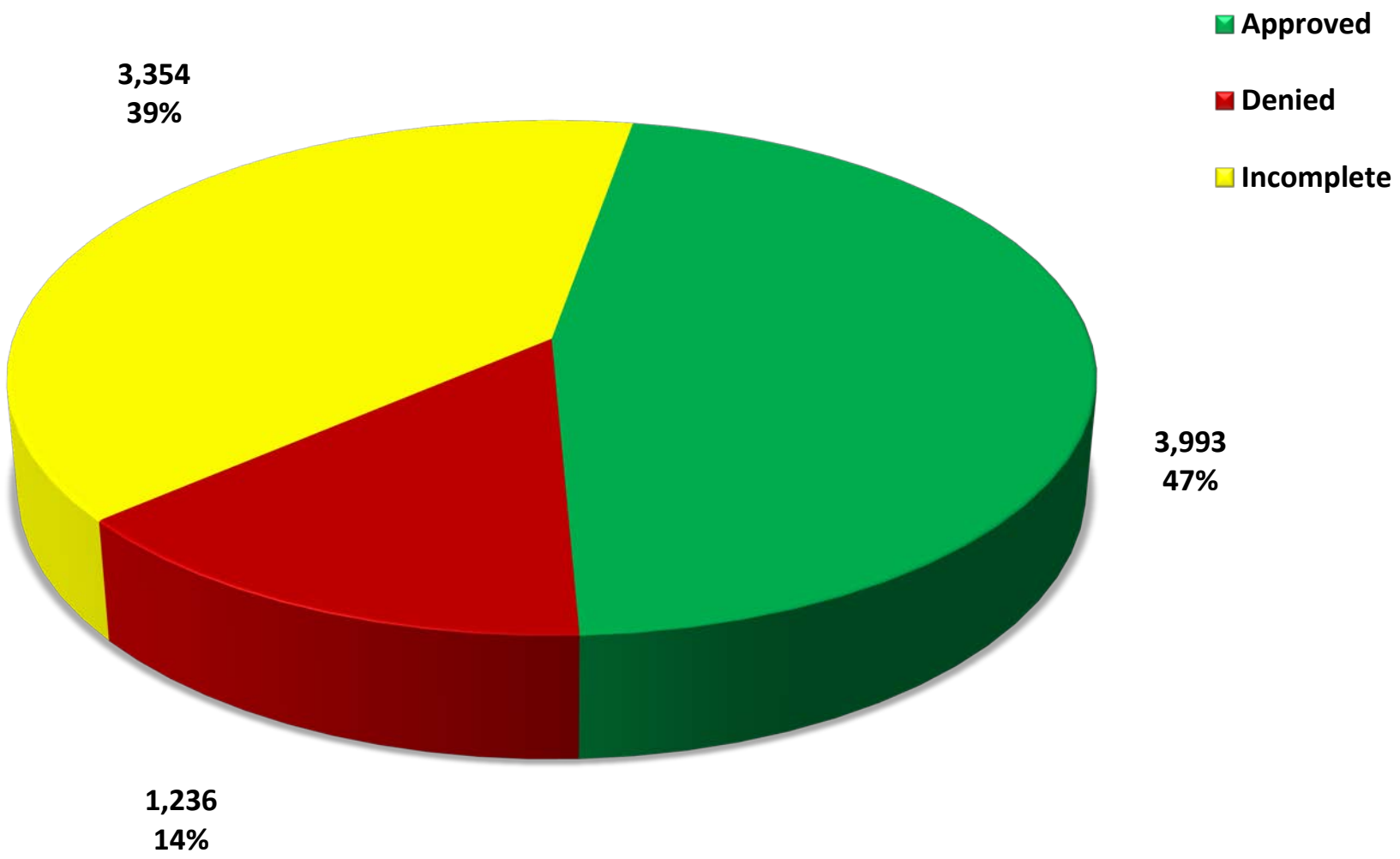
Michelle Rice
Sr. Vice President, External Affairs
National Hemophilia Foundation

Kathleen Montgomery
Executive Director
Oklahoma Hemophilia Foundation

[1] MASAC Document #253 (2018) Recommendation Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. www.hemophilia.org
[2] MASAC Document #166 (2005) MASAC Resolution Regarding Preferred Drug Lists. www.hemophilia.org

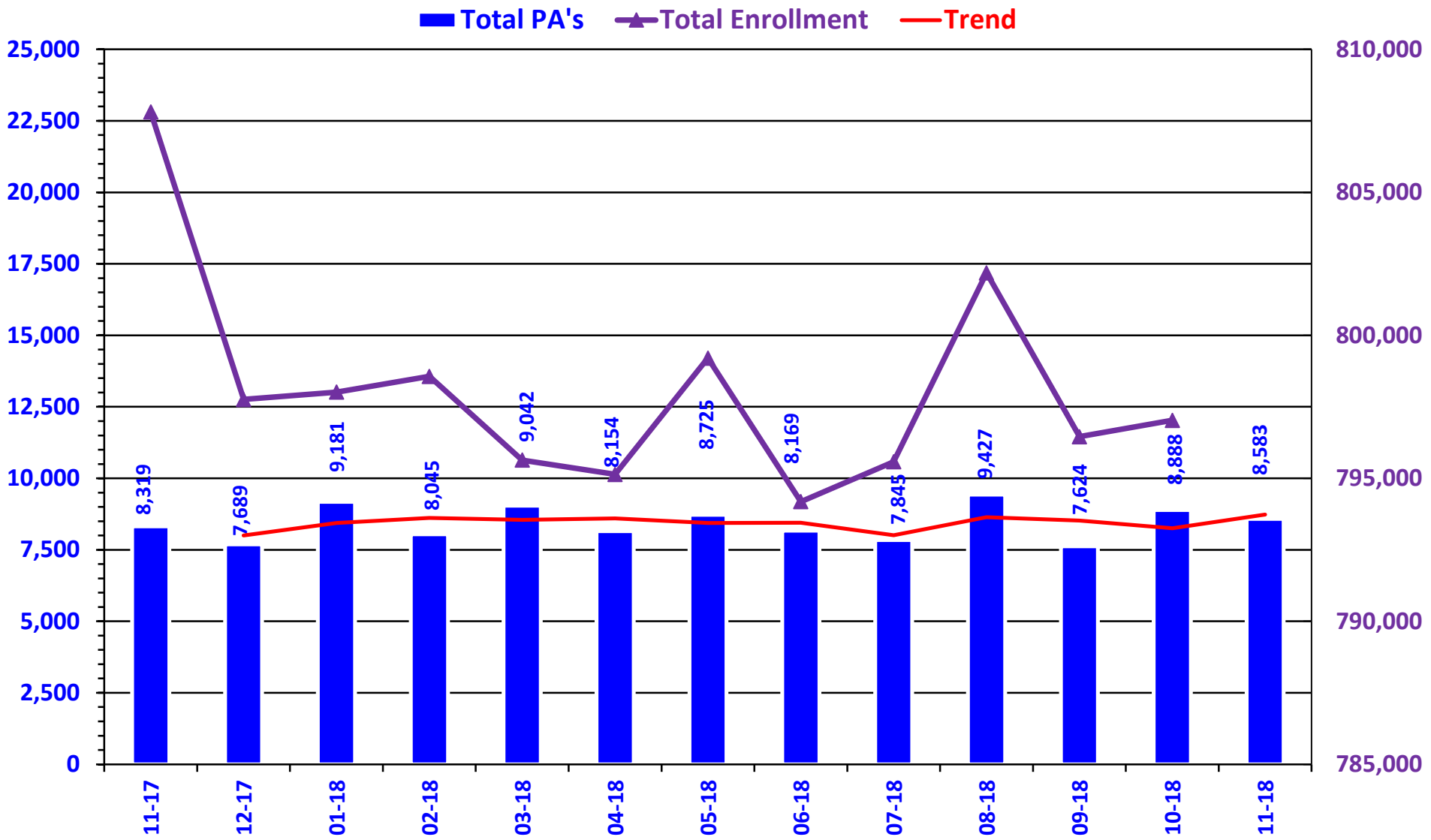
Appendix B

PRIOR AUTHORIZATION ACTIVITY REPORT: NOVEMBER 2018



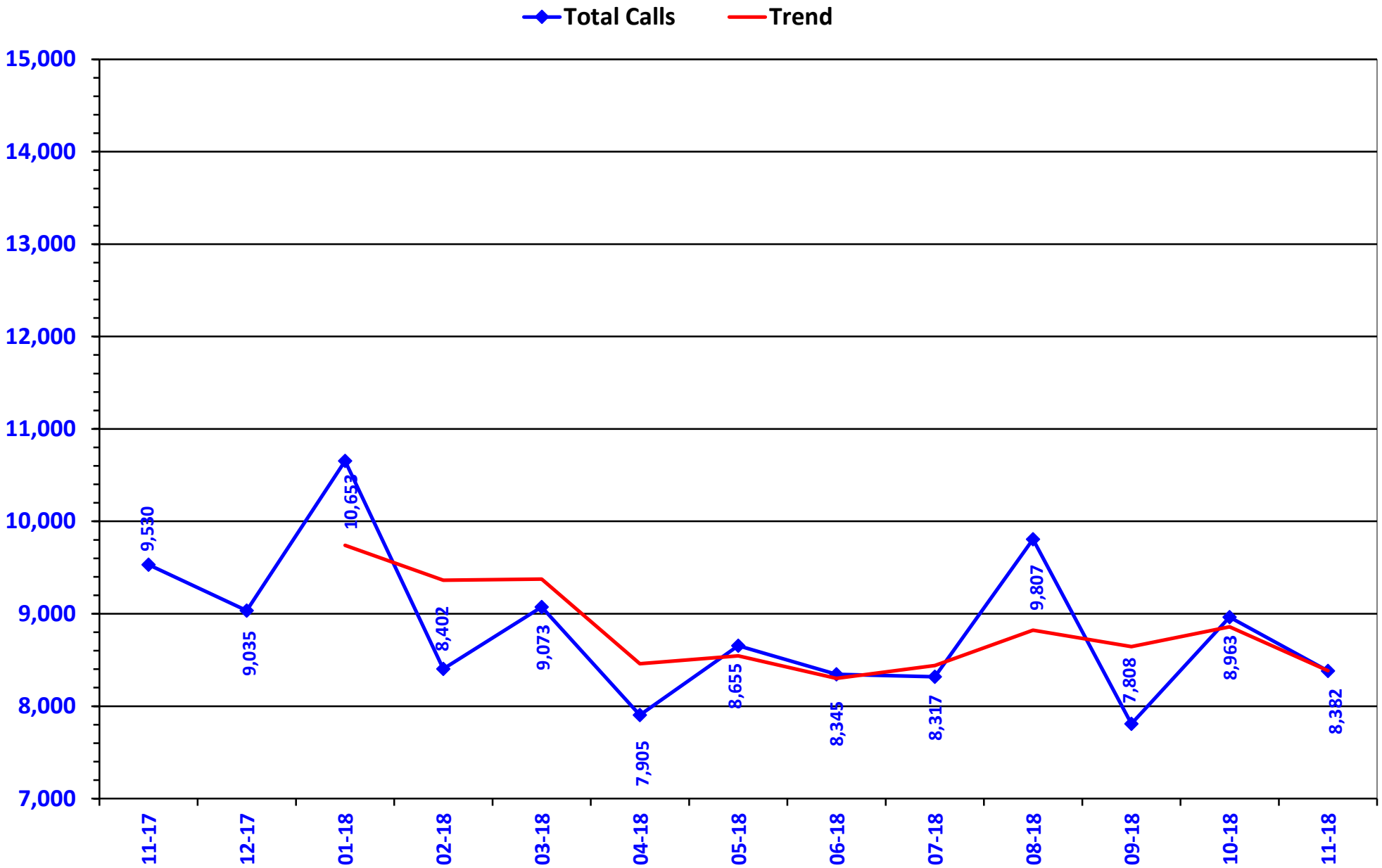
PA totals include approved/denied/incomplete/overrides

PRIOR AUTHORIZATION REPORT: NOVEMBER 2017 – NOVEMBER 2018



PA totals include approved/denied/incomplete/overrides

CALL VOLUME MONTHLY REPORT:
NOVEMBER 2017 – NOVEMBER 2018



Prior Authorization Activity

11/1/2018 Through 11/30/2018

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Advair/Symbicort/Dulera	117	10	24	83	155
Analgesic - NonNarcotic	27	0	3	24	0
Analgesic - Narcotic	351	163	45	143	158
Angiotensin Receptor Antagonist	16	6	4	6	359
Antiasthma	72	15	20	37	251
Antibiotic	33	14	2	17	195
Anticonvulsant	148	59	25	64	315
Antidepressant	203	60	32	111	329
Antidiabetic	259	86	43	130	349
Antigout	10	5	1	4	359
Antihistamine	13	3	4	6	267
Antimigraine	94	5	25	64	111
Antineoplastic	71	53	5	13	158
Antiparasitic	16	4	2	10	5
Antiulcers	165	42	55	68	118
Antiviral	12	4	2	6	44
Anxiolytic	88	35	5	48	311
Atypical Antipsychotics	242	132	21	89	345
Biologics	117	66	15	36	291
Bladder Control	59	11	16	32	333
Blood Thinners	267	146	16	105	339
Botox	46	35	5	6	337
Buprenorphine Medications	424	304	20	100	79
Cardiovascular	98	46	14	38	337
Chronic Obstructive Pulmonary Disease	165	39	33	93	334
Constipation/Diarrhea Medications	122	25	41	56	201
Contraceptive	16	10	0	6	292
Dermatological	136	21	52	63	217
Diabetic Supplies	443	260	14	169	216
Endocrine & Metabolic Drugs	175	110	14	51	127
Erythropoietin Stimulating Agents	26	10	7	9	107
Fibromyalgia	218	39	93	86	337
Gastrointestinal Agents	120	24	26	70	193
Growth Hormones	77	57	3	17	149
Hepatitis C	179	112	23	44	9
HFA Rescue Inhalers	63	1	15	47	360
Insomnia	37	4	16	17	221
Insulin	100	31	14	55	335
Miscellaneous Antibiotics	19	4	1	14	13
Multiple Sclerosis	54	29	8	17	169
Muscle Relaxant	39	7	8	24	24
Nasal Allergy	81	11	28	42	135
Neurological Agents	107	36	20	51	229
NSAIDs	156	19	35	102	208
Ocular Allergy	25	11	4	10	159
Ophthalmic Anti-infectives	13	3	3	7	14
Osteoporosis	19	6	0	13	327
Other*	364	74	98	192	269
Otic Antibiotic	22	2	4	16	6
Respiratory Agents	33	19	0	14	165

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

	Total	Approved	Denied	Incomplete	Average Length of Approvals in Days
Statins	16	3	1	12	268
Stimulant	718	331	60	327	345
Synagis	254	100	63	91	137
Testosterone	43	15	6	22	335
Topical Antifungal	40	5	11	24	90
Topical Corticosteroids	64	1	39	24	360
Vitamin	73	24	17	32	155
Pharmacotherapy	75	70	0	5	302
Emergency PAs	0	0	0	0	
Total	**7,040**	**2,817**	**1,161**	**3,062**	
Overrides					
Brand	59	31	4	24	213
Compound	30	25	0	5	37
Cumulative Early Refill	2	1	0	1	180
Diabetic Supplies	7	6	0	1	164
Dosage Change	295	276	3	16	12
High Dose	3	2	1	0	223
Ingredient Duplication	11	9	0	2	9
Lost/Broken Rx	87	82	3	2	13
NDC vs Age	291	192	23	76	262
Nursing Home Issue	77	71	1	5	13
Opioid MME Limit	1	1	0	0	1
Opioid Quantity	40	32	3	5	130
Other*	42	36	1	5	13
Quantity vs. Days Supply	515	348	31	136	245
STBS/STBSM	24	18	3	3	82
Stolen	12	10	1	1	13
Temporary Unlock	2	2	0	0	18
Third Brand Request	45	34	1	10	23
Overrides Total	**1,543**	**1,176**	**75**	**292**	
Total Regular PAs + Overrides	**8,583**	**3,993**	**1,236**	**3,354**	

Denial Reasons	
Unable to verify required trials.	2,681
Does not meet established criteria.	1,258
Lack required information to process request.	650
Other PA Activity	
Duplicate Requests	705
Letters	12,838
No Process	6
Changes to existing PAs	726
Helpdesk Initiated Prior Authorizations	552
PAs Missing Information	41

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

Chronic Medication Adherence Program Update

Oklahoma Health Care Authority
December 2018

Prescriber Mailing: Maintenance Diabetes and Cardiovascular Medications

The Chronic Medication Adherence (CMA) educational mailing is processed quarterly and sent to prescribers with members on chronic maintenance medications for diabetes (DM), blood pressure, or cholesterol. The purpose of these mailings is to encourage medication adherence and improve the quality of care for SoonerCare members on these medications.

Previously, prescribers were selected randomly to receive letters if they met the inclusion criteria for the mailing module. In February 2016, the CMA mailing changed to sending the educational letters to the same consistent prescribers. Included prescribers will receive 4 letters per year to better inform them of their SoonerCare patients using maintenance medications and to make their patients' adherence more convenient to track over time including any improvements or changes. In February 2018, the mailing was updated to include both cardiovascular (CV) and DM medications in each mailing rather than alternating with each mailing. Inclusion criteria required the prescriber to have ≥2 SoonerCare patients taking DM, blood pressure, and cholesterol medications. The consistent prescriber list is updated approximately once per year to account for providers who move out of state, retire, or no longer contract with SoonerCare. The review period for each mailing is one year and patients are assigned to prescribers if they are the last prescriber of record for a maintenance medication on paid pharmacy claims.

Each mailing includes a prescriber summary report with a "star rating" based on their overall percentage of patients considered adherent to chronic maintenance medications. Adherence is estimated by measuring the Proportion of Days Covered (PDC), or percent of days in the past year covered by prescription claims. A patient is considered adherent if their PDC ≥80%. A patient is considered non-adherent if their PDC is <80%. A higher percentage (and corresponding star rating) is better and indicates that more of their patients are adherent to their maintenance medications. Each mailing also includes a list of medication adherence patient resources intended to offer prescribers methods to improve their patients' adherence.

Cardiovascular Mailing Summary

- Addresses adherence to maintenance renin angiotensin system (RAS) antagonists [i.e., angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), direct renin inhibitors] and HMG-CoA reductase inhibitors (i.e., statins)

Date Letter Processed	Total Letters Mailed	Total Members Included
February 2015	345	6,672
August 2015	259	4,497
February 2016	231	3,835

Date Letter Processed	Total Letters Mailed	Total Members Included
August 2016	221	4,588
February 2017	207	4,025
August 2017	192	3,334

Adherence is shown in the Provider Summary Report as a percentage for RAS antagonists and as a percentage for statins, with a corresponding star rating for each category. The star ratings for the percentage of patients that are adherent to RAS antagonists or statins are based on the 2018 Medicare Star Ratings. However, a rating of zero stars is exclusive to SoonerCare. The following key is shown to illustrate the star ratings and adherence percentages for each star rating.

RAS Antagonists:

5 Stars: Excellent (≥89%)

4 Stars: Above Average (≥86% to <89%)

3 Stars: Average (≥83% to <86%)

2 Stars: Below Average (≥78% to <83%)

1 Star: Poor (≥60% to <78%)

0 Stars: Very Poor (<60%)

Statins:

5 Stars: Excellent (≥86%)

4 Stars: Above Average (≥82% to <86%)

3 Stars: Average (≥79% to <82%)

2 Stars: Below Average (≥73% to <79%)

1 Star: Poor (≥60% to <73%)

0 Stars: Very Poor (<60%)

Diabetes Mailing Summary

- Addresses adherence to maintenance medications for DM excluding insulin and Symlin® (pramlintide)

Date Letter Processed	Total Letters Mailed	Total Members Included
November 2014	457	2,894
May 2015	177	975
November 2015	378	2,288
May 2016	224	2,127
November 2016	212	1,633
May 2017	192	1,484
November 2017	172	1,341

Adherence is shown in the Provider Summary Report as a percentage and corresponding star rating for all DM medications (excluding insulin and Symlin®). The star ratings for the percentage of patients that are adherent to DM medications are based on the 2018 Medicare Star Ratings. However, a rating of zero stars is exclusive to SoonerCare. The following key is shown to illustrate the star ratings and adherence percentages for each star rating.

Diabetes Medications:

5 Stars: Excellent (≥86%)

4 Stars: Above Average (≥84% to <86%)

3 Stars: Average (≥80% to <84%)

2 Stars: Below Average (≥76% to <80%)

1 Star: Poor (≥60% to <76%)

0 Stars: Very Poor (<60%)

Combined Mailing Summary

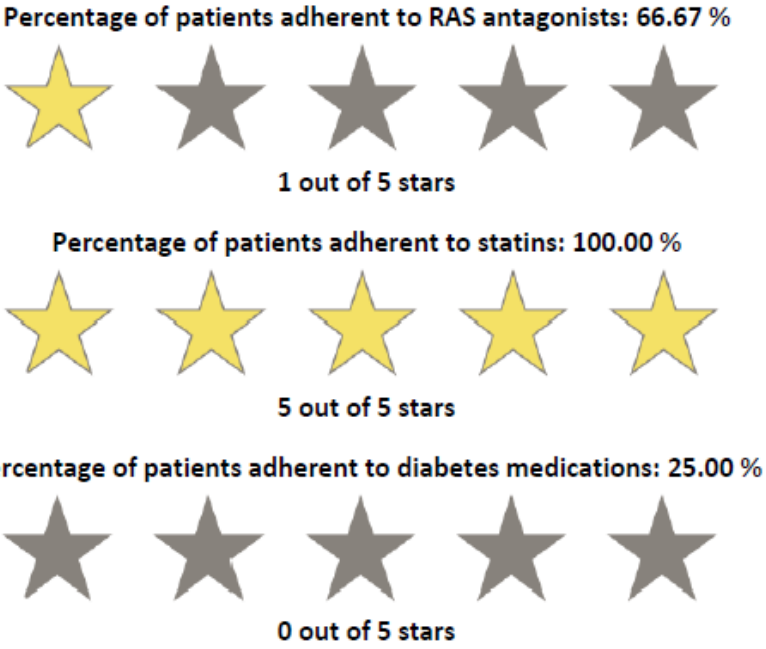
- Includes both CV and DM modules in one mailing; DM and CV inclusion criteria and star ratings remained the same as previous mailings

Date Letter Processed	Total Letters Mailed	Total Members Included
February 2018	278	7,190
May 2018	274	7,038
August 2018	272	6,900
November 2018	259	6,411

Example Star Rating[1]

Report date: <Report Date>
NPI: <Prescriber NPI>

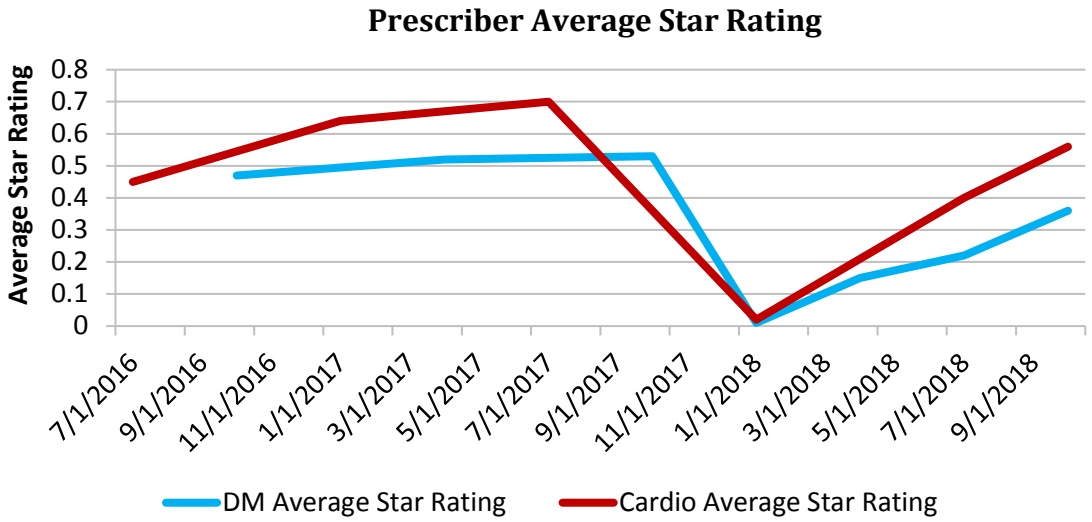
Provider: <Provider Name>
SoonerCare Provider ID: <Provider ID>



Chronic Medication Adherence Trends

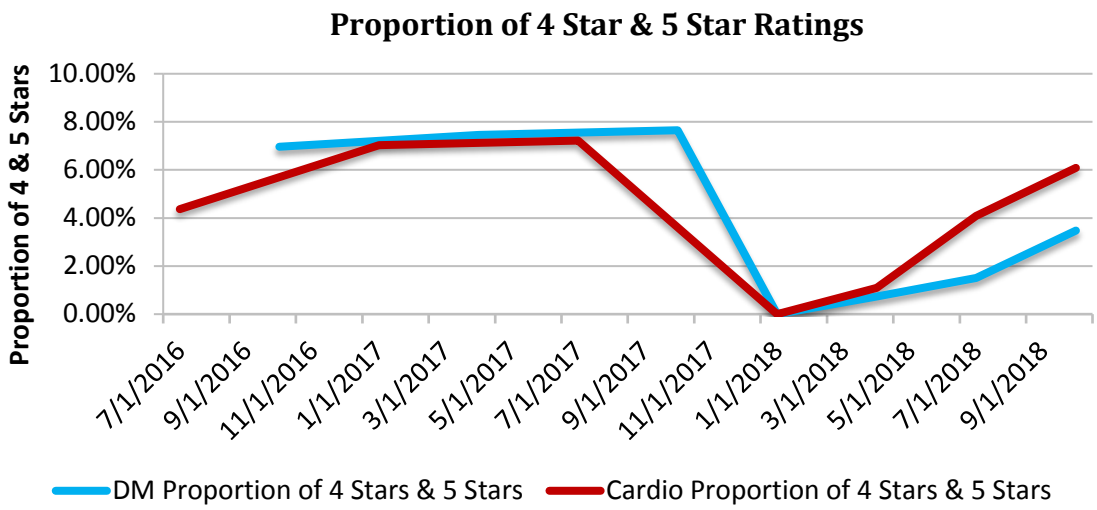
The following line graph shows trends in the average star rating for prescribers included in the mailing since July 2016. This graph is specific to those prescribers included in the mailings and differentiates between DM and CV (i.e., statins and RAS antagonists) modules. It is important to note that the prescriber mailing list was updated in February 2018 to include a larger number of prescribers as well as prescribers who were not previously receiving a mailing. Although trends are tracked over time, it may be more meaningful to evaluate 2018 as a new data set.

Prescribers selected for initial inclusion in the mailing were those prescribers with a 0 star rating and ≥2 patients in all categories (DM, statins, and RAS antagonists). An increase in the average star rating was seen for both mailing modules with a larger increase in the CV star ratings. Despite favorable increases in the average star ratings, opportunities for further enhancements continue to exist.



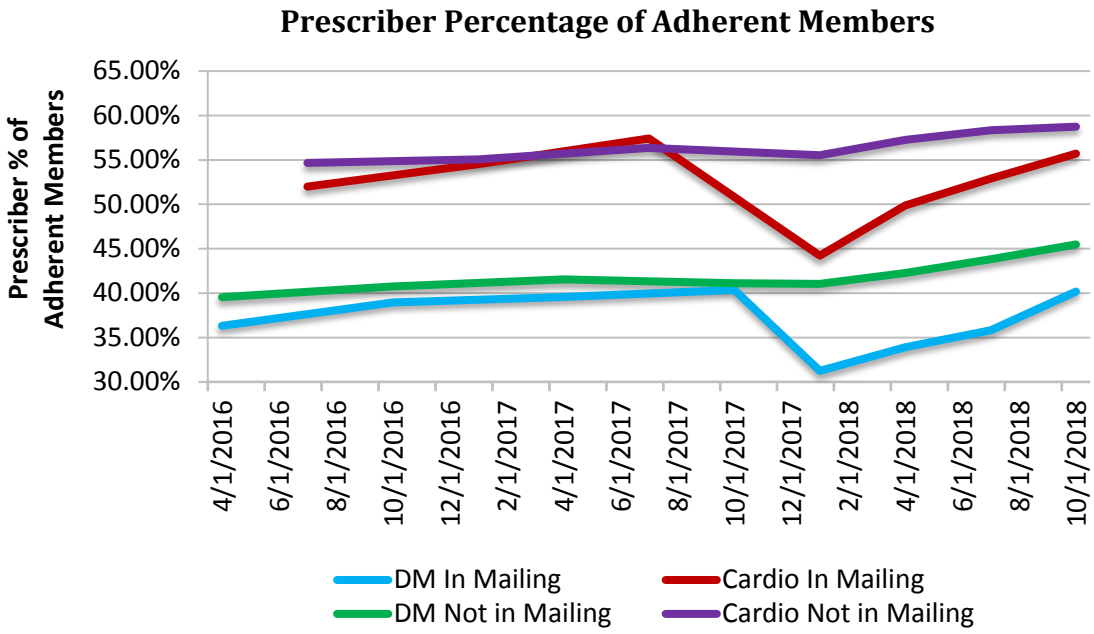
The following line graph shows trends in the proportion of prescribers with 4 star and 5 star ratings included in the mailing since July 2016. This graph is specific to those prescribers included in the mailings and differentiates between DM and CV modules. It is important to note that the prescriber mailing list was updated in February 2018 to include a larger number of prescribers as well as prescribers who were not previously receiving a mailing. Although trends are tracked over time, it may be more meaningful to evaluate 2018 as a new data set.

An increase in the proportion of 4 star and 5 star ratings was seen for both mailing modules with a larger increase in the CV module. Similar to the average star rating, while favorable increases were seen, opportunities for further enhancements continue to exist.



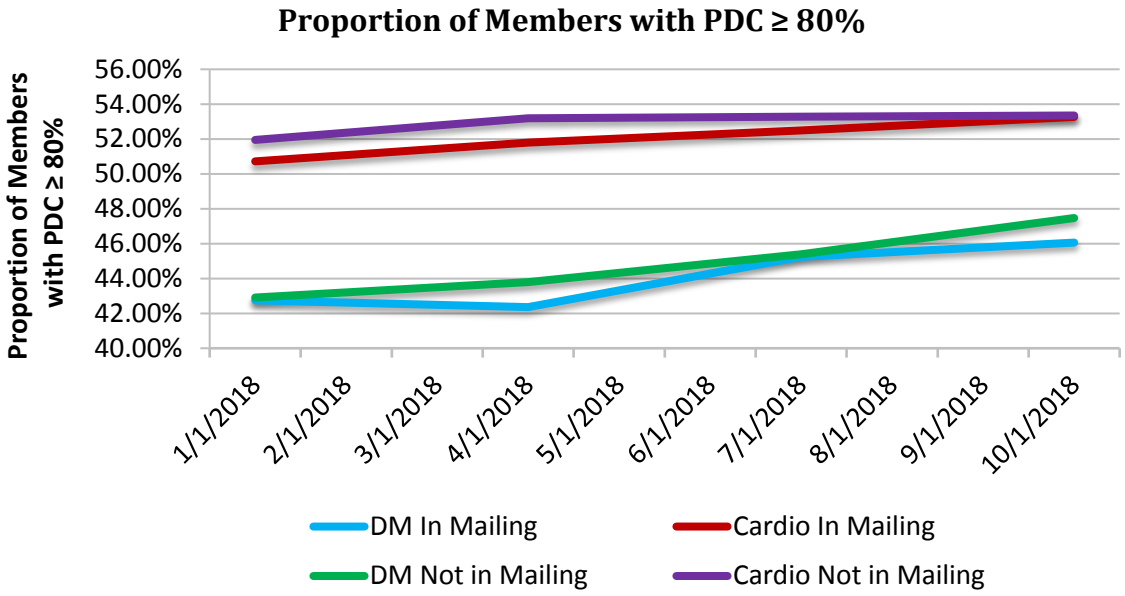
The following line graph shows trends in the average prescriber percentage of adherent members for prescribers included in the mailing compared to those not included in the mailing for both modules since April 2016. Those considered adherent had a PDC of ≥80%. It is important to note that the prescriber mailing list was updated in February 2018 to include a larger number of prescribers as well as prescribers who were not previously receiving a mailing. Although trends are tracked over time, it may be more meaningful to evaluate 2018 as a new data set. Please note, the vertical axis starts at a percentage of 30% in order to reflect small changes.

An increase in the prescriber percentage of adherent members was seen for both modules for those prescribers included in the mailing compared to a relatively linear trend for prescribers not included in the mailing. This indicates prescriber mailings may have a positive impact on the percentage of adherent members for prescribers.



The following line graph shows trends in the proportion of members with a PDC ≥80% for those with prescribers included in the mailing compared to those with prescribers not included in the mailing since January 2018. Please note, the vertical axis starts at a percentage of 40% in order to reflect small changes.

Unlike prescribers included in the mailings, members included in the mailings are not consistent and may change over time due to medication discontinuations or changing to a prescriber not included in the mailing. Despite member variability, overall trends show an increase in PDC over time for both members included in the mailing and members not included in the mailing.



Conclusions

Data specific to prescribers in the mailing shows an overall trend towards higher average star ratings and an increase in the prescriber percentage of adherent members using maintenance DM and CV medications. Trends in prescriber specific measures continue to show improvement and while favorable increases were seen, opportunities for further enhancements continue to exist. The College of Pharmacy will continue to monitor member adherence with the goal of achieving a member PDC of ≥80% and a 5 star rating of prescriber percentage of adherent members. New interventions will be implemented where appropriate, and results will be reported to the Drug Utilization Review (DUR) Board when available.

[1] Centers for Medicare & Medicaid Services (CMS): Medicare 2018 Part C & D Star Rating Technical Notes. Available online at: https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovgenin/performancedata.html. Last revised 03/27/2016. Last accessed 11/21/2018.

Appendix C

Vote to Prior Authorize Hemlibra® (Emicizumab-kxwh), Feiba® (Anti-Inhibitor Coagulant Complex), NovoSeven® RT [Coagulation Factor VIIa (Recombinant)], and Jivi® [Antihemophilic Factor (Recombinant), PEGylated-aucl]

Oklahoma Health Care Authority
December 2018

Introduction[1,2,3]

Hemophilia is a rare X-linked blood clotting disorder. It occurs in approximately 1 out of every 5,000 male births, and there is an estimated 20,000 males in the United States living with hemophilia. Patients with hemophilia have a mutation in one of the genes responsible for making a clotting protein needed to form blood clots. There are several different types of hemophilia. Those with hemophilia A are missing or have a decrease in clotting factor VIII (FVIII). Approximately 80% of patients with hemophilia are FVIII deficient. Patients who are missing factor IX or who have a decrease in clotting factor IX are classified as having hemophilia B, and make up about 20% of patients living with hemophilia.

The diagnosis of hemophilia is made by genetic testing. Many patients have a family history of hemophilia and are tested soon after birth. In approximately one-third of patients with hemophilia, there is no family history and a spontaneous gene mutation is responsible.

Most treatments for hemophilia revolve around replacing the missing clotting protein. There have been advances over the last few decades in factor replacement products. When factor concentrates were introduced, the products were blood donor derived, and each lot consisted of donor blood from thousands of people. As biological technology progressed, recombinant factor replacement was brought to market and has been improved in incremental steps to the current extended half-life factor replacement products. The clotting replacement factors are given intravenously. Patients and caregivers are taught how to administer these products at home, and treatment can be given on-demand when a bleeding episode occurs or prophylactically to prevent bleeding.

Good quality medical care from health care providers who are experts in hemophilia can help prevent some of the serious issues associated with hemophilia. Comprehensive hemophilia treatment centers (HTC) are usually the best choice for specialized hemophilia care. HTCs have a team of health care practitioners who have an expertise and focus in caring for patients with rare bleeding disorders which consists of hematologists, nurses, social workers, physical therapists, and others.

Approximately 1 in 5 patients with hemophilia A and 1 in 100 patients with hemophilia B will develop an antibody to factor replacement products. These antibodies are called inhibitors. Inhibitor development is a major complication for patients living with hemophilia and can increase the risk of morbidity. Treatment becomes difficult, very costly, and carries a large burden for the patient and caregivers. Depending on the inhibitor levels, the treatment options

vary. If the inhibitor level is low, then using large doses of clotting factor to overcome the inhibitor is an option. Some undergo immune tolerance induction (ITI) which attempts to teach the body that factor is a normal part of the blood. ITI requires large doses of factor everyday for weeks to months and possibly years. Bypassing agents (BPAs) are used to treat patients with high inhibitor levels. BPAs can be used prophylactically to prevent bleeding and can also be used to treat bleeding episodes. There are currently two BPAs on the market, Feiba® and NovoSeven® RT. Recently, the FDA approved a new treatment for patients with hemophilia A with inhibitors (and without), Hemlibra® (emicizumab-kxwh).

Recommendations

The Oklahoma Health Care Authority recommends the prior authorization of Jivi® [antihemophilic factor (recombinant) PEGylated-aucl], Hemlibra® (emicizumab-kxwh), Feiba® (anti-inhibitor coagulant complex), and NovoSeven® RT [coagulation factor VIIa (recombinant)] with the following criteria:

Adynovate®, Afstyla®, Alprolix®, Eloctate®, Idelvion®, Jivi®, and Rebinyn® Approval Criteria:

1. An FDA approved indication; and
2. Requested medication must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders; and
3. A patient-specific, clinically significant reason why the member cannot use the following:
    a. Hemophilia A: Advate® or current factor VIII replacement product; or
    b. Hemophilia B: Benefix® or current factor IX replacement product; and
4. A half-life study must be performed to determine the appropriate dose and dosing interval; and
5. Initial approvals will be for the duration of the half-life study. If the half-life study shows significant benefit in prolonged half-life, subsequent approvals will be for the duration of one year.

Hemlibra® (Emicizumab-kxwh) Approval Criteria:

1. Member must have a diagnosis of hemophilia A; and
2. Hemlibra® must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders; and
3. Prescriber must be able to monitor appropriate blood clotting tests and levels utilizing testing which accounts for the interaction of Hemlibra® and blood factors by following the Medical and Scientific Advisory Council (MASAC) guidance; and
4. For members with hemophilia A with an inhibitor to factor VIII:
    a. Member must have failed immune tolerance induction (ITI) or is not a good candidate for ITI; and
    b. Member's hemophilia cannot be managed without the use of bypassing agent(s) (e.g., Feiba®, NovoSeven® RT) as prophylaxis for prevention of bleeding episodes, or the member is unable to maintain venous access for daily infusions; and
    c. Member's hemophilia is not currently controlled with the use of bypassing agent(s); and

   d. Prescriber must counsel member and/or caregiver on the risks of utilizing Feiba® for breakthrough bleeding while on Hemlibra®, and member should be monitored closely if any bypassing agent is given; or
5. For members with hemophilia A without an inhibitor:
   a. Member's current prophylaxis therapy is not adequate to prevent spontaneous bleeding episodes, or the member is unable to maintain venous access for prophylactic infusions; and
   b. Treatment plan must be made to address breakthrough bleeds and procedures; and
   c. Routine lab screening must occur for factor VIII inhibitor while using Hemlibra® since this would change the treatment plan for bleeds and procedures; and
6. First dose must be given in a health care facility; and
7. In order to calculate appropriate dosing, the member's recent weight must be provided and have been taken within the last 3 months.
8. Initial approvals will be for 3 months of therapy. Subsequent approvals will be the duration of 1 year if there has been a decrease in the member's spontaneous bleeding episodes since beginning Hemlibra® treatment.

Feiba® (Anti-Inhibitor Coagulation Complex) Approval Criteria:

1. Member must be diagnosed with hemophilia A or B with an inhibitor; and
2. Feiba® must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders.

NovoSeven® RT [Coagulation Factor VIIa (Recombinant)] Approval Criteria:

1. An FDA approved diagnosis of one of the following:
   a. Hemophilia A or B with inhibitors; or
   b. Congenital factor VII deficiency; or
   c. Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets; or
   d. Acquired hemophilia; and
2. NovoSeven® RT must be prescribed by a hematologist specializing in rare bleeding disorders or a mid-level practitioner with a supervising physician that is a hematologist specializing in rare bleeding disorders.

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[1] Centers for Disease Control and Prevention (CDC). Basics About Hemophilia. Available online at: https://www.cdc.gov/ncbddd/hemophilia/facts.html. Last revised 08/28/2018. Last accessed 11/20/2018.
[2] CDC. Hemophilia Treatment. Available online at: https://www.cdc.gov/ncbddd/hemophilia/treatment.html. Last revised 08/16/2018. Last accessed 11/20/2018
[3] CDC. Hemophilia Inhibitors. Available online at: https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html. Last revised 08/17/2108. Last accessed 11/20/2018.

Appendix D

Vote to Prior Authorize Onpattro™ (Patisiran) and Tegsedi™ (Inotersen)

Oklahoma Health Care Authority
December 2018

Introduction[1,2]

- **Onpattro™ (patisiran)** contains a transthyretin (TTR)-directed small interfering ribonucleic acid (siRNA) and is indicated for the treatment of the polyneuropathy of hereditary TTR-mediated amyloidosis (hATTR amyloidosis) in adults. Patisiran is a double-stranded siRNA that causes degradation of mutant and wild-type TTR messenger RNA (mRNA) through RNA interference, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Patisiran is supplied as a sterile, preservative-free, 10mg/5mL (2mg/mL) solution for intravenous (IV) infusion in single-dose glass vials. The recommended dosage is 0.3mg/kg once every 3 weeks for patients weighing <100kg and 30mg once every 3 weeks for patients weighing ≥100kg. All patients should receive pre-medication with IV corticosteroid, oral acetaminophen, IV histamine-1 (H_1) antagonist, and IV histamine-2 (H_2) antagonist prior to patisiran administration to reduce the risk of infusion-related reactions (IRRs). Additionally, patisiran treatment leads to a decrease in serum vitamin A levels; therefore, supplementation of vitamin A at the recommended daily allowance (RDA) is advised. The Wholesale Acquisition Cost (WAC) of Onpattro™ (patisiran) is $1,900.00 per milliliter. This results in a cost per dose of $28,500.00 and a yearly cost of $484,500.00 for the maximum dose of 30mg administered every 3 weeks. Dosing is weight-based; therefore, treatment costs will vary.
- **Tegsedi™ (inotersen)** is a TTR-directed antisense oligonucleotide indicated for the treatment of the polyneuropathy of hATTR amyloidosis in adults. Inotersen causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. Inotersen is supplied in a single-dose, prefilled syringe containing 284mg of inotersen, and is available in cartons containing one or four prefilled syringes. The recommended dose of inotersen is 284mg injected subcutaneously (sub-Q) once weekly. The first injection administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional. Patients and/or caregivers should be trained in the sub-Q administration of inotersen in accordance with the *Instructions for Use* in the product package labeling. Inotersen contains a boxed warning as it causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-threatening. Inotersen can also cause glomerulonephritis that may require immunosuppressive treatment and result in dialysis-dependent renal failure. Due to the risks associated with inotersen, lab monitoring is required before, during, and after treatment; for this reason, inotersen only is available through the Tegsedi™ Risk Evaluation and Mitigation Strategy (REMS)

Program. Like patisiran, inotersen leads to a decrease in serum vitamin A levels; therefore, vitamin A supplementation at the RDA is advised. The WAC of Tegsedi™ (inotersen) is $5,766.67 per milliliter. This results in a cost per dose of $8,650.01 and a yearly cost of $449,800.52.

Recommendations

The College of Pharmacy recommends the prior authorization of Onpattro™ (patisiran) and Tegsedi™ (inotersen) with the following criteria:

Onpattro™ (Patisiran) Approval Criteria:

1. An FDA approved indication for the treatment of polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis; and
2. Diagnosis confirmed by the following:
    a. Tissue (fat pad) biopsy confirming amyloid deposits; and
    b. Genetic confirmation of transthyretin (*TTR*) gene mutation (e.g., Val30Met); and
3. Onpattro™ must be prescribed by or in consultation with a cardiologist, geneticist, or neurologist or an advanced care practitioner with a supervising physician who is a cardiologist, geneticist, or neurologist; and
4. Prescriber must confirm the member will take the recommended daily allowance of vitamin A; and
5. Prescriber must confirm that member will be pre-medicated with intravenous (IV) corticosteroid, oral acetaminophen, IV histamine-1 (H_1) antagonist, and IV histamine-2 (H_2) antagonist 60 minutes prior to Onpattro™ administration to reduce the risk of infusion-related reactions; and
6. Onpattro™ will not be approved for concomitant use with Tegsedi™; and
7. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling; and
8. Onpattro™ approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

Tegsedi™ (Inotersen) Approval Criteria:

1. An FDA approved indication for the treatment of the polyneuropathy of hereditary transthyretin-mediated (hATTR) amyloidosis; and
2. Diagnosis confirmed by the following:
    a. Tissue (fat pad) biopsy confirming amyloid deposits; and
    b. Genetic confirmation of transthyretin (*TTR*) gene mutation (e.g., Val30Met); and
3. Tegsedi™ must be prescribed by or in consultation with a cardiologist, geneticist, or neurologist or an advanced care practitioner with a supervising physician who is a cardiologist, geneticist, or neurologist; and
4. Prescriber must confirm the member will take the recommended daily allowance of vitamin A; and
5. Prescriber must agree to monitor ALT, AST, and total bilirubin prior to initiation of Tegsedi™ and every 4 months during treatment; and

6. Prescriber must confirm the first injection of Tegsedi™ administered by the patient or caregiver will be performed under the guidance of a health care professional; and
7. Prescriber must confirm the patient or caregiver has been trained by a health care professional on the subcutaneuos (sub-Q) administration and proper storage of Tegsedi™; and
8. Tegsedi™ will not be approved for concomitant use with Onpattro™; and
9. Prescriber, pharmacy, and member must be enrolled in the Tegsedi™ Risk Evaluation and Mitigation Strategy (REMS) program and maintain enrollment throughout therapy; and
10. Tegsedi™ approvals will be for the duration of 6 months. Reauthorization may be granted if the prescriber documents the member is responding well to treatment; and
11. A quantity limit of four syringes per 28 days will apply.

[1] Onpattro™ Prescribing Information. Alnylam Pharmaceuticals, Inc. Available online at: http://www.alnylam.com/wp-content/uploads/2018/08/ONPATTRO-Prescribing-Information.pdf. Last revised 08/2018. Last accessed 11/16/2018.
[2] Tegsedi™ Prescribing Information. Akcea Therapeutics, Inc. Available online at: https://tegsedi.com/prescribing-information.pdf. Last revised 10/2018. Last accessed 11/16/2018.

Appendix E

Vote to Prior Authorize Zemdri™ (Plazomicin), Xerava™ (Eravacycline), Nuzyra™ (Omadacycline), Seysara™ (Sarecycline), and Ximino™ (Minocycline Extended-Release)

Oklahoma Health Care Authority
December 2018

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

- **Avycaz® (ceftazidime/avibactam)** was approved by the U.S. Food and Drug Administration (FDA) in February 2018 for the treatment of adult patients with hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by designated susceptible Gram-negative microorganisms. Ceftazidime/avibactam was first FDA approved in 2015 for the treatment of adult patients with complicated intra-abdominal infections (cIAI), used in combination with metronidazole, or complicated urinary tract infections (cUTI), including pyelonephritis, caused by designated susceptible Gram-negative microorganisms. Ceftazidime/ avibactam is supplied as a 2.5 gram single-dose vial (SDV), containing 2 grams ceftazidime and 0.5 grams avibactam, for reconstitution and dilution prior to intravenous (IV) infusion. The recommended dosage of ceftazidime/avibactam for all FDA-approved indications is 2.5 grams administered every 8 hours by IV infusion over 2 hours in patients 18 years of age and older with creatinine clearance (CrCl) >50mL/min for a treatment duration of 5 to 14 days for patients with cIAI or 7 to 14 days for patients with cUTI or HABP/VABP. The Wholesale Acquisition Cost (WAC) of Avycaz® is $327.68 per 2.5 gram SDV, resulting in an estimated cost of $13,762.56 for 14 days of Avycaz® therapy.
- **Zemdri™ (plazomicin)**, an aminoglycoside antibacterial, was approved by the FDA in June 2018, for the treatment of adult patients with cUTI, including pyelonephritis, caused by designated susceptible microorganisms. Plazomicin has a boxed warning for the risk of nephrotoxicity, ototoxicity, neuromuscular blockade, and fetal harm. Plazomicin is supplied as a 500mg/10mL SDV for injection, and the recommended dosage of plazomicin for patients with CrCl >90mL/min is 15mg/kg administered every 24 hours by IV infusion over 30 minutes for a maximum of 7 days of IV plazomicin therapy. The WAC of Zemdri™ is $315 per 500mg/10mL SDV, resulting in an estimated cost of $4,410 for 7 days of Zemdri™ therapy for a patient weighing 60kg.
- **Xerava™ (eravacycline)**, a tetracycline-class antibacterial, was approved by the FDA in August 2018 for the treatment of adult patients with cIAI caused by designated susceptible microorganisms. Eravacycline is supplied as a 50mg SDV for reconstitution and dilution prior to IV infusion, and the recommended dosage of eravacycline is 1mg/kg administered every 12 hours by IV infusion over approximately 60 minutes for a treatment duration of 4 to 14 days. The WAC of Xerava™ is $43.75 per 50mg SDV,

resulting in an estimated cost of $2,450 for 14 days of Xerava™ therapy for a patient weighing 60kg.

- **Nuzyra™ (omadacycline)**, a tetracycline-class antibacterial, was approved by the FDA in October 2018 for the treatment of adult patients with community-acquired bacterial pneumonia (CABP) or acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible microorganisms. Nuzyra™ is supplied as 150mg oral tablets and as a 100mg SDV for reconstitution and dilution prior to IV infusion. The recommended dosage of omadacycline for the diagnosis of CABP is a loading dose of 200mg via IV infusion on day 1, followed by maintenance doses of 100mg via IV infusion once daily or 300mg by mouth once daily for a treatment duration of 7 to 14 days. The efficacy and safety of an oral loading dose were not evaluated in patients with CABP. The recommended dosage of omadacycline for the diagnosis of ABSSSI is a loading dose of 200mg via IV infusion on day 1 or 450mg by mouth once daily on day 1 and day 2, followed by maintenance doses of 100mg via IV infusion once daily or 300mg by mouth once daily for a treatment duration of 7 to 14 days. Cost information for Nuzyra™ is not yet available.
- **Seysara™ (sarecycline)**, a tetracycline-class antibacterial, was approved by the FDA in October 2018 for the treatment of inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris in patients 9 years of age and older. Sarecycline is supplied as 60mg, 100mg, and 150mg oral tablets, and the recommended dosage of sarecycline is once daily with or without food, based on body weight: 60mg for patients who weigh 33 to 54kg, 100mg for patients who weigh 55 to 84kg, or 150mg for patients who weigh 85 to 136kg. Cost information for Seysara™ is not yet available.

Cost Comparison: Minocycline Products

There are several cost-effective generic options available for SoonerCare members who require antibiotic therapy. The following table shows a cost comparison of minocycline extended-release (ER) and immediate-release (IR) products. Currently, Solodyn®, Minolira™, and minocycline IR tablets require prior authorization. Minocycline IR capsules are available without prior authorization.

Minocycline Products:

Product	Cost Per Unit	Cost Per 30-Day Course of Therapy[+]
Ximino™ (minocycline) 90mg ER capsule	**$23.30**	**$699.00**
Solodyn® (minocycline) 105mg ER tablet	$38.80	$1,164.00
Minolira™ (minocycline) 105mg ER tablet	$21.67	$650.10
minocycline 100mg tablet	$2.51	$150.60
minocycline 100mg capsule	$0.37	$22.20

[+]Based on recommended dosing regimen for acne vulgaris.
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 Costs (SMAC) if NADAC unavailable.
ER = etended-release

Recommendations

The College of Pharmacy recommends the prior authorization of Zemdri™ (plazomicin vial for IV infusion), Xerava™ (eravacycline vial for IV infusion), Nuzyra™ (omadacycline tablet and vial for IV infusion), and Seysara™ (sarecycline tablet) with the following criteria:

Zemdri™ (Plazomicin) Approval Criteria:

1. An FDA approved diagnosis of complicated urinary tract infection (cUTI), including pyelonephritis, caused by designated susceptible microorganisms; and
2. A patient-specific, clinically significant reason why the member cannot use an appropriate alternative aminoglycoside (e.g., gentamicin, tobramycin) or other cost-effective therapeutic equivalent alternative(s); and
3. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Xerava™ (Eravacycline) Approval Criteria:

1. An FDA approved diagnosis of complicated intra-abdominal infections (cIAI) caused by designated susceptible microorganisms; and
2. Member must be 18 years of age or older; and
3. A patient-specific, clinically significant reason why the member cannot use an appropriate penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenam (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s); and
4. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

Nuzyra™ (Omadacycline) Approval Criteria [Community-Acquired Bacterial Pneumonia (CABP) Diagnosis]:

1. An FDA approved diagnosis of CABP caused by designated susceptible microorganisms; and
2. Member must be 18 years of age or older; and
3. A patient-specific, clinically significant reason why the member cannot use an appropriate beta-lactam (e.g., ceftriaxone, cefotaxime, ceftaroline, ertapenem, ampicillin/sulbactam) in combination with a macrolide (e.g., azithromycin, clarithromycin) or doxycycline, monotherapy with a respiratory fluoroquinolone (e.g., levofloxacin, gemifloxacin), or other cost-effective therapeutic equivalent alternative(s); and
4. Approval quantity will be based on Nuzyra™ prescribing information and FDA approved dosing regimen(s).
    a. For Nuzyra™ vials, an initial quantity limit of 4 vials for a 3-day supply will apply. Continued authorization will require a patient-specific, clinically significant

reason why the member cannot switch to the oral tablet formulation for the remainder of therapy.

Nuzyra™ (Omadacycline) Approval Criteria [Acute Bacterial Skin and Skin Structure Infections (ABSSSI) Diagnosis]:

1. An FDA approved diagnosis of ABSSSI caused by designated susceptible microorganisms; and
2. Member must be 18 years of age or older; and
3. A patient-specific, clinically significant reason why the member cannot use vancomycin, linezolid, doxycycline, trimethoprim/sulfamethoxazole, or other cost-effective therapeutic equivalent alternative(s); and
4. Use of Nuzyra™ vials will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation; and
5. Approval quantity will be based on Nuzyra™ prescribing information and FDA approved dosing regimen(s).

Seysara™ (Sarecycline) Approval Criteria:

1. An FDA approved diagnosis of inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris; and
2. Member must be 9 years of age or older; and
3. Seysara™ is not covered for members older than 20 years of age; and
4. A patient-specific, clinically significant reason why the member cannot use minocycline, doxycycline, tetracycline, or other cost-effective therapeutic equivalent alternative(s); and
5. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate strength according to package labeling; and
6. A quantity limit of 30 tablets per 30 days will apply.

The College of Pharmacy also recommends the following changes to the Various Systemic Antibiotics Prior Authorization category:

1. Add Ximino™ (minocycline ER capsules) to the Antibiotic Special Formulation category. Current special formulation criteria will apply.
2. Update the current approval criteria for Avycaz® (ceftazidime/avibactam) based on the new FDA approved indication for the treatment of HABP/VABP.

The proposed changes can be seen in red in the following criteria:

Oral Antibiotic Special Formulation Approval Criteria:

1. Member must have a patient-specific, clinically significant reason why the immediate-release formulation and/or other cost-effective therapeutic equivalent alternative(s) cannot be used.
2. The following oral antibiotics currently require prior authorization and the special formulation approval criteria will apply:
    - Amoxicillin 500mg tablets

- Amoxicillin/clavulanate potassium extended-release (ER) tablets (Augmentin XR®)
- Amoxicillin 775mg ER tablets (Moxatag®)
- Cephalexin 250mg and 500mg tablets
- Cephalexin 750mg capsules
- Doxycycline hyclate 75mg and 100mg tablets (Acticlate®)
- Doxycycline hyclate delayed-release (DR) tablets (Doryx®)
- Doxycycline monohydrate 75mg and 150mg capsules and tablets
- Doxycycline monohydrate 40mg DR capsules (Oracea®)
- Minocycline ER capsules (Ximino™)
- Minocycline ER tablets (Minolira™)
- Minocycline ER tablets (Solodyn®)

Avycaz® (Ceftazidime/Avibactam) Approval Criteria:

1. An FDA approved diagnosis of one of the following infections caused by designated susceptible microorganisms:
    a. Complicated intra-abdominal infections (cIAI), used in combination with metronidazole; or
    b. Complicated urinary tract infections (cUTI), including pyelonephritis; or
    c. Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP); and
2. Member must be 18 years of age or older; and
3. For the diagnosis of cIAI, Avycaz® must be used in combination with metronidazole; and
4. A patient-specific, clinically significant reason why the member cannot use an appropriate penicillin/beta lactamase inhibitor combination (e.g., piperacillin/ tazobactam), a carbapenam (e.g., ertapenem, meropenem, imipenem/cilastatin), a cephalosporin (e.g., ceftriaxone, ceftazidime) in combination with metronidazole, or other cost-effective therapeutic equivalent alternative(s).
5. A quantity limit of 42 vials per 14 days will apply.

[1] Allergan News Release. FDA Approves Avycaz® (Ceftazidime and Avibactam) for the Treatment of Patients with Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia. Available online at: https://www.allergan.com/news/news/thomson-reuters/fda-approves-avycaz-ceftazidime-and-avibactam-for. Issued 02/01/2018. Last accessed 11/16/2018.

[2] Avycaz® (Ceftazidime/Avibactam) Prescribing Information. Allergan. Available online at: http://www.allergan.com/assets/pdf/avycaz_pi. Last revised 02/2018. Last accessed 11/16/2018.

[3] Achaogen News Release. Update -- Zemdri™ Approved by FDA for the Treatment of Adults with Complicated Urinary Tract Infections (cUTI). Available online at: http://investors.achaogen.com/news-releases/news-release-details/update-zemdritm-plazomicin-approved-fda-treatment-adults. Issued 06/26/2018. Last accessed 11/16/2018.

[4] Zemdri™ (Plazomicin) Prescribing Information. Achaogen, Inc. Available online at: https://www.zemdri.com/assets/pdf/Prescribing-Information.pdf. Last revised 06/2018. Last accessed 11/16/2018.

[5] Tetraphase Pharmaceuticals News Release. Tetraphase Pharmaceuticals Announces FDA Approval of Xerava™ (Eravacycline) for Complicated Intra-Abdominal Infections (cIAI). Available online at: https://ir.tphase.com/news-releases/news-release-details/tetraphase-pharmaceuticals-announces-fda-approval-xeravatm. Issued 08/27/2018. Last accessed 11/16/2018.

[6] Xerava™ (Eravacycline) Prescribing Information. Tetraphase Pharmaceuticals, Inc. Available online at: https://www.xerava.com/assets/pdf/prescribinginformation.pdf. Last revised 08/2018. Last accessed 11/16/2018.

[7] Paratek News Release. Paratek Announces FDA Approval of Nuzyra™ (Omadacycline). *GlobeNewswire*. Available online at: https://globenewswire.com/news-release/2018/10/02/1600459/0/en/Paratek-Announces-FDA-Approval-of-NUZYRA-Omadacycline.html. Issued 10/02/2018. Last accessed 11/16/2018.

[8] Nuzyra™ (Omadacycline) Prescribing Information. Paratek Pharmaceuticals, Inc. Available online at: http://nuzyra.com/PI.pdf. Last revised 10/2018. Last accessed 11/16/2018.

[9] Paratek News Release. FDA Approves Seysara™ (Sarecycline) for the Treatment of Moderate to Severe Acne. *GlobeNewswire*. Available online at: https://globenewswire.com/news-release/2018/10/02/1588602/0/en/FDA-Approves-SEYSARA-Sarecycline-for-the-Treatment-of-Moderate-to-Severe-Acne.html. Issued 10/02/2018. Last accessed 11/16/2018.

[10] Seysara™ (Sarecycline) Prescribing Information. Allergan. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209521s000lbl.pdf. Last revised 10/2018. Last accessed 11/16/2018.

Appendix F

Vote to Prior Authorize Signifor® LAR (Pasireotide)

Oklahoma Health Care Authority
December 2018

Introduction[1]

Signifor® LAR (pasireotide) is a somatostatin analogue (SSA) indicated for the treatment of patients with acromegaly or Cushing's disease that do not respond to surgery or are not candidates for surgery. Signifor® LAR is available as 10mg, 20mg, 30mg, 40mg, and 60mg vials intended for intramuscular (IM) injection. Pasireotide long-acting-release (LAR) should be reconstituted and administered immediately by a health care professional. The recommended initial dosing of pasireotide LAR for acromegaly is 40mg IM once every 4 weeks and for Cushing's disease is 10mg IM once every 4 weeks. Dose adjustments may be required based on patient response and tolerability.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 28 Days
Signifor® LAR (pasireotide) 40mg vial	**$12,308.80/vial**	**$12,308.80**
Sandostatin® LAR Depot (octreotide) 20mg vial	$5,535.49/vial	$5,535.49
Somatuline® Depot (lanreotide) 90mg/0.3mL syringe	$5,295.87/0.3mL	$5,295.87

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.
Unit = vial or 0.3mL syringe

Recommendations

The College of Pharmacy recommends the prior authorization of Signifor® LAR (pasireotide) with the following criteria:

Signifor® LAR (Pasireotide) Approval Criteria:

1. An FDA approved diagnosis of one of the following:
    a. Members with acromegaly who have had an inadequate response to surgery or for whom surgery is not an option; or
    b. Members with Cushing's disease from a pituitary tumor for whom pituitary surgery is not an option or has not been curative; and
2. For a diagnosis of acromegaly, the member must have a documented trial with octreotide long-acting or lanreotide depot with an inadequate response or have a patient-specific, clinically significant reason why the other long-acting somatostatin analogs (SSAs) are not appropriate for the member; and
3. Pasireotide LAR must be prescribed by an endocrinologist or in consultation with an endocrinologist; and
4. Pasireotide LAR must be administered by a health care professional; and
5. Prescriber must document that the member has had an inadequate response to surgery or is not a candidate for surgery; and

6. Prescriber must verify liver function tests (LFTs) (e.g., ALT, AST, bilirubin) will be monitored when starting treatment and periodically thereafter; and
7. Authorizations will be for the duration of 12 months; and
8. Reauthorization may be granted if the prescriber documents the member is responding well to treatment.

[1] Signifor® LAR Prescribing Information. Novartis Pharmaceuticals, Corp. Available online at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203255s004lbl.pdf. Last revised 06/2018. Last accessed 10/16/2018.

Appendix G

Vote to Prior Authorize Symdeko® (Tezacaftor/Ivacaftor) and Orkambi® (Lumacaftor/Ivacaftor Oral Granules) and to Update the Kalydeco® (Ivacaftor) Prior Authorization Criteria

Oklahoma Health Care Authority
December 2018

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

- **Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets):** In February 2018, the U.S. Food and Drug Administration (FDA) approved Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets) to treat cystic fibrosis (CF) in patients 12 years of age and older who have 2 copies of the *F508del* mutation or 1 mutation that is responsive to Symdeko®. Symdeko® is co-packaged as tezacaftor 100mg/ivacaftor 150mg fixed-dose combination tablets and ivacaftor 150mg tablets. The recommended dose for adults and pediatric patients 12 years of age and older is 1 tablet (containing tezacaftor 100mg/ivacaftor 150mg) in the morning and 1 tablet (containing ivacaftor 150mg) in the evening, approximately 12 hours apart. Symdeko® should be taken with fat-containing food.
- **Orkambi® (lumacaftor/ivacaftor oral granules):** In August 2018, the FDA approved an expanded age range for Orkambi® to include treatment in children 2 through 5 years of age with CF who have 2 copies of the *F508del-CFTR* mutation, and approved a new oral granule formulation of Orkambi® in 2 dosage strengths (lumacaftor 100mg/ivacaftor 125mg and lumacaftor 150mg/ivacaftor 188mg) for weight-based dosing. The recommended dose for pediatric patients 2 through 5 years of age and weighing <14kg is one packet of lumacaftor 100mg/ivacaftor 125mg oral granules mixed with 1 teaspoon (5mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. The recommended dose for pediatric patients 2 through 5 years of age and weighing ≥14kg is 1 packet of lumacaftor 150mg/ivacaftor 188mg oral granules mixed with 5mL of soft food or liquid an administered orally every 12 hours with fat-containing food. Orkambi® was first FDA approved in 12 years of age and older in July 2015 and in September 2016 was approved for expanded use in children 6 to 11 years of age.
- **Kalydeco® (ivacaftor):** In August 2018, the FDA approved Kalydeco® (ivacaftor) to include use in children with CF 12 months of age and older who have at least 1 mutation in their *CFTR* gene that is responsive to Kalydeco® based on clinical and/or *in vitro* assay data. This FDA approval is based on data from an ongoing Phase 3 open-label safety study (ARRIVAL) of 25 children with CF 12 to <24 months of age who have 1 of 10 mutations in the *CFTR* gene (*G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, *G1349D,* or *R117H*). The study is ongoing in infants younger than 1 year of age. Kalydeco® was previously FDA approved for the treatment of CF in patients 2 years of age and older who have 1 of 38 ivacaftor-responsive mutations in the *CFTR* gene based on clinical and/or *in vitro* assay data. Kalydeco® is available as 150mg oral tablets and

50mg and 75mg unit-dose packets of oral granules. The recommended dose for patients 12 months to <6 years of age and weighing 7kg to <14kg is (1) 50mg packet mixed with 1 teaspoon (5mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. For patients 12 months to <6 years of age and ≥14kg, the recommended dose is (1) 75mg packet mixed with 1 teaspoon (5mL) of soft food or liquid and administered orally every 12 hours with fat-containing food. The recommended dose for patients 6 years of age and older is (1) 150mg tablet taken orally every 12 hours with fat-containing food.

Recommendations

The College of Pharmacy recommends the prior authorization of Symdeko® (tezacaftor/ivacaftor and ivacaftor tablets) and recommends updating the current Orkambi® (lumacaftor/ivacaftor) and Kalydeco® (ivacaftor) prior authorization criteria. The following criteria would apply (changes noted in red):

Symdeko® (Tezacaftor/Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in patients who are homozygous for the *F508del* mutation or who have at least 1 mutation in the CF transmembrane conductance regulator (*CFTR*) gene detected by genetic testing that is responsive to tezacaftor/ivacaftor based on *in vitro* data and/or clinical evidence; and
2. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing, when recommended by the mutation test instructions for use; and
3. Member must be 12 years of age or older; and
4. Members using Symdeko® must be supervised by a pulmonary specialist; and
5. If the member is currently stabilized on Orkambi® (lumacaftor/ivacaftor) and experiencing adverse effects associated with Orkambi® use, the prescriber must indicate that information on the prior authorization request; and
6. The prescriber must verify that the member has been counseled on proper administration of Symdeko® including taking with a fat-containing food; and
7. The prescriber must verify that ALT, AST, and bilirubin will be assessed prior to initiating Symdeko®, every 3 months during the first year of treatment, and annually thereafter; and
8. Members must not be taking any of the following medications concomitantly with Symdeko®: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort; and
9. A quantity limit of 2 tablets per day or 56 tablets per 28 days will apply.
10. Initial approval will be for the duration of 3 months, after which time compliance will be required for continued approval. After 6 months of utilization, compliance and information regarding efficacy, such as improvement in FEV_1, will be required for continued approval. Additionally after 6 months of utilization, information regarding efficacy as previously mentioned or fewer adverse events must be provided for members who switched from Orkambi® to Symdeko®.

Orkambi® (Lumacaftor/Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of cystic fibrosis (CF) in patients who are homozygous for the *F508del* mutation in the CF transmembrane conductance regulator (*CFTR*) gene detected by genetic testing; and
2. If the member's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene; and
3. Orkambi® will not be approved for patients with CF other than those homozygous for the *F508del* mutation; and
4. Member must be ~~6~~ 2 years of age or older; and
5. Members using Orkambi® must be supervised by a pulmonary specialist; and
6. The prescriber must verify that ALT, AST, and bilirubin will be assessed prior to initiating Orkambi®, every 3 months during the first year of treatment, and annually thereafter; and
7. Members must not be taking any of the following medications concomitantly with Orkambi®: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort; and
8. A quantity limit of 4 tablets per day or 112 tablets per 28 days will apply or a quantity limit of 2 granule packets per day or 56 packets per 28 days will apply.
9. An age restriction of 2 years to 5 years of age will apply to Orkambi® oral granule packets. Members 6 years of age or older will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation.
10. Initial approval will be for the duration of 3 months, after which time compliance will be required for continued approval. After 6 months of utilization, compliance and information regarding efficacy, such as improvement in FEV_1, will be required for continued approval.

Kalydeco® (Ivacaftor) Approval Criteria:

1. An FDA approved diagnosis of of cystic fibrosis (CF) with a mutation in the CF transmembrane conductance regulator (*CFTR*) gene detected by genetic testing that is responsive to ivacaftor based on clinical and/or *in vitro* assay data; and
2. Documentation must be submitted with results of *CFTR* genetic testing; and
3. Member must be ~~2~~ 1 year of age or older; and
4. A quantity limit of 2 tablets or 2 granule packets per day (56 per 28 days) will apply; and
5. An age restriction of 2 years to less than 6 years of age will apply to Kalydeco® oral granule packets. Members 6 years of age or older will require a patient-specific, clinically significant reason why the member cannot use the oral tablet formulation.
6. Initial approval will be for the duration of 3 months, after which time compliance will be required for continued approval. After 6 months of utilization, compliance and information regarding efficacy, such as improvement in FEV_1, will be required for continued approval.

[1] Symdeko® (tezacaftor/ivacaftor and ivacaftor) Prescribing Information. Vertex Pharmaceuticals, Inc. Available online at: https://pi.vrtx.com/files/uspi_tezacaftor_ivacaftor.pdf. Last revised 02/2018. Last accessed 11/28/2018.

[2] Vertex Pharmaceuticals, Inc. FDA Approves Symdeko™ (tezacaftor/ivacaftor and ivacaftor) to treat the Underlying Cause of Cystic Fibrosis in People Ages 12 and Older with Certain Mutations in the CFTR Gene. Available online at https://investors.vrtx.com/news-releases/news-release-details/fda-approves-symdekotm-tezacaftorivacaftor-and-ivacaftor-treat?ReleaseID=1057241. Issued 02/12/2018. Last accessed 11/28/2018.

[3] Vertex Pharmaceuticals, Inc. FDA Approves Orkambi® (lumacaftor/ivacaftor) as First Medicine to Treat the Underlying Cause of Cystic Fibrosis for Children Ages 2-5 Years with Most Common Form of the Disease. Available online at: https://investors.vrtx.com/news-releases/news-release-details/fda-approves-orkambir-lumacaftorivacaftor-first-medicine-treat. Issued 08/07/2018. Last accessed 11/28/2018.

[4] Vertex Pharmaceuticals, Inc. FDA Approves Orkambi® (lumacaftor/ivacaftor) - the First Medicine to Treat the Underlying Cause of Cystic Fibrosis for People Ages 12 and Older with Two Copies of the F508del Mutation. Available online at: https://investors.vrtx.com/news-releases/news-release-details/fda-approves-orkambitm-lumacaftorivacaftor-first-medicine-treat. Issued 07/02/2015. Last accessed 11/28/2018.

[5] Vertex Pharmaceuticals, Inc. U.S. Food and Drug Administration Approves Orkambi® (lumacaftor/ivacaftor) for Use in Children with Cystic Fibrosis Ages 6 through 11 who have Two Copies of the F508del Mutation. Available online at: https://investors.vrtx.com/news-releases/news-release-details/us-food-and-drug-administration-approves-orkambir?ReleaseID=991350. Issued 09/28/2016. Last accessed 11/28/2018.

[6] Orkambi® (lumacaftor/ivacaftor) Prescribing Information. Vertex Pharmaceuticals, Inc. Available online at: https://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf. Last revised 08/2018. Last accessed 11/28/2018.

[7] Kalydeco® (ivacaftor) Prescribing Information. Vertex Pharmaceuticals, Inc. Available online at: https://pi.vrtx.com/files/uspi_ivacaftor.pdf. Last revised 08/2018. Last accessed 11/28/2018.

[8] Vertex Pharmaceuticals, Inc. FDA Approves Kalydeco® (ivacaftor) as First and Only Medicine to Treat Underlying Cause of CF in Children Ages 12 to <24 Months with Certain Mutations in the CFTR Gene. Available online at: https://investors.vrtx.com/news-releases/news-release-details/fda-approves-kalydecor-ivacaftor-first-and-only-medicine-treat. Issued 08/15/2018. Last accessed 11/28/2018.

Appendix H

Fiscal Year 2018 Annual Review of Maintenance Asthma and Chronic Obstructive Pulmonary Disease (COPD) Medications and 30-Day Notice to Prior Authorize Lonhala® Magnair® (Glycopyrrolate Inhalation Solution), Yupelri™ (Revefenacin Inhalation Solution), and Dupixent® (Dupilumab Injection)

Oklahoma Health Care Authority
December 2018

Current Prior Authorization Criteria

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

Tier-1 products indicated for the member's age 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.

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.

Breo® Ellipta® (Fluticasone Furoate/Vilanterol) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) or chronic bronchitis and/or emphysema associated with COPD; and
    a. For a diagnosis of COPD or chronic bronchitis and/or emphysema associated with COPD, trials of Advair® and Symbicort®, consisting of at least 30 days each within the last 90 days that did not adequately control COPD symptoms; or
2. An FDA approved diagnosis of asthma in patients 18 years of age and older; and
    a. For a diagnosis of asthma, trials of Advair® and Dulera® consisting of at least 30 days each within the last 90 days that did not adequately control asthma symptoms.

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® and Dulera® 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 1 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.

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 trial of all available Tier-1 inhaled corticosteroids or a patient-specific, clinically significant reason why they are not appropriate for the member.

Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA)	
Tier-1*	**Tier-2**
Long-Acting Beta$_2$ Agonists* (LABA)	
salmeterol inhalation powder (Serevent®)	arformoterol nebulizer solution (Brovana®)
	formoterol nebulizer solution (Perforomist®)
	indacaterol inhalation powder (Arcapta® Neohaler®)
	olodaterol inhalation spray (Striverdi® Respimat®)
Long-Acting Muscarinic Antagonists (LAMA)	
tiotropium inhalation powder (Spiriva® Handihaler®)	aclidinium inhalation powder (Tudorza® PressAir®)
	glycopyrrloate inhalation powder (Seebri® Neohaler®)
	tiotropium soft mist inhaler (Spiriva® Respimat®)+
	umeclidinium inhalation powder (Incruse® Ellipta®)

*Combination agents that contain a long-acting beta$_2$ agonist (LABA) ingredient qualify as Tier-1 agents.
Tier-1 medications do not require prior authorization.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
+Unique criteria applies for a diagnosis of asthma.

Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonist (LAMA) Tier-2 Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema; and
3. A 4-week trial of at least 1 long-acting beta$_2$ agonist (LABA) and a 4-week trial of 1 long-acting muscarinic antagonist (LAMA) within the past 90 days; or
4. A documented adverse effect, drug interaction, or contraindication to all available Tier-1 products.

5. A clinical exception may apply for members who are unable to effectively use hand-actuated devices, such as Spiriva® Handihaler®, or who are stable on nebulized therapy.

Spiriva® Respimat® (Tiotropium Bromide Soft Mist Inhaler) Approval Criteria [Asthma Diagnosis]:

1. Member must have an FDA approved diagnosis of asthma; and
2. Member must be 6 years of age or older; and
3. Member must have used a high-dose inhaled corticosteroid and long-acting $beta_2$ agonist (ICS/LABA) product for at least 1 month immediately prior to request for authorization; and
4. Member must have had a trial of a leukotriene receptor antagonist (LTRA) for at least 1 month in the last 90 days; and
5. Member must have a history of exacerbations despite required trials; and
6. Member must remain on an ICS or ICS/LABA while on tiotropium therapy; and
    a. Member's asthma must be considered uncontrolled by prescriber:
        i. Member requires rescue inhaler >2 days per week for reasons other than prevention of exercise induced bronchospasms; or
        ii. Member requires oral systemic corticosteroids; or
    b. A clinical situation warranting initiation of tiotropium therapy in addition to an ICS/LABA due to severity of asthma; and
7. A patient-specific, clinically significant reason the member is unable to use Spiriva® Handihaler® (tiotropium) which does not require prior authorization.

Anoro® Ellipta® (Umeclidinium/Vilanterol), Bevespi Aerosphere® (Glycopyrrolate/Formoterol Fumarate), Stiolto® Respimat® (Tiotropium/Olodaterol), and Utibron® Neohaler® (Indacaterol/Glycopyrrolate) Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD); and
3. A patient-specific, clinically significant reason why the member cannot use Tier-1 long-acting $beta_2$ agonist (LABA) and long-acting muscarinic antagonist (LAMA) individual components.

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 4-week trial of at least 1 long-acting $beta_2$ agonist (LABA) and a 4-week trial of 1 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 an ICS/LABA combination with a LAMA.

Daliresp® (Roflumilast) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) with history of chronic bronchitis; and

2. Forced expiratory volume (FEV) ≤50% of predicted; and
3. Member is inadequately controlled on long-acting bronchodilator therapy (must have ≥3 claims for long-acting bronchodilators in the previous 6 months).

Cinqair® (Reslizumab) Approval Criteria:

1. An FDA approved indication of add-on maintenance treatment of patients with severe asthma with an eosinophilic phenotype; and
2. Member must be 18 years of age or older; and
3. Member must have a blood eosinophil count ≥400cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 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 1 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 FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. Cinqair® must be administered in a health care setting by a health care professional prepared to manage anaphylaxis; and
8. Cinqair® 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 12 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 6 months after which time compliance will be evaluated for continued approval.
10. Member's weight should be provided on prior authorization requests. Weights should have been taken within the last 4 weeks to provide accurate weight-based dosing.

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

1. An FDA approved diagnosis of EGPA; and
2. A diagnosis of granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) will not be approved; and
3. Member meets one of the following:
    a. Member must have a past history of at least 1 confirmed EGPA relapse [requiring increase in oral corticosteroid (OCS) dose, initiation/increased dose of immunosuppressive therapy, or hospitalization] within the past 12 months; or
    b. Member must have refractory disease within the last 6 months following induction of a standard treatment regimen administered compliantly for at least 3 months; and

4. Failure to achieve remission despite OCS therapy (oral prednisone equivalent ≥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 12 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 health care setting by a health care 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 6 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.

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 12 years of age or older; and
3. Member must have a baseline blood eosinophil count ≥150cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 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 1 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 products, the highest FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. Nucala® must be administered in a health care setting by a health care 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 12 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 6 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 1 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 20 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 3 months; and
7. Prescribed Xolair® dose must be an FDA approved regimen per Xolair® prescribing information; and
8. Xolair® must be administered in a health care setting by a health care 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 had at least 2 asthma exacerbations requiring systemic corticosteroids within the past 12 months or require daily systemic corticosteroids to prevent serious exacerbations; and
11. Both the prior authorization request form and statement of medical necessity form must be submitted for approval consideration; and
12. Initial approvals will be for the duration of 6 months after which time compliance will be evaluated for continued approval.

Xolair® (Omalizumab) Approval Criteria [Chronic Idiopathic Urticaria (CIU) Diagnosis]:

1. An FDA approved diagnosis of CIU; and
2. Member must be 12 years of age or older; and
3. Other forms of urticaria must be ruled out; and
4. Other potential causes of urticaria must be ruled out; and
5. Member must have an Urticaria Activity Score (UAS) ≥16; and
6. Prescriber must be an allergist, immunologist, dermatologist, or be an advanced care practitioner with a supervising physician that is an allergist, immunologist, or dermatologist; and
7. Member must have tried and failed to obtain relief from other treatments including the following trials within the last 6 months (member must fail all classes unless contraindicated):
    a. At least 2 different H_1-antihistamine trials for a minimum duration of 2 weeks each:
        i. One trial must be a second generation antihistamine dosed 4 times the maximum FDA dose; and
        ii. One trial must be tried in combination with an H_2-antihistamine; and

b. A 4-week trial of a leukotriene receptor antagonist (LTRA) in combination with a 4-week trial of doxepin 10mg to 50mg daily; and

8. Initial dosing will only be approved for 150mg every 4 weeks. If the member has inadequate results at this dose, then the dose may be increased to 300mg every 4 weeks.
9. Initial approvals will be for the duration of 3 months.

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 a baseline blood eosinophil count ≥300cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 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 1 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 FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. Fasenra™ must be administered in a health care setting by a health care 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 12 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 6 months after which time compliance will be evaluated for continued approval.
10. A quantity limit of 1 prefilled syringe per 56 days will apply.

Utilization of Maintenance Asthma and COPD Medications: Fiscal Year 2018

Comparison of Fiscal Years

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	7,354	32,390	$11,087,058.07	$342.30	$11.20	1,041,719	990,129
2018	9,018	38,619	$13,706,133.98	$354.91	$11.58	1,287,935	1,183,126
% Change	**22.50%**	**19.10%**	**23.50%**	**3.70%**	**3.40%**	**23.60%**	**19.40%**
Change	**1,664**	**6,229**	**$2,619,075.91**	**$12.61**	**$0.38**	**246,216**	**192,997**

*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.
Please note, this data does not include asthma-indicated monoclonal antibodies.

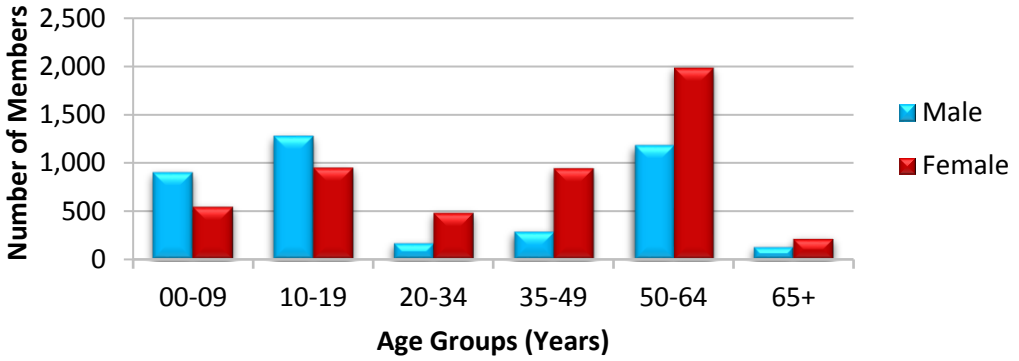
Comparison of Fiscal Years: Asthma-Indicated Monoclonal Antibodies¥

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	25	99	$410,260.58	$4,144.05	$148.00	418	2,772
2018	20	80	$370,876.98	$4,635.96	$163.53	326	2,268
% Change	**-20.00%**	**-19.20%**	**-9.60%**	**11.90%**	**10.50%**	**-22.00%**	**-18.20%**
Change	**-5**	**-19**	**-$39,383.60**	**$491.91**	**$15.53**	**-92**	**-504**

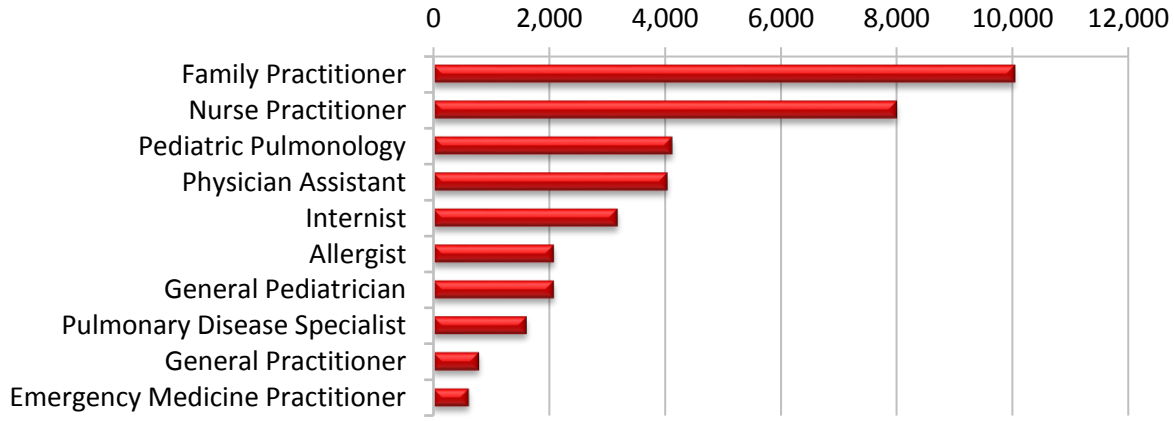
¥Pharmacy claims data only.
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

- Please note, Cinqair® (reslizumab) is billed by medical claims only and not reflected in the above pharmacy claims data. Fiscal Year 2018 medical claim utilization details for Xolair® (omalizumab), Cinqair® (reslizumab), and Nucala® (mepolizumab) can be found at the end of this report.

Demographics of Members Utilizing Maintenance Asthma and COPD Medications



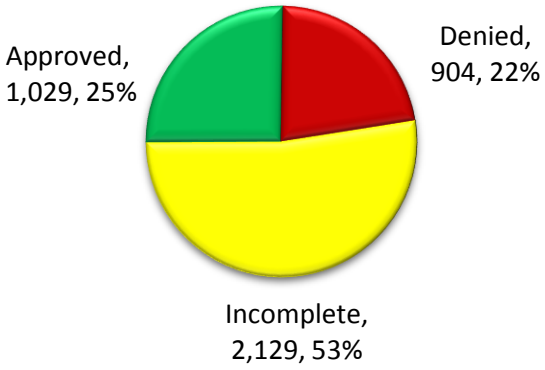
Top Prescriber Specialties of Maintenance Asthma and COPD Medications by Number of Claims



Prior Authorization of Maintenance Asthma and COPD Medications

There were 4,062 prior authorization requests submitted for maintenance asthma and COPD medications during fiscal year 2018. Of those prior authorization requests, 162 were submitted for monoclonal antibody medications. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31]

Anticipated Patent Expiration(s):

- Dulera® (mometasone/formoterol inhalation aerosol): May 2020
- Perforomist® (formoterol nebulizer solution): June 2021
- Brovana® (arformoterol nebulizer solution): November 2021
- Daliresp® (roflumilast oral tablet): March 2024
- Tudorza® PressAir® (aclidinium inhalation powder): April 2027
- Arcapta® Neohaler® (indacaterol inhalation powder): October 2028
- Seebri® Neohaler® (glycopyrrolate inhalation powder): October 2028
- Utibron® Neohaler® (indacaterol/glycopyrrolate inhalation powder): October 2028
- Symbicort® (budesonide/formoterol inhalation aerosol): October 2029
- Spiriva® HandiHaler® (tiotropium inhalation powder): April 2030
- Striverdi® Respimat® (olodaterol inhalation spray): October 2030
- Stiolto® Respimat® (tiotropium bromide/olodaterol inhalation spray): October 2030
- Breo® Ellipta® (fluticasone furoate/vilanterol inhalation powder): October 2030
- Incruse® Ellipta® (umeclidinium inhalation powder): October 2030
- Arnuity® Ellipta® (fluticasone furoate inhalation powder): October 2030
- Anoro® Ellipta® (umeclidinium/vilanterol inhalation powder): November 2030
- Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/vilanterol inhalation powder): November 2030
- Bevespi Aerosphere® (glycopyrrolate/formoterol fumarate inhalation aerosol): March 2031
- Spiriva® Respimat® (tiotropium soft mist inhaler): April 2031
- QVAR® RediHaler™ (beclomethasone dipropionate inhalation aerosol): July 2031
- ArmonAir™ RespiClick® (fluticasone propionate inhalation powder): February 2032

- AirDuo™ RespiClick® (fluticasone propionate/salmeterol inhalation powder): October 2034

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

- **December 2017:** Lonhala® Magnair® (glycopyrrolate inhalation solution)
- **November 2018:** Yupelri™ (revefenacin inhalation solution)

New Indication(s):

- **April 2018:** The FDA approved Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/ vilanterol) for an expanded indication for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and/or emphysema. Trelegy™ Ellipta® is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations. The approval is based on a supplemental New Drug Application (sNDA) supported by data from the landmark InforMing the PAthway of COPD Treatment (IMPACT) study which showed Trelegy™ Ellipta® was superior to the inhaled corticosteroid/long-acting beta$_2$-adrenergic agonist (ICS/LABA), Breo® Ellipta® (fluticasone furoate/vilanterol), and long-acting muscarinic antagonist/long-acting beta$_2$-adrenergic agonist (LAMA/LABA), Anoro® Ellipta® (umeclidinium/vilanterol), on multiple clinically important endpoints, including reducing exacerbations and improving lung function and health related quality of life (QOL). Trelegy™ Ellipta® was originally FDA approved in September 2017 for the long-term, once-daily, maintenance treatment of COPD patients who are receiving fluticasone furoate/ vilanterol and require additional bronchodilation or who are receiving fluticasone furoate/vilanterol and umeclidinium.
- **May 2018:** The FDA expanded the approval age for the use of Arnuity® Ellipta® (fluticasone furoate), a once-daily ICS for the maintenance treatment of asthma. The expanded approval is for the use of Arnuity® Ellipta® as maintenance treatment of asthma as prophylactic therapy in children 5 to 11 years of age, delivered as a 50mcg once-daily dose using the Ellipta® inhaler. Arnuity® Ellipta® (100mcg and 200mcg) was previously FDA approved in August 2014 for the maintenance treatment of asthma in patients 12 years of age and older.
- **October 2018:** The FDA approved Dupixent® (dupilumab) as an add-on maintenance therapy for the treatment of moderate-to-severe asthma in patients 12 years of age and older with an eosinophilic phenotype or with oral corticosteroid (OCS)-dependent asthma. Dupilumab inhibits the overactive signaling of interleukin-4 (IL-4) and IL-13, 2 key proteins that contribute to the Type 2 (T2) inflammation that may underlie moderate-to-severe asthma. The pivotal asthma trial program evaluated 2,888 adult and adolescent patients with moderate-to-severe asthma in 3 randomized, placebo-controlled, multicenter trials (Trial 1, Trial 2, and Trial 3) for 6 months to 1 year (24 to 52 weeks). All trials enrolled patients irrespective of minimum baseline eosinophil levels. In Trial 2 (the largest trial), dupilumab reduced exacerbations and improved lung function in the overall population. Benefits in exacerbations were seen in patients with eosinophil counts ≥150cells/mcL, which represented 70% of the patients enrolled. Efficacy improved in patients with higher eosinophil counts. In Trial 3, which evaluated

severe, OCS-dependent patients, dupilumab reduced average daily OCS use by 70% compared to 42% with placebo. More than half of patients treated with dupilumab completely eliminated utilization of OCS. Effects on lung function and on OCS and exacerbation reduction were similar for dupilumab irrespective of baseline blood eosinophil levels. In the asthma clinical trials, the adverse reactions that occurred with dupilumab at a rate of ≥1% and more frequently than the respective comparator were injection site reactions, sore throat, and an increase in the number of eosinophils. Dupilumab was originally FDA approved in March 2017 for the treatment of adults with moderate-to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies, or when those therapies are not advisable.

- **October 2018:** The FDA approved new labeling for Stiolto® Respimat® (tiotropium bromide/olodaterol) that includes data showing a meaningful reduction in COPD exacerbations driven by tiotropium, which is the active ingredient in Spiriva® Respimat®. The FDA also revised the indication for Stiolto® Respimat®, which is now approved for the treatment of patients with COPD, including chronic bronchitis and emphysema. Previously, the Stiolto® Respimat® indication was for the treatment of airflow limitation in patients with COPD, including chronic bronchitis and emphysema. The revised language broadens the indication and illustrates that Stiolto® Respimat® does more than simply improve airflow. The Stiolto® Respimat® label will be updated to include clinical trial data of Spiriva® Respimat® that shows a decrease in exacerbations, as well as data from the DYNAGITO® trial, a 52-week study involving more than 7,800 patients, comparing Stiolto® Respimat® to Spiriva® Respimat® in the reduction of COPD exacerbations.

Generic [Abbreviated New Drug Application (ANDA)] Approval(s):

- **October 2018:** Breckenridge Pharmaceutical, Inc. announced that the FDA has granted final approval for its ANDA for roflumilast 500mcg tablets, generic for Daliresp® tablets. Roflumilast is a selective phosphodiesterase 4 (PD-4) inhibitor indicated to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. AstraZeneca, Breckenridge, and Ferrer International have entered into a confidential settlement agreement regarding the Hatch-Waxman litigation for roflumilast. Breckenridge, as authorized by the settlement agreement, may sell or offer to sell roflumilast at a later date. Further announcements will be made prior to product launch.

Over-The-Counter (OTC) Approval(s):

- **November 2018:** Primatene® MIST (epinephrine inhalation aerosol) was approved by the FDA to provide temporary relief of symptoms of mild, intermittent asthma. This OTC drug is approved only for those who have been diagnosed with asthma by a health care provider. The former OTC Primatene® MIST was taken off the market in 2011 because it contained chlorofluorocarbon (CFC) propellants, which are known to deplete the ozone layer. This new version contains hydrofluoroalkane (HFA) propellants, which are permitted under current law. Primatene® MIST is not a covered SoonerCare product.

Pipeline:

- **January 2018:** Teva Pharmaceutical Industries, Ltd. announced that a Phase 3 registration study evaluating subcutaneously (sub-Q) administered Cinqair® (reslizumab) did not meet its primary endpoint of significantly reducing the frequency of clinical asthma exacerbations in patients with uncontrolled asthma and elevated blood eosinophils >300cells/mcL. A Phase 3 claim-support study evaluating sub-Q reslizumab in patients with OCS-dependent asthma did not meet its primary endpoint of reduction in daily OCS dose. No new safety concerns were identified in review of the data from these studies and no cases of anaphylaxis related to reslizumab were reported. Teva will review the full data to determine next steps.
- **August 2018:** Genentech announced that the FDA has granted Breakthrough Therapy designation for Xolair® (omalizumab) for the prevention of severe allergic reactions following accidental exposure to one or more foods in people with allergies. Breakthrough Therapy designation was granted on the basis of data from 7 clinical studies over the last decade assessing the efficacy and safety of omalizumab against a range of food allergens including peanut, milk, egg, and others. These studies of omalizumab, as monotherapy or in combination with oral immunotherapy, were supported by Genentech and independent sponsors including the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the National Institutes of Health (NIH). Genentech and Novartis Pharmaceuticals are working closely with NIAID and the Consortium of Food Allergy Research (CoFAR) to initiate a potentially pivotal study evaluating the efficacy and safety of omalizumab in multiple food allergies.
- **September 2018:** GlaxoSmithKline (GSK) received a Complete Response Letter (CRL) from the FDA regarding its application for Nucala® (mepolizumab) as an add-on treatment to ICS-based maintenance treatment for the reduction of exacerbations in patients with COPD, guided by blood eosinophil counts. The CRL states that more clinical data are required to support an approval. GSK will work closely with the FDA to determine the appropriate next steps for the supplementary Biologics License Application (sBLA). The rejection comes following the July 2018 meeting outcome of the Pulmonary Allergy Drugs Advisory Committee of the FDA. The committee voted on the basis of data presented that the risk-benefit profile was not adequate to support approval (3 for, 16 against). The committee also voted that there was not substantial evidence of the efficacy (3 for, 16 against) but there was adequate evidence of the safety (17 for, 2 against) of mepolizumab in this population, and the committee suggested further data to characterize the patient population that would be most likely to benefit from this targeted biologic therapy.
- **September 2018:** AnaptysBio, Inc. announced positive topline proof-of-concept data for etokimab, its investigational anti-IL-33 therapeutic antibody, in an ongoing single-dose Phase 2a clinical trial in adult patients with severe eosinophilic asthma. Patients administered etokimab rapidly improved their forced expiratory volume in 1 second (FEV_1) with an 8% FEV_1 improvement over placebo at day 2. FEV_1 improvement was sustained through day 64, with an 11% increase over placebo. Blood eosinophil reduction was sustained through the interim analysis period, with a 31% reduction at day 2 and a 46% reduction at day 64 over placebo. Etokimab was generally well

tolerated in all patients and no serious adverse events were reported as of this interim analysis. This Phase 2a trial is currently ongoing and the company plans to report full data from this trial at a medical conference in 2019 following trial completion. AnaptysBio plans to continue development of etokimab in eosinophilic asthma with a multi-dose Phase 2b placebo-controlled trial, which is expected to be initiated in 2019.

- **September 2018:** AstraZeneca and its partner Amgen, Inc. announced that the FDA has granted Breakthrough Therapy designation for tezepelumab in patients with severe asthma without an eosinophilic phenotype, who are receiving an ICS/LABA with or without OCS and additional asthma controllers. The Breakthrough Therapy designation is based on the tezepelumab Phase 2b PATHWAY data that showed a significant reduction in the annual asthma exacerbation rate compared with placebo in a broad population of severe asthma patients irrespective of patient phenotype including T2 biomarker status. Currently available biologic therapies only target T2-driven inflammation. Tezepelumab is a potential first-in-class medication that blocks thymic stromal lymphopoietin (TSLP), an upstream modulator of multiple inflammatory pathways. Tezepelumab is currently in development in the Phase 3 PATHFINDER clinical trial program.
- **October 2018:** Verona Pharma announced that it has enrolled the last patient in its Phase 2 randomized, double-blind, 3-way trial evaluating the effect of nebulized RPL554 as an add-on to dual therapy using LAMA/LABA and triple therapy (LAMA/LABA with ICS) in the maintenance treatment of patients with moderate-to-severe COPD. A total of 79 patients with COPD have enrolled. Patients already receiving ICS therapy will continue a stable dose of ICS throughout the study, thus providing additional data on "triple therapy" use. Following a 7- to 14-day washout period in advance of dosing and between study arms, patients will receive 3 days of treatment with each of 2 dose strengths (1.5mg or 6mg) of nebulized RPL554 or placebo twice daily. The primary endpoint of this trial is improvement in lung function with RPL554 versus placebo (as add-on to tiotropium/olodaterol), as measured by peak FEV_1. RPL554, is a first-in-class, inhaled, dual inhibitor of the enzymes PD-3 and PD-4 that acts as both a bronchodilator and an anti-inflammatory agent in a single compound. In previous clinical trials, RPL554 has been observed to result in bronchodilator effects when used alone or as an add-on treatment to other COPD bronchodilators. RPL554 improved FEV_1 over 4 weeks in patients with moderate-to-severe COPD when compared to placebo and improved COPD symptoms and QOL in a Phase 2b European study performed in 403 patients. In addition, RPL554 has shown anti-inflammatory effects in a standard challenge study with COPD-like inflammation in human subjects. RPL554 has been well tolerated in these studies and has a favorable safety and tolerability profile, having been administered to more than 730 subjects in 12 clinical trials. Verona Pharma is developing RPL554 for the treatment of COPD, cystic fibrosis, and potentially asthma. Following data analysis, top line data is expected to be available in January 2019.
- **October 2018:** Synairgen announced that dosing has commenced in part 2 of its Phase 2 clinical trial for its inhaled interferon-beta (IFN-beta) therapeutic candidate, SNG001, in patients with COPD. Part 1 of the trial successfully assessed the safety and antiviral biomarker activity of SNG001 in COPD patients when patients were free of viral

infection. The aim of part 2 is to study the efficacy and safety of inhaled SNG001 in up to 120 COPD patients with a confirmed respiratory viral infection. IFN-beta is a naturally-occurring antiviral protein produced by lung cells upon exposure to a respiratory virus. Lung cells from patients with COPD have been shown to have a poor antiviral response *in vitro.* Treating cells with SNG001 has been shown to orchestrate antiviral defense mechanisms which protect COPD lung cells against respiratory viruses in *in vitro* models. In addition, independent research published by *Nature Communications* suggests that the increased risk of pneumonia associated with the use of ICS to treat exacerbations in COPD could be due to suppression of IFNs and proposes that inhaled IFN-beta therapy could be protective.

- **October 2018:** Sanofi announced 2 Phase 3 placebo-controlled trials evaluating Dupixent® (dupilumab) in adults with inadequately-controlled chronic rhinosinusitis with nasal polyps (CRSwNP) met all primary and secondary endpoints. At 24 weeks, patients treated with dupilumab added to a standard-of-care corticosteroid nasal spray experienced a 51 and 57% improvement in their nasal congestion/obstruction severity compared to 15 and 19% improvement with nasal spray alone (-1.25 and -1.34 for dupilumab compared to -0.38 and -0.45 for placebo, on a 0 to 3 scale). Dupilumab-treated patients had a 27 and 33% reduction in their nasal polyps score compared to a 4 and 7% increase for placebo (-1.71 and -1.89 for dupilumab compared to 0.10 and 0.17 for placebo, on a 0 to 8 scale that measures bilateral polyps size by endoscopy). Dupilumab also met all secondary endpoints in both trials, including demonstrating a significant reduction in the need for systemic corticosteroids or surgery, and improvements in smell and chronic rhinosinusitis symptoms. In a pre-specified group of patients with comorbid asthma, dupilumab significantly improved lung function and asthma control ($P<0.0001$ for all primary and secondary endpoints in both trials). The rates of adverse events were generally similar across dupilumab and placebo, and no new or unexpected side effects were observed. Detailed results from the Phase 3 trials, SINUS-24 and SINUS-52, will be submitted for presentation at future medical meetings, and will form part of the companies' regulatory submissions.

News:

- **December 2017:** The FDA removed a boxed warning of asthma death risk on medications delivering combinations of ICS and LABA drugs. The agency required GSK, Merck, and AstraZeneca, which all manufacture fixed-dose combination drugs containing an ICS and LABA, to conduct several large, randomized, double-blind, active-controlled clinical safety trials to evaluate the risk of asthma-related events for the combination compared with ICS alone. The primary efficacy endpoint was asthma exacerbation or an in-patient hospitalization or emergency department visit due to asthma requiring systemic corticosteroids. The 4 trials included more than 41,000 patients with subgroup analyses for gender, adolescents (12 to 18 years old), and African Americans. After reviewing the 26-week trials, the FDA determined that ICS/LABA inhalers did not result in significantly more serious asthma-related side effects than ICS alone in either the overall trial population or the subgroups. A description of the 4 trials will be included in the *Warnings and Precautions* section of the drugs' labels.

The boxed warning changes apply to Advair Diskus® (fluticasone propionate/salmeterol), Advair® HFA (fluticasone propionate/salmeterol), AirDuo™ RespiClick® (fluticasone propionate/salmeterol), Breo® Ellipta® (fluticasone furoate/vilanterol), Dulera® HFA (mometasone/formoterol), and Symbicort® (budesonide/formoterol).

- **February 2018:** Teva Pharmaceutical Industries, Ltd. announced the launch of QVAR® RediHaler™ (beclomethasone dipropionate HFA) and the discontinuation of QVAR® (beclomethasone dipropionate HFA). QVAR® RediHaler™ is now commercially available in both 40mcg and 80mcg strengths by prescription. QVAR® RediHaler™ is the first and only breath-actuated aerosol ICS for the maintenance treatment of asthma as a prophylactic therapy in patients 4 years of age and older. QVAR® RediHaler™ differs from conventional metered-dose inhalers (MDIs) as it delivers medication via a breath-actuated inhaler, eliminating the need for hand-breath coordination during inhalation. QVAR® RediHaler™ administers the same active ingredient found in the previously available QVAR®, but utilizes breath-actuated inhaler technology. Because the medication delivery is breath-actuated, it should not be used with a spacer or volume holding chamber.
- **March 2018:** GSK presented positive results from the OSMO study at the American Academy of Allergy, Asthma & Immunology (AAAAI) and World Allergy Organization (WAO) Joint Congress in Orlando. The results showed that severe asthma patients who are uncontrolled despite receiving Xolair® (omalizumab) and who are eligible for treatment with Nucala® (mepolizumab), experienced improved asthma control when switched to mepolizumab. OSMO is an open-label, single-arm study which investigated whether patients who had been receiving omalizumab, a biologic targeting immunoglobulin E (IgE) in patients with allergic sesitization, for an average of 2.5 years and continued to have uncontrolled severe asthma, gained better asthma control following a switch to mepolizumab, a biologic targeting IL-5 for patients with severe eosinophilic asthma. In the study, 145 patients who were documented to have experienced at least 2 asthma exacerbations in the year prior to enrollment were switched directly to mepolizumab without a wash-out period, and were followed for 32 weeks. Patients met the primary endpoint of asthma control with clinically significant improvements, as evaluated by the Asthma Control Questionnaire (ACQ-5), with a mean change from baseline of -1.45 at week 32 as well as all secondary endpoints and other key endpoints: rate of exacerbations requiring OCS reduced by 64% versus prior 12 months (3.26 to 1.18), rate of exacerbations requiring an emergency department visit or hospitalization reduced by 69% versus prior 12 months (0.63 to 0.19), improvement in pre-bronchodilator FEV_1 of 159mL versus baseline, improvement in QOL as evaluated by the St. George's Respiratory Questionnaire (SGRQ) versus baseline [-19 units, compared with minimal clinically important difference (MCID) -4.0], reduction in blood eosinophils of approximately 80% by week 4 versus baseline, and safety profile was consistent with the known profile of the treatment.
- **March 2018:** Boehringer Ingelheim announced data from the landmark 52-week DYNAGITO® trial which showed that in patients with COPD, Stiolto® Respimat® (tiotropium/olodaterol) lowered the rate of moderate-to-severe exacerbations

compared with Spiriva® Respimat® (tiotropium). The pre-specified significance level of P<0.01 for the primary endpoint of DYNAGITO® was not met. Treatment with tiotropium/ olodaterol resulted in a 7% lower rate of moderate-to-severe COPD exacerbations compared with tiotropium alone (P=0.0498). The study, involving more than 7,800 people with COPD over 1 year, was published in *The Lancet Respiratory Medicine.*

- **May 2018:** AstraZeneca announced results from the Phase 3 SYGMA trials of Symbicort® Turbuhaler® (budesonide/formoterol) given as an anti-inflammatory reliever 'as needed' versus 2 different treatment regimens in patients with mild asthma. The data were published in *The New England Journal of Medicine (NEJM)* and were presented in May 2018 at the American Thoracic Society (ATS) 2018 International Congress. The SYGMA trials were designed to evaluate the efficacy of Symbicort® Turbuhaler®, taken only as needed, as an anti-inflammatory reliever versus current standard of care therapies in mild asthma. Both trials met their primary efficacy outcomes. Symbicort® Turbuhaler® 'as needed' demonstrated superior asthma-symptom control (34.4% vs. 31.1%) assessed according to electronically recorded well-controlled asthma weeks (eWCAW) and a 64% reduction in exacerbations versus short-acting beta$_2$-agonist (SABA) 'as needed'. Symbicort® Turbuhaler® used 'as needed' was non-inferior to twice-daily budesonide maintenance therapy plus SABA 'as needed' in reducing the risk of severe asthma exacerbations (0.11 vs. 0.12), which was achieved with 25% of the budesonide maintenance dose. Symbicort® Turbuhaler® taken only 'as needed' did not achieve non-inferiority in eWCAW versus twice-daily budesonide plus SABA. Symbicort® is currently FDA approved in the MDI device, but not the Turbuhaler® device.
- **November 2018:** The California Technology Assessment Forum (CTAF) will convene to review the Institute for Clinical and Economic Review (ICER)'s assessment of biologic therapies for treatment of asthma associated with T2 inflammation in November 2018. The draft report, "Biologic Therapies for Treatment of Asthma Associated with Type 2 Inflammation: Effectiveness, Value, and Value-Based Price Benchmarks," concluded that all 5 biologic medications currently approved for uncontrolled moderate-to-severe asthma [Dupixent® (dupilumab), Xolair® (omalizumab), Nucala® (mepolizumab), Cinqair® (reslizumab), and Fasenra™ (benrazlizumab)] modestly reduce asthma exacerbations and improve daily QOL. However, the treatments' net prices seem way out of alignment with these incremental clinical benefits, according to the report. The report concluded that to align costs with the added benefits for patients, the current net prices of these treatments would need to be discounted between 50 and 79%. The Final Evidence Report and Meeting Summary is estimated to be available to the public as of December 20, 2018.

Guideline Update(s):

- **January 2018:** The most recent update of the European guidelines for the treatment of chronic urticaria were published in the journal *Allergy* and marks the fourth update by the group since 2006. The updated 2017 European guidelines were written in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI), the European Union (EU)-founded network of excellence, the Global Allergy and Asthma

European Network (GA2LEN), the European Dermatology Forum (EDF), and the WAO. The AAAAI and the American College of Allergy, Asthma, and Immunology (ACAAI) also participated in the review and update. Previously in 2014, the American group, along with the Joint Council of Allergy, Asthma, and Immunology (JCAAI), published guidelines (called "Practice Parameters") in *The Journal of Allergy and Clinical Immunology*. As in the 2014 guidelines, the 2017 guidelines continue to recommend a stepwise approach for the treatment of chronic urticaria beginning with avoidance of triggers and treatment with an H_1-antihistamine. Second-generation H_1-antihistamines are recommended over first-generation H_1-antihistamines because of their better safety profile. Approximately, 40 to 50% of patients with chronic spontaneous urticaria (CSU), also known as chronic idiopathic urticaria (CIU), will not respond to standard doses of H_1-antihistamines. The next step would be to increase the dose of the second-generation H_1-antihistamine. The guideline states that the majority of patients with urticaria not responding to standard doses will benefit from up-dosing of antihistamines and highlights studies that have documented the benefit of using up to 4-fold higher than licensed approved dosing. In contrast to the 2014 guidelines, and because of insufficient evidence in the literature, the 2017 revision does not recommend adding another second-generation H_1-antihistamine, a H_2-antagonist, a leukotriene receptor antagonist (LTRA), or a first-generation H_1-antihistamine as next steps in treatment of antihistamine-resistant cases of chronic urticaria. While many patients respond to up-dosing with second-generation H_1-antihistamines, around half of chronic urticaria patients will not achieve satisfactory control with antihistamine treatment even at 4 times the standard dose. For such patients, the 2017 guideline recommends adding omalizumab to the second-generation H_1-antihistamine. If response to omalizumab is not satisfactory, then cyclosporin A is recommended as an add-on treatment to second-generation H_1-antihistamines, if not contraindicated. The use of systemic corticosteroids in the treatment of chronic urticaria is generally to be avoided and long-term use of systemic corticosteroids is not recommended because of the myriad of associated side effects. The 2017 guideline suggests that a short course of OCS of up to 10 days may be helpful in reducing disease duration/activity in acute urticaria or exacerbations of CSU.

- **November 2018:** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has published the *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2019 Report*. The GOLD 2019 report is a revision of the GOLD 2017 report following systematic literature searches and double-blind review by the GOLD Science committee; the GOLD report has been updated to include key peer-reviewed research publications from January 2017 to July 2018. Some updates include a new section on blood eosinophil count, more discussion of the evidence around use of combination therapies in patients with history of exacerbations, updated algorithms for the initiation of and follow-up management of pharmacological treatment, and new diagrams to improve clarity and to line up with latest evidence. Specific recommendations for the treatment of GOLD groups A ,B, C, and D have been revised, and recommendations regarding the follow-up pharmacological management have also been updated and emphasize the need to review, assess, and adjust.

Lonhala® Magnair® (Glycopyrrolate Inhalation Solution) Product Summary[32,33]

Indication(s): Lonhala® Magnair® (glycopyrrolate inhalation solution) is an anticholinergic indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD.

Dosing:

- Lonhala® Magnair® is supplied as a sterile solution for inhalation in a unit-dose, single-use, low-density polyethylene (LDPE) vial. Each 1mL vial contains 25mcg of glycopyrrolate.
- The recommended regimen for the maintenance treatment of COPD is the contents of one Lonhala® vial via inhalation twice daily.
- Lonhala® Magnair® is for oral inhalation only. Lonhala® solution should not be swallowed.
- Lonhala® vials should only be used with the Magnair® Nebulizer System.

Mechanism of Action: Glycopyrrolate is a LAMA, which is often referred to as an anticholinergic. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

Safety:

- Acutely Deteriorating COPD: Lonhala® Magnair® should not be initiated in acutely deteriorating COPD or to treat acute symptoms.
- Paradoxical Bronchospasm: If paradoxical bronchospasm occurs, Lonhala® Magnair® should be discontinued immediately and alternative therapy instituted.
- Worsening of Narrow-Angle Glaucoma: Worsening of narrow-angle glaucoma may occur.
- Worsening of Urinary Retention: Worsening of urinary retention may occur.

Use in Specific Populations:

- Renal Impairment: Use of Lonhala® Magnair® in patients with severe renal impairment should be considered if the potential benefit of the treatment outweighs the risk.

Efficacy: The safety and efficacy of Lonhala® Magnair® were evaluated in 2 dose-ranging studies, (2) 12-week placebo-controlled confirmatory studies (GOLDEN-3 and GOLDEN-4) enrolling 1,293 COPD patients, and a 48-week long-term, open-label, active-controlled safety study (GOLDEN-5) of 1,087 COPD patients. The efficacy of Lonhala® Magnair® is based primarily on the dose-ranging studies in 378 subjects with COPD and the 2 placebo-controlled confirmatory studies. The primary endpoint for the placebo-controlled studies was the change from baseline in trough FEV_1 at day 84 versus placebo.

- In GOLDEN-3, the change from baseline FEV_1 least squares (LS) mean was 0.089L for Lonhala® Magnair®-treated patients versus -0.008L for placebo-treated patients [difference: 0.096L; 95% confidence interval (CI): 0.059, 0.133].
- In GOLDEN-4, the change from baseline FEV_1 LS mean was 0.092L for Lonhala® Magnair®-treated patients versus 0.011L for placebo-treated patients (difference: 0.081L; 95% CI: 0.042, 0.120).

- In GOLDEN-5, the overall treatment emergent adverse events incidences were similar for the Lonhala® Magnair® and Spiriva® HandiHaler® (tiotropium) groups over 48 weeks.

Cost Comparison:

Medication	Cost Per Unit	Cost Per 30 Days	Cost Per Year
Lonhala® Magnair® (glycopyrrolate inhalation solution) 25mcg/mL	**$18.12**	**$1,087.20***	**$13,046.40***
Spiriva® HandiHaler® (tiotropium inhalation powder) 18mcg	$12.73	$381.90+	$4,582.80+

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. Spiriva® HandiHaler® was FDA approved in 2009 and has a significant federal rebate.
Unit = capsule or vial for oral inhalation
*Lonhala® Magnair® price does not reflect cost of starter kit that includes the nebulizer and accessories. Lonhala® Magnair® price is based on FDA approved regimen of one Lonhala® vial twice daily.
+Spiriva® HandiHaler® (tiotropium inhalation powder) FDA approved regimen is two inhalations of the powder contents from a single Spiriva® capsule (18mcg) once daily.

Yupelri™ (Revefenacin Inhalation Solution) Product Summary[34,35]

Indication(s): Yupelri™ (revefenacin inhalation solution) is an anticholinergic indicated for the maintenance treatment of patients with COPD.

Dosing:

- Yupelri™ is supplied in a unit-dose vial for nebulization. Each vial contains 175mcg/3mL solution.
- The recommended regimen is one 175mcg vial (3mL) once daily used with a standard jet nebulizer with a mouthpiece connected to an air compressor.
- Yupelri™ is for oral inhalation only. Yupelri™ should not be swallowed.

Mechanism of Action: Revefenacin is a LAMA, which is often referred to as an anticholinergic. In the airways, it exhibits pharmacological effects through inhibition of M3 receptor at the smooth muscle leading to bronchodilation.

Safety:

- Acutely Deteriorating COPD: Yupelri™ should not be initiated in acutely deteriorating COPD or to treat acute symptoms.
- Paradoxical Bronchospasm: If paradoxical bronchospasm occurs, Yupelri™ should be discontinued immediately and alternative therapy instituted.
- Worsening of Narrow-Angle Glaucoma: Worsening of narrow-angle glaucoma may occur.
- Worsening of Urinary Retention: Worsening of urinary retention may occur. Caution should be used in patients with prostatic hyperplasia or bladder neck obstruction.
- Immediate Hypersensitivity: Immediate hypersensitivity reactions may occur. If such a reaction occurs, therapy with Yupelri™ should be stopped at once and alternative treatments should be considered.

Use in Specific Populations:

- Hepatic Impairment: Yupelri™ use should be avoided in patients with hepatic impairment.

Efficacy: The safety and efficacy of Yupelri™ 175mcg once daily were evaluated in 2 dose-ranging trials, 2 replicate 12-week, Phase 3 confirmatory clinical trials, and a 52-week safety trial. The efficacy of Yupelri™ is primarily based on the 2 replicate 12-week, Phase 3 placebo-controlled trials in 1,229 subjects with moderate-to-severe COPD. The primary endpoint was change from baseline in trough FEV_1 at day 85.

- In study 1, the LS mean change in FEV_1 was 127mL for Yupelri™-treated patients versus -19mL for placebo-treated patients (difference: 146mL; 95% CI: 103.7, 188.8).
- In study 2, the LS mean change in FEV_1 was 102mL for Yupelri™-treated patients versus -45mL for placebo-treated patients (difference: 147mL; 95% CI: 97.0, 197.1).

Cost: Cost information for Yupelri™ (revefenacin inhalation solution) cost is not yet available.

Recommendations

The College of Pharmacy recommends the placement of Lonhala® Magnair® (glycopyrrolate inhalation solution) and Yupelri™ (revefenacin inhalation solution) into Tier-2 of the Long-Acting $Beta_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonist (LAMA) Product Based Prior Authorization (PBPA) category with the following criteria:

Long-Acting $Beta_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonist (LAMA) Tier-2 Approval Criteria:

1. Member must be 18 years of age or older; and
2. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD), chronic bronchitis, or emphysema; and
3. A 4-week trial of at least 1 long-acting $beta_2$ agonist (LABA) and a 4-week trial of 1 long-acting muscarinic antagonist (LAMA) within the past 90 days; or
4. A documented adverse effect, drug interaction, or contraindication to all available Tier-1 products.
5. A clinical exception may apply for members who are unable to effectively use hand-actuated devices, such as Spiriva® Handihaler®, or who are stable on nebulized therapy.

Long-Acting $Beta_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA)	
Tier-1*	**Tier-2**
Long-Acting $Beta_2$ Agonists* (LABA)	
salmeterol inhalation powder (Serevent®)	arformoterol nebulizer solution (Brovana®)
	formoterol nebulizer solution (Perforomist®)
	indacaterol inhalation powder (Arcapta® Neohaler®)
	olodaterol inhalation spray (Striverdi® Respimat®)
Long-Acting Muscarinic Antagonists (LAMA)	
tiotropium inhalation powder (Spiriva® Handihaler®)	aclidinium inhalation powder (Tudorza® PressAir®)
	glycopyrrloate inhalation powder (Seebri® Neohaler®)

Long-Acting Beta$_2$ Agonists (LABA) and Long-Acting Muscarinic Antagonists (LAMA)	
Tier-1*	**Tier-2**
	glycopyrrolate inhalation solution (Lonhala® Magnair®)
	revefenacin inhalation solution (Yupelri™)
	tiotropium soft mist inhaler (Spiriva® Respimat®)+
	umeclidinium inhalation powder (Incruse® Ellipta®)

*Combination agents that contain a long-acting beta$_2$ agonist (LABA) ingredient qualify as Tier-1 agents.
Tier-1 medications do not require prior authorization with a COPD diagnosis.
Tier structure based on supplemental rebate participation and/or National Average Drug Acquisition Costs (NADAC) or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
+Unique criteria applies for a diagnosis of asthma.

The College of Pharmacy also recommends updating the current prior authorization criteria for Dupixent® (dupilumab), Arnuity® Ellipta® (fluticasone furoate), AirDuo™ RespiClick® (fluticasone propionate/salmeterol), Breo® Ellipta® (fluticasone furoate/vilanterol), Trelegy™ Ellipta® (fluticasone furoate/umeclidinium/vilanterol), Xolair® (omalizumab), and Fasenra™ (benralizumab). The following criteria would apply (changes noted in red):

Dupixent® (Dupilumab Injection) Approval Criteria [Eosinophilic Phenotype Asthma Diagnosis]:

1. An FDA approved indication for add-on maintenance treatment of patients with moderate-to-severe eosinophilic phenotype asthma or oral corticosteroid-dependent asthma; and
2. Member must be 12 years of age or older; and
3. Member must have a baseline blood eosinophil count of ≥150cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 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 1 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 products, the highest FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. The prescriber must verify the member has been counseled on proper administration and storage of Dupixent®; and
8. Dupixent® 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 12 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 6 months after which time compliance will be evaluated for continued approval; and
10. Quantities approved must not exceed FDA recommended dosing requirements.

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

1. An FDA approved diagnosis of asthma; and
2. Member must be at or above the minimum age indicated; and
3. ~~Member must be 12 years of age or older; and~~
4. A patient-specific, clinically significant reason why Flovent® (fluticasone propionate) is not an option 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 Advair®, Dulera®, and Symbicort® or a reason why Advair®, Dulera®, and Symbicort® 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.

Breo® Ellipta® (Fluticasone Furoate/Vilanterol) Approval Criteria:

1. An FDA approved diagnosis of chronic obstructive pulmonary disease (COPD) or chronic bronchitis and/or emphysema associated with COPD; and
    a. For a diagnosis of COPD or chronic bronchitis and/or emphysema associated with COPD, trials of Advair® and Symbicort®, consisting of at least 30 days each within the last 90 days that did not adequately control COPD symptoms; or
2. An FDA approved diagnosis of asthma in patients 18 years of age and older; and
    a. For a diagnosis of asthma, trials of Advair®, Dulera®, and Symbicort® consisting of at least 30 days each within the last ~~90~~ 120 days that did not adequately control asthma symptoms.

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, or to reduce exacerbations of COPD in patients with a history of exacerbations; and
2. A 4-week trial of at least 1 long-acting beta$_2$ agonist (LABA) and a 4-week trial of 1 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 an ICS/LABA combination with a LAMA.

Xolair® (Omalizumab) Approval Criteria [Chronic Idiopathic Urticaria Diagnosis]:

1. An FDA approved diagnosis of chronic idiopathic urticaria; and

2. Member must be 12 years of age or older; and
3. Other forms of urticaria must be ruled out; and
4. Other potential causes of urticaria must be ruled out; and
5. Member must have an Urticaria Activity Score (UAS) ≥16; and
6. Prescriber must be an allergist, immunologist, dermatologist, or be an advanced care practitioner with a supervising physician that is an allergist, immunologist, or dermatologist; and
7. ~~Member must have tried and failed to obtain relief from other treatments including the following trials within the last 6 months (member must fail all classes unless contraindicated):~~
   a. ~~At least 2 different H_1-antihistamine trials for a minimum duration of 2 weeks each:~~
      i. ~~One~~ A trial ~~must be~~ of a second generation antihistamine dosed 4 times the maximum FDA dose within the last 3 months for at least 4 weeks (or less if symptoms are intolerable); and
      ii. ~~One trial must be tried in combination with an H_2-antihistamine; and~~
   c. ~~A 4-week trial of a leukotriene receptor antagonist in combination with a 4-week trial of doxepin 10mg to 50mg daily; and~~
8. Initial dosing will only be approved for 150mg every 4 weeks. If the member has inadequate results at this dose, then the dose may be increased to 300mg every 4 weeks.
9. Initial approvals will be for the duration of 3 months.

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 12 years of age or older; and
3. Member must have a baseline blood eosinophil count of ~~300~~ ≥150cell/mcL (can apply to either a recent level or in history prior to oral corticosteroid use); and
4. Member must have had at least 2 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 1 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 FDA approved dose meets this criteria); and
6. Member must have failed at least 1 other asthma controller medication used in addition to the high-dose ICS compliantly for at least the past 3 months; and
7. Fasenra™ must be administered in a health care setting by a health care 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 12 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 6 months after which time compliance will be evaluated for continued approval.
10. A quantity limit of 1 prefilled syringe per 56 days will apply.

Utilization Details of Maintenance Asthma and COPD Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
COMBINATION ICS/LABA PRODUCTS						
TIER-1						
ADVAIR DISKU AER 250/50MCG	7,997	2,595	$2,896,703.57	$11.97	$362.22	21.18%
ADVAIR HFA AER 115/21MCG	5,576	1,669	$1,958,768.03	$11.31	$351.29	14.32%
SYMBICORT AER 160/4.5MCG	3,361	647	$1,034,440.84	$9.80	$307.78	7.57%
ADVAIR DISKU AER 500/50MCG	2,533	695	$1,196,399.03	$15.63	$472.32	8.75%
ADVAIR DISKU AER 100/50MCG	2,398	919	$692,093.76	$9.50	$288.61	5.06%
DULERA AER 200/5MCG	2,379	736	$688,523.93	$9.41	$289.42	5.04%
ADVAIR HFA AER 230/21MCG	1,670	469	$757,986.46	$14.41	$453.88	5.54%
DULERA AER 100/5MCG	1,296	456	$371,507.28	$9.10	$286.66	2.72%
ADVAIR HFA AER 45/21MCG	831	295	$222,154.86	$8.42	$267.33	1.62%
SYMBICORT AER 80/4.5MCG	611	149	$159,549.66	$8.25	$261.13	1.17%
SUBTOTAL	**28,652**	**8,630**	**$9,978,127.42**	**$11.31**	**$348.25**	**72.97%**
TIER-2						
BREO ELLIPTA INH 100-25MCG	134	29	$43,327.87	$10.70	$323.34	0.32%
SUBTOTAL	**134**	**29**	**$43,327.87**	**$10.70**	**$323.34**	**0.32%**
INDIVIDUAL COMPONENT LABA PRODUCTS						
TIER-1						
SEREVENT DIS AER 50MCG	686	243	$245,006.81	$11.66	$357.15	1.79%
SUBTOTAL	**686**	**243**	**$245,006.81**	**$11.66**	**$357.15**	**1.79%**
TIER-2						
BROVANA NEB 15MCG	71	15	$60,697.53	$29.00	$854.89	0.44%
PERFOROMIST NEB 20MCG	23	7	$20,910.86	$30.31	$909.17	0.15%
SUBTOTAL	**94**	**22**	**$81,608.39**	**$29.32**	**$868.17**	**0.59%**
INDIVIDUAL COMPONENT LAMA PRODUCTS						
TIER-1						
SPIRIVA CAP HANDIHLR 18MCG	8,178	2,101	$3,047,823.14	$12.38	$372.69	22.29%
SUBTOTAL	**8,178**	**2,101**	**$3,047,823.14**	**$12.38**	**$372.69**	**22.29%**
TIER-2						
SPIRIVA SPR 2.5MCG	266	65	$99,616.01	$11.94	$374.50	0.73%
INCRUSE ELPT INH 62.5MCG	77	17	$24,521.05	$10.62	$318.46	0.18%
TUDORZA PRES AER 400MCG	49	8	$15,638.24	$10.43	$319.15	0.11%
LONHALA MAGN SOL 25MCG	1	1	$1,139.85	$37.99	$1,139.85	0.01%
SUBTOTAL	**393**	**91**	**$140,915.15**	**$11.57**	**$358.56**	**1.03%**
COMBINATION LABA/LAMA PRODUCTS						
ANORO ELLIPT AER 62.5/25MCG	192	38	$71,492.25	$12.41	$372.36	0.52%
STIOLTO AER 2.5/2.5MCG	66	15	$22,953.33	$11.59	$347.78	0.17%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
BEVESPI AER 9/4.8MCG	16	5	$5,329.19	$11.41	$333.07	0.04%
UTIBRON NEOHALER 62.5/25MCG	2	2	$715.66	$11.93	$357.83	0.01%
SUBTOTAL	**276**	**60**	**$100,490.43**	**$12.16**	**$364.10**	**0.74%**
COMBINATION LABA/LAMA/ICS PRODUCTS						
TRELEGY ELLIPTA 100/62.5/25MCG	6	2	$3,140.62	$17.45	$523.44	0.02%
SUBTOTAL	**6**	**2**	**$3,140.62**	**$17.45**	**$523.44**	**0.02%**
PHOSPHODIESTERASE-4 ENZYME INHIBITOR PRODUCTS						
DALIRESP TAB 500MCG	200	28	$65,694.15	$10.95	$328.47	0.48%
SUBTOTAL	**200**	**28**	**$65,694.15**	**$10.95**	**$328.47**	**0.48%**
TOTAL	**38,619**	**9,018***	**$13,706,133.98**	**$11.58**	**$354.91**	**100%**

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

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
MONOCLONAL ANTIBODY PRODUCTS: PHARMACY CLAIMS						
XOLAIR SOL 150MG	69	16	$327,908.92	$169.73	$4,752.30	88.41%
FASENRA INJ 30MG/ML	6	3	$28,575.96	$145.80	$4,762.66	7.70%
NUCALA INJ 100MG	5	2	$14,392.10	$102.80	$2,878.42	3.88%
TOTAL	**80**	**20***	**$370,876.98**	**$163.53**	**$4,635.96**	**100%**

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

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	TOTAL UNITS	COST/ CLAIM	% COST
MONOCLONAL ANTIBODY PRODUCTS: MEDICAL CLAIMS						
OMALIZUMAB INJ 5MG (J2357)	76	7	$200,733.30	5,730	$2,641.23	99.95%
MEPOLIZUMAB INJ (J2182)	3	1	$7,725.00	300	$2,575.00	0.04%
RESLIZUMAB INJ (J2786)	1	1	$2,088.32	251	$2,088.32	0.01%
TOTAL	**80**	**9***	**$210,546.62**	**6,281**	**$2,631.83**	**100%**

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

Utilization Details of Inhaled Corticosteroids: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
INHALED CORTICOSTEROID PRODUCTS						
TIER-1						
FLOVENT HFA AER 110MCG	19,775	8,249	$4,565,219.59	$6.41	$230.86	34.88%
FLOVENT HFA AER 44MCG	17,604	7,866	$3,075,504.79	$5.38	$174.70	23.50%
QVAR AER 40MCG	6,004	2,754	$945,577.87	$4.25	$157.49	7.22%
BUDESONIDE SUS 0.25MG/2ML	4,106	2,427	$569,818.62	$5.59	$138.78	4.35%
BUDESONIDE SUS 0.5MG/2ML	4,042	1,979	$615,436.73	$5.98	$152.26	4.70%
QVAR AER 80MCG	3,730	1,631	$775,763.64	$5.85	$207.98	5.93%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ DAY	COST/ CLAIM	% COST
FLOVENT HFA AER 220MCG	2,972	1,289	$1,071,181.53	$9.52	$360.42	8.18%
PULMICORT INH 90MCG	1,091	484	$192,856.50	$6.61	$176.77	1.47%
PULMICORT INH 180MCG	896	457	$198,929.79	$5.60	$222.02	1.52%
FLOVENT DISK AER 100MCG	795	318	$147,492.78	$5.74	$185.53	1.13%
ALVESCO AER 80MCG	550	252	$133,156.06	$7.80	$242.10	1.02%
FLOVENT DISK AER 250MCG	515	172	$126,915.43	$7.83	$246.44	0.97%
ASMANEX 60 AER 220MCG	436	152	$96,341.47	$6.68	$220.97	0.74%
ASMANEX 30 AER 220MCG	400	139	$72,481.47	$5.98	$181.20	0.55%
FLOVENT DISK AER 50MCG	366	144	$64,775.16	$5.56	$176.98	0.49%
ASMANEX HFA AER 100MCG	327	158	$57,970.96	$4.34	$177.28	0.44%
BUDESONIDE SUS 1MG/2ML	309	115	$185,972.19	$22.17	$601.85	1.42%
ALVESCO AER 160MCG	276	126	$66,842.92	$7.18	$242.18	0.51%
ASMANEX 30 AER 110MCG	220	88	$37,289.30	$5.63	$169.50	0.28%
AEROSPAN AER 80MCG	177	92	$34,153.48	$5.22	$192.96	0.26%
ASMANEX HFA AER 200MCG	132	64	$28,523.60	$5.57	$216.09	0.22%
ASMANEX 120 AER 220MCG	89	48	$25,779.37	$6.49	$289.66	0.20%
SUBTOTAL	**64,812**	**29,004**	**$13,087,983.25**	**$6.03**	**$201.94**	**99.98%**
		TIER-2				
QVAR REDIHAL AER 40MCG	1	1	$167.29	$2.79	$167.29	0.00%
ARNUITY ELPT INH 200MCG	1	1	$223.08	$7.44	$223.08	0.00%
SUBTOTAL	**2**	**2**	**$390.37**	**$4.34**	**$195.19**	**0.00%**
TOTAL	**64,814**	**25,418***	**$13,088,373.62**	**$6.03**	**$201.94**	**100%**

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

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Appendix I

Fiscal Year 2018 Annual Review of Thrombocytopenia Medications and 30-Day Notice to Prior Authorize Tavalisse™ (Fostamatinib), Doptelet® (Avatrombopag), and Mulpleta® (Lusutrombopag)

Oklahoma Health Care Authority
December 2018

Current Prior Authorization Criteria

Nplate® (Romiplostim) Approval Criteria:

1. An FDA approved diagnosis of chronic immune (idiopathic) thrombocytopenia purpura (ITP); and
2. Previous insufficient response with at least 1 of the following treatments:
   a. Corticosteroids; or
   b. Immunoglobulins; or
   c. Splenectomy; and
3. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
4. Nplate® (romiplostim) is not being used in an attempt to normalize platelet counts; and
5. Must be prescribed by, or in consultation with, a hematologist or oncologist; and
6. Initial dosing of 1mcg/kg once weekly as a subcutaneous injection with recent patient weight in kilograms provided; and
7. Continuation criteria:
   a. Weekly CBCs with platelet count and peripheral blood smears until stable platelet count (≥50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved, then obtain monthly thereafter; and
   b. Dosing adjustments:
      i. Platelets <50 x 10^9/L, increase dose by 1mcg/kg; or
      ii. Platelets >200 x 10^9/L for 2 consecutive weeks, reduce dose by 1mcg/kg; or
      iii. Platelets >400 x 10^9/L, do not dose. Continue to assess platelet count weekly. When platelets <200 x 10^9/L, resume at a dose reduced by 1mcg/kg; and
8. Discontinuation criteria:
   a. Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum weekly dose of 10mcg/kg; and
9. Approval period will be for 4 weeks initially, and then quarterly.

Promacta® (Eltrombopag) Approval Criteria:

1. An FDA approved diagnosis of chronic immune (idiopathic) thrombocytopenia (ITP); and
   a. Previous insufficient response to at least 1 of the following:
      i. Corticosteroids; or
      ii. Immunoglobulins; or
      iii. Splenectomy; and

   b. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
   c. Must be prescribed by, or in consultation with, a hematologist or oncologist; or
2. An FDA approved diagnosis of thrombocytopenia in patients with chronic hepatitis C (CHC) to allow initiation and maintenance of interferon (IFN)-based therapy; and
   a. Promacta® must be prescribed by a gastroenterologist, infectious disease specialist, or transplant specialist or the member must have been evaluated by a gastroenterologist, infectious disease specialist, or transplant specialist for hepatitis C therapy within the last 3 months; and
   b. Patient must be prescribed IFN for treatment of CHC infection; or
3. An FDA approved diagnosis of severe aplastic anemia (SAA); and
   a. Previous insufficient response or documented contraindication or intolerance to immunosuppressive therapy; and
   b. Must be prescribed by, or in consultation with, a hematologist or oncologist; and
4. For the diagnoses of chronic ITP and CHC-associated thrombocytopenia, initial approvals will be for the duration of 1 month. For the diagnosis of SAA, initial approvals will be for the duration of 4 months. Subsequent approvals may be authorized if the prescriber documents the member is responding well to therapy and the following criteria is met, based upon member's diagnoses:
   a. For All Diagnoses:
      i. Must not have excessive platelet count responses. Promacta® should be discontinued if platelets exceed 400 x 10^9/L after 2 weeks of therapy at the lowest dose; and
      ii. Prescriber documents liver function tests are being monitored and levels are acceptable to the prescriber.
   b. Chronic ITP:
      i. Documentation that platelet count has increased to a level sufficient to avoid clinically important bleeding or that a dose increase is planned, if not already on maximum dose. Promacta® should be discontinued if the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 4 weeks of therapy at the maximum daily dose of 75mg.
   c. CHC-Associated Thrombocytopenia:
      i. Documentation that member continues to be on antiviral therapy. Promacta® should be discontinued when antiviral therapy is discontinued.
   d. SAA:
      i. Documentation that member has had a hematologic response (e.g., increase in platelet count, increase in hemoglobin, increase in absolute neutrophil count, reduction in frequency of platelet or red blood cell transfusions). Promacta® should be discontinued if no hematologic response has occurred after 16 weeks of therapy.

Utilization of Thrombocytopenia Medications: Fiscal Year 2018

Comparison of Fiscal Years: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	14	66	$479,717.62	$7,268.45	$244.01	1,858	1,966
2018	23	125	$1,085,861.96	$8,686.90	$295.07	4,626	3,680
% Change	**64.30%**	**89.40%**	**126.40%**	**19.50%**	**20.90%**	**149.00%**	**87.20%**
Change	**9**	**59**	**$606,144.34**	**$1,418.45**	**$51.06**	**2,768**	**1,714**

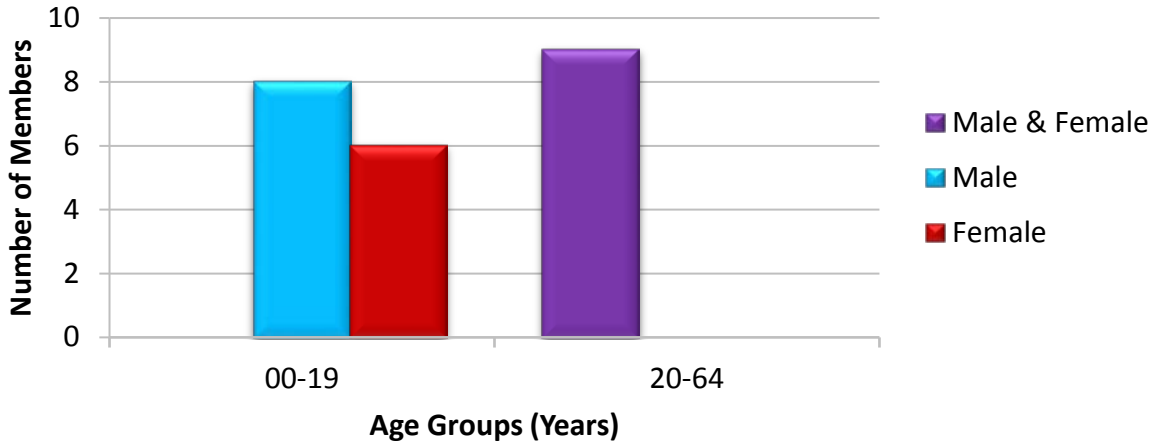
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Fiscal Year 2018 Utilization of Nplate®: Medical Claims

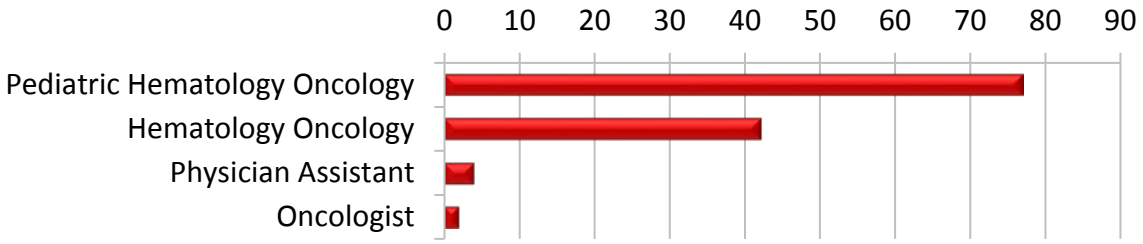
Fiscal Year	*Total Members	+Total Claims	Total Cost	Cost/ Claim	Total Units
2018	7	47	$108,352.68	$2,305.38	1,767

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

Demographics of Members Utilizing Thrombocytopenia Medications

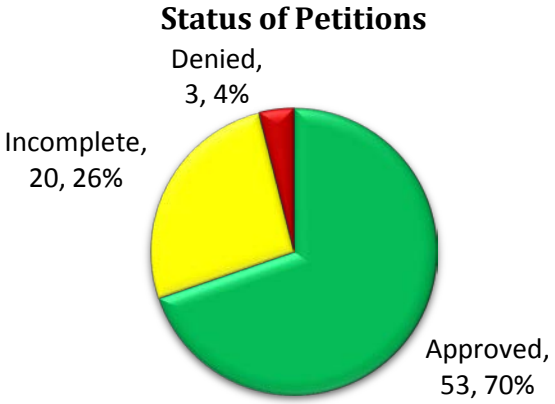


Top Prescriber Specialties of Thrombocytopenia Medications by Number of Claims



Prior Authorization of Thrombocytopenia Medications

There were 76 prior authorization requests submitted for thrombocytopenia medications during fiscal year 2018. The prior authorization for Promacta® (eltrombopag) was implemented on February 17, 2018; members currently on therapy at the time of implementation were grandfathered. The following chart shows the status of the submitted petitions for fiscal year 2018.



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

Anticipated Patent Expiration(s):

- Promacta® (eltrombopag): February 2028

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

- **April 2018:** Rigel Pharmaceuticals, Inc. announced the FDA approved Tavalisse™ (fostamatinib disodium hexahydrate) for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Fostamatinib is an oral spleen tyrosine kinase (SYK) inhibitor that targets the underlying autoimmune cause of the disease by impeding platelet destruction.
- **May 2018:** Dova Pharmaceuticals, Inc. announced the FDA approved Doptelet® (avatrombopag), a once-daily, orally administered, thrombopoietin (TPO) receptor agonist for the treatment of thrombocytopenia in adult patients with chronic liver disease (CLD) who are scheduled to undergo a procedure.
- **August 2018:** Shionogi & Co., Ltd. announced that the FDA approved Mulpleta® (lusutrombopag), a once-daily, orally administered, small molecule TPO receptor agonist for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure.
- **November 2018:** Novartis announced that the FDA expanded the use of Promacta® (eltrombopag) to be used in combination with standard immunosuppressive therapy to treat patients 2 years of age and older with treatment-resistant severe aplastic anemia (SAA). The FDA also designated the drug as a Breakthrough Therapy for decreasing the risk of hemorrhage in patients with radiation sickness.

Pipeline:

- **Efgartigimod:** In September 2018, Argenx announced positive topline results from its Phase 2 proof-of-concept trial of efgartigimod in adult primary ITP patients. The Phase 2 data of efgartigimod showed a favorable tolerability and safety profile consistent with the Phase 1 trial and the Phase 2 proof-of-concept trial in generalized myasthenia gravis (gMG). Patients treated with efgartigimod had clinically meaningful platelet count improvements across doses and ITP classifications, including newly diagnosed, persistent, and chronic, and correlated with a consistent reduction in immunoglobulin G (IgG) levels. Argenx plans to begin Phase 3 development in ITP for intravenous (IV) efgartigimod and also expects to initiate a Phase 2 trial in ITP using a subcutaneous (sub-Q) formulation of efgartigimod. Efgartigimod is also being further evaluated in gMG and pemphigus vulgaris. Additionally, Argenx plans to study efgartigimod in chronic inflammatory demyelinating polyneuropathy.

Tavalisse™ (Fostamatinib) Product Summary[7,8]

Indication(s): Tavalisse™ (fostamatinib) is a kinase inhibitor indicated for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment.

Dosing:

- Tavalisse™ (fostamatinib) is supplied as 100mg and 150mg tablets.
- The recommended initial dose of fostamatinib is 100mg orally twice daily with or without food. After 4 weeks, it is recommended to increase the dose to 150mg twice daily, if needed, to achieve platelet counts of ≥50 x 10^9/L as necessary to reduce the risk of bleeding.
- It is recommended to manage adverse reactions using dose reduction, interruption of treatment, or discontinuation.
- If the platelet count does not increase to a level sufficient to avoid clinically important bleeding after 12 weeks of treatment, it is recommended to discontinue fostamatinib.

Mechanism of Action: Fostamatinib is a tyrosine kinase inhibitor with demonstrated activity against SYK. The major metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors and B-cell receptors. R406 reduces antibody-mediated destruction of platelets.

Contraindication(s): None

Warnings and Precautions:

- Hypertension: Hypertension can occur with fostamatinib treatment. Hypertensive crisis has occurred in 1% of patients. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects of fostamatinib. It is recommended to monitor the patient's blood pressure every 2 weeks until stable, then monthly and adjust or initiate antihypertensive therapy to ensure maintenance of blood pressure control during fostamatinib therapy. If increased blood pressure persists despite appropriate

therapy, fostamatinib treatment may need to be interrupted, dose reduced, or discontinued.

- Hepatotoxicity: Elevated liver function tests, mainly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), can occur with fostamatinib. It is recommended to monitor liver function tests monthly during treatment. If ALT or AST increase more than 3 times the upper limit of normal (ULN), hepatotoxicity should be managed by fostamatinib interruption, dose reduction, or discontinuation.
- Diarrhea: Diarrhea occurred in 31% of patients treated with fostamatinib, and 1% of patients experienced severe diarrhea. Patients should be monitored for the development of diarrhea and appropriate management of diarrhea using supportive care measures (e.g., dietary changes, hydration, antidiarrheal medication) should begin early after the onset of symptoms.
- Neutropenia: Neutropenia occurred in 6% of patients treated with fostamatinib, and febrile neutropenia occurred in 1% of patients. It is recommended to monitor the absolute neutrophil count (ANC) monthly and monitor for infection during treatment. Toxicity should be managed with fostamatinib interruption, dose reduction, or discontinuation.
- Embryo-Fetal Toxicity: Based on findings from animal studies and fostamatinib's mechanism of action, fostamatinib can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fostamatinib to pregnant rats and rabbits during organogenesis caused adverse development outcomes including embryo-fetal mortality (post-implantation loss), alterations in growth (lower fetal weights), and structural abnormalities (variations and malformations) at maternal exposures (AUCs) approximately 0.3 and 10 times the human exposure at the maximum recommended human dose (MRHD), respectively. Pregnant women should be advised of the potential risk to a fetus and females of reproductive potential should use effective contraception during treatment and for at least 1 month after the last dose.

Use in Specific Populations:

- Pregnancy: Based on findings from animal studies and fostamatinib's mechanism of action, fostamatinib can cause fetal harm when administered to a pregnant woman. Pregnant women should be advised of the potential risk to a fetus.
- Lactation: There are no data on the presence of fostamatinib and/or its metabolites in human milk, the effects on the breastfed child, or on milk production. The major active metabolite, R406, was detected in rodent maternal milk in concentrations 5- to 10-fold higher than in maternal plasma. Due to the potential for serious adverse reactions in breastfed children from fostamatinib, lactating women should be advised not to breastfeed during treatment with fostamatinib and for at least 1 month after the last dose.
- Females and Males of Reproductive Potential: For females of reproductive potential, pregnancy status should be verified prior to initiating fostamatinib. Females of reproductive potential should be advised to use effective contraception during treatment with fostamatinib and for at least 1 month after the last dose. There are no

data on the effect of fostamatinib on human fertility; however, based on the finding of reduced pregnancy rates in animal studies, fostamatinib may affect female fertility.

- Pediatric Use: The safety and effectiveness of fostamatinib have not been established in pediatric patients. Fostamatinib is not recommended for use in patients younger than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies.
- Geriatric Use: Of the 102 patients with ITP who received fostamatinib, 28 (27%) were 65 years of age and older, while 11 (11%) were 75 years of age and older. In patients 65 years of age and older, 6 (21%) patients experienced serious adverse events and 5 (18%) experienced adverse events leading to treatment withdrawal while in patients younger than 65 years of age, 7 (9%) and 5 (7%) experienced serious adverse events and adverse events leading to treatment withdrawal, respectively. No overall differences in effectiveness were observed in these patients compared to younger patients.

Drug Interactions:

- Strong CYP3A4 Inhibitors: Concomitant use of fostamatinib with a strong CYP3A4 inhibitor increases exposure to the major active metabolite, R406. It is recommended to monitor for toxicities of fostamatinib that may require dose reduction when given concurrently with a strong CYP3A4 inhibitor.
- Strong CYP3A4 Inducers: Concomitant use of fostamatinib with a strong CYP3A4 inducer (e.g., rifampicin) reduces exposure to R406. Concomitant use of fostamatinib with a strong CYP3A4 inducer is not recommended.

Adverse Reactions: The most common adverse reactions with fostamatinib (≥5% and more than placebo) in clinical studies were diarrhea, hypertension, nausea, respiratory infection, dizziness, increased ALT/AST, rash, abdominal pain, fatigue, chest pain, and neutropenia.

Efficacy: Fostamatinib was studied in 2 placebo-controlled efficacy and safety studies (FIT-1 and FIT-2), and in an open-label extension study (FIT-3).

Placebo-Controlled Studies:

- A total of 150 patients with persistent or chronic ITP, who had an insufficient response to previous treatment (i.e., corticosteroids, immunoglobulins, splenectomy, and/or a TPO receptor agonist) were enrolled in 2 identical, double-blind, placebo-controlled studies that were conducted in different countries. For each study, patients were randomized 2:1 to fostamatinib or placebo for 24 weeks. Randomization was stratified with respect to prior splenectomy and severity of thrombocytopenia. Stable concurrent ITP therapy [glucocorticoids (<20mg prednisone equivalent per day), azathioprine, or danazol] was allowed, and rescue therapy was permitted, if needed. All patients initially received fostamatinib at 100mg twice daily (or matching placebo). Based on platelet count and tolerability, the dose was increased to 150mg twice daily (or matching placebo) in 88% of patients at week 4 or later. Patients who did not respond to treatment after 12 weeks, as well as patients who completed the 24-week double-blind study, were eligible to enroll in the open-label extension study.

Study Outcomes	FIT-1 Study		FIT-2 Study	
	Fostamatinib (N=51) N (%)	Placebo (N=25) N (%)	Fostamatinib (N=50) N (%)	Placebo (N=24) N (%)
Stable platelet response^	9 (18)*	0 (0)*	8 (16)[+]	1 (4)[+]
Rolled over into FIT-3 study at week 12	28 (55)	22 (88)	33 (66)	19 (79)
Completed study (week 24)	12 (24)	1 (4)	13 (26)	2 (8)

*P=0.03; p-value from Fisher Exact test

[+]Did not demonstrate a statistically significant difference between treatment arms

^Includes all patients with platelet counts and excludes patients whose platelet counts were measured following rescue therapy after week 10; stable platelet response was prospectively defined as a platelet count of ≥50 x 10^9/L on at least 4 of the 6 visits between weeks 14 and 24.

Extension Study:

- The FIT-3 trial is an open-label extension study. Patients who completed 24 weeks of treatment in FIT-1 or FIT-2, or who did not respond to treatment any time after 12 weeks, were eligible to enroll in this study. Patients remained blinded to their treatment assignment from the previous study, so their starting dose in this study was based on their final platelet count. Patients designated as responders (defined as an achievement of platelet count of ≥50 x 10^9/L) at the time of roll over continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders (defined as platelet count <50 x 10^9/L) received fostamatinib 100mg twice daily regardless of their dose and regimen in the prior study. In the extension study, 123 patients were enrolled, 44 patients previously randomized to placebo and 79 patients previously randomized to fostamatinib. Stable response in this study was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count <50 x 10^9/L, without an intervening visit with a platelet count ≥50 x 10^9/L (unrelated to rescue therapy), within a period of 12 weeks following initial achievement of the targeted platelet count. Sixty-one of the 123 subjects (50%) have discontinued from the study early. In the prospectively defined analysis, the 44 patients treated with placebo in the prior study were evaluated for stable response for fostamatinib. Ten of these patients (23%) met the criteria for stable response. Among the patients who achieved stable response in the three trials, 18 patients maintained the platelet count of at least 50 x 10^9/L for 12 months or longer.

Cost Comparison:

Medication	Cost Per Tablet	Cost Per Month	Cost Per Year
Tavalisse™ (fostamatinib) 100mg	**$157.50**	**$9,450.00***	**$113,400.00***
Promacta® (eltrombopag) 50mg	$213.13	$6,393.90[+]	$76,726.80[+]

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. Promacta® was FDA approved in 2008 and has a significant federal rebate.

*Tavalisse™ cost based on initial dose of 100mg orally twice daily.

[+]Promacta® cost based on initial dose of 50mg once daily for most adult and pediatric patients 6 years of age and older with a diagnosis of chronic ITP.

Doptelet® (Avatrombopag) Product Summary[9]

Indication(s): Doptelet® (avatrombopag) is a TPO receptor agonist indicated for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure.

Dosing:

- Doptelet® (avatrombopag) is supplied as 20mg tablets.
- It is recommended to begin dosing avatrombopag 10 to 13 days prior to a scheduled procedure and patients should undergo their procedure within 5 to 8 days after the last dose.
- The recommended dose of avatrombopag is based on a patient's platelet count prior to a scheduled procedure. It is recommended to take avatrombopag orally with food once daily for 5 consecutive days.
- Recommended dose:

Platelet Count (x 10^9/L)	Once Daily Dose
<40	60mg (3 tablets)
40 to <50	40mg (2 tablets)

Mechanism of Action: Avatrombopag is an orally bioavailable, small molecule TPO receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased production of platelets. Avatrombopag does not compete with TPO for binding to the TPO receptor and has an additive effect with TPO on platelet production.

Contraindication(s): None

Warnings and Precautions:

- Thrombotic/Thromboembolic Complications: Avatrombopag is a TPO receptor agonist and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with CLD. Avatrombopag should not be administered to patients with CLD in an attempt to normalize platelet counts. It is recommended to monitor platelet counts and to also monitor for thromboembolic events and institute treatment promptly.

Use in Specific Populations:

- Pregnancy: Based on findings from animal reproduction studies, avatrombopag may cause fetal harm when administered to a pregnant woman. The available data on avatrombopag in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes.
- Lactation: There is no information on the presence of avatrombopag in human milk, the effects on the breastfed child, or the effects on milk production. Avatrombopag was present in the milk of lactating rats. Due to the potential for serious adverse reactions in a breastfed child from avatrombopag, breastfeeding is not recommended during treatment with avatrombopag and for at least 2 weeks after the last dose.
- Pediatric Use: The safety and effectiveness of avatrombopag have not been established in pediatric patients.

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

Adverse Reactions: The most common adverse reactions with avatrombopag (≥3%) in clinical studies were pyrexia, abdominal pain, nausea, headache, fatigue, and peripheral edema.

Efficacy: The efficacy of avatrombopag for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials. In each study, patients were assigned to the low baseline platelet count cohort (<40 x 10^9/L) or the high baseline platelet count cohort (≥40 x 10^9/L to <50 x 10^9/L) based on their platelet count at baseline. Patients were then randomized 2:1 to either avatrombopag or placebo. Patients were stratified according to hepatocellular cancer (HCC) status and risk of bleeding associated with the elective procedure (low, moderate, or high). Patients undergoing neurosurgical interventions, thoracotomy, laparotomy, or organ resection were not eligible for enrollment. Patients in the low baseline platelet count cohort received avatrombopag 60mg or matching placebo once daily for 5 days and patients in the high baseline platelet count cohort received avatrombopag 40mg or matching placebo once daily for 5 days. Eligible patients were scheduled to undergo their procedure (low, moderate, or high bleeding risk) 5 to 8 days after their last dose of treatment. Patient populations were similar between the pooled low and high baseline platelet count cohorts. The major efficacy outcome was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Additional secondary efficacy outcomes were the proportion of patients who achieved platelet counts of >50 x 10^9/L on the day of procedure and the change in platelet count from baseline to procedure day. In both baseline platelet count cohorts, patients in the avatrombopag treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant.

Low Baseline Platelet Count Cohort				
	Study 1		**Study 2**	
Category	**Avatrombopag 60mg (N=90)**	**Placebo (N=48)**	**Avatrombopag 60mg (N=70)**	**Placebo (N=43)**
Responders (95% CI)	66% (56, 75)	23% (11, 35)	69% (58, 79)	35% (21, 49)
Difference of Proportion vs. Placebo* (95% CI)	43% (27, 58)		34% (16, 52)	

*Difference of proportion vs. placebo = proportion of responders for avatrombopag – proportion of responders for placebo

High Baseline Platelet Count Cohort				
	Study 1		Study 2	
Category	Avatrombopag 40mg (N=59)	Placebo (N=34)	Avatrombopag 40mg (N=58)	Placebo (N=33)
Responders (95% CI)	88% (80, 96)	38% (22, 55)	88% (80, 96)	33% (17, 49)
Difference of Proportion vs. Placebo* (95% CI)	50% (32, 68)		55% (37, 73)	

*Difference of proportion vs. placebo = proportion of responders for avatrombopag – proportion of responders for placebo

Cost Comparison:

Medication	Cost Per Tablet	Cost Per Treatment
Doptelet® (avatrombopag) 20mg	**$944.00**	**$14,160.00***
Mulpleta® (lusutrombopag) 3mg	$1,214.29	$8,500.03+

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.
*Doptelet® cost based on recommended dose for patient with platelet count <40 x 10^9/L (i.e., 60mg once daily for 5 days).
+Mulpleta® cost based on recommended dose of 3mg once daily for 7 days.

Mulpleta® (Lusutrombopag) Product Summary[10]

Indication(s): Mulpleta® (lusutrombopag) is a TPO receptor agonist indicated for the treatment of thrombocytopenia in adult patients with CLD who are scheduled to undergo a procedure.

Dosing:

- Mulpleta® (lusutrombopag) is supplied as 3mg tablets.
- The recommended dose is 3mg orally once daily with or without food for 7 days.
- It is recommended to begin Mulpleta® (lusutrombopag) dosing 8 to 14 days prior to a scheduled procedure, and patients should undergo their procedure 2 to 8 days after the last dose.

Mechanism of Action: Lusutrombopag is an orally bioavailable, small molecule TPO receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation.

Contraindication(s): None

Warnings and Precautions:

- Thrombotic/Thromboembolic Complications: Lusutrombopag is a TPO receptor agonist, and TPO receptor agonists have been associated with thrombotic and thromboembolic complications in patients with CLD. Lusutrombopag should not be administered to patients with CLD in an attempt to normalize platelet counts. It is recommended to monitor platelet counts and to also monitor for thromboembolic events and institute treatment promptly.

Use in Specific Populations:

- Pregnancy: There are no available data on lusutrombopag in pregnant women to inform the drug-associated risk. In animal reproduction studies, oral administration of lusutrombopag to pregnant rats during organogenesis and the lactation period resulted in adverse developmental outcomes. Pregnant women should be advised of the potential risk to a fetus.
- Lactation: There is no information on the presence of lusutrombopag in human milk, the effects on the breastfed child, or the effects on milk production. Lusutrombopag was present in the milk of lactating rats. Due to the potential for serious adverse reactions in a breastfed child from lusutrombopag, breastfeeding is not recommended during treatment with lusutrombopag and for at least 28 days after the last dose.
- Pediatric Use: The safety and effectiveness of lusutrombopag have not been established in pediatric patients.
- Geriatric Use: Clinical studies of lusutrombopag did not include sufficient numbers of subjects 65 years of age and older to determine whether they respond differently from younger subjects.

Adverse Reaction(s): The most common adverse reaction with lusutrombopag (≥3%) in clinical studies was headache.

Efficacy: The efficacy of lusutrombopag for the treatment of thrombocytopenia in patients with CLD who are scheduled to undergo a procedure was evaluated in 2 randomized, double-blind, placebo-controlled trials. Patients with CLD who were undergoing an invasive procedure and had a platelet count $<50 \times 10^9$/L were eligible to participate. Patients undergoing laparotomy, thoracotomy, open-heart surgery, craniotomy, or organ resection were excluded. Patients with a history of splenectomy, partial splenic embolization, or thrombosis and those with Child-Pugh class C liver disease, absence of hepatopetal blood flow, or a prothrombotic condition other than CLD were not allowed to participate. Patients were randomized 1:1 to receive 3mg lusutrombopag or placebo once daily for up to 7 days. Randomization was stratified by liver ablation/coagulation or other procedures and the platelet count at screening/baseline. In study 1, the major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure. In study 2, the major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding (i.e., platelet preparations, other blood preparations, including red blood cells and plasma, volume expanders) from randomization through 7 days after the primary invasive procedure. Additional efficacy outcomes in both trials included the proportion of patients who required no platelet transfusion during the study, proportion of responders, duration of increase in the platelet counts defined as the number of days during which the platelet count was maintained $\geq 50 \times 10^9$/L, and the time course of platelet counts. In both trials, responders were defined as patients who had a platelet count of $\geq 50 \times 10^9$/L with an increase of $\geq 20 \times 10^9$/L from baseline.

Study 1			
Endpoint	Proportion (n/N) Exact 95% CI		Treatment Difference (95% CI) P-value
	Lusutrombopag (N=49)	Placebo (N=48)	
Not requiring platelet transfusion prior to invasive procedure*	78% (38/49) (63, 88)	13% (6/48) (4.7, 25)	64 (49, 79) <0.0001
Responder during study+	76% (37/49) (61, 87)	6% (3/48) (1.3, 17)	68 (54, 82) <0.0001

CI = confidence interval

*A platelet transfusion was required if the platelet count was <50 x 10^9/L.

+Platelet count reached ≥50 x 10^9/L and increased ≥20 x 10^9/L from baseline.

Study 2			
Endpoint	Proportion (n/N) Exact 95% CI		Treatment Difference (95% CI) P-value
	Lusutrombopag (N=108)	Placebo (N=107)	
Not requiring platelet transfusion prior to invasive procedure* or rescue therapy for bleeding from randomization through 7 days after invasive procedure	65% (70/108) (55, 74)	29% (31/107) (21, 39)	37 (25, 49) <0.0001
Responder during study+	65% (70/108) (55, 74)	13% (14/107) (7.3, 21)	52 (41, 62) <0.0001

CI = confidence interval

*A platelet transfusion was required if the platelet count was <50 x 10^9/L.

+Platelet count reached ≥50 x 10^9/L and increased ≥20 x 10^9/L from baseline.

Cost Comparison:

Medication	Cost Per Tablet	Cost Per Treatment
Mulpleta® (lusutrombopag) 3mg	**$1,214.29**	**$8,500.03+**
Doptelet® (avatrombopag) 20mg	$944.00	$14,160.00*

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.

+Mulpleta® cost based on recommended dose of 3mg once daily for 7 days.

*Doptelet® cost based on recommended dose for patient with platelet count <40 x 10^9/L (i.e., 60mg once daily for 5 days).

Recommendations

The College of Pharmacy recommends the prior authorization of Tavalisse™ (fostamatinib), Doptelet® (avatrombopag), and Mulpleta® (lusutrombopag) with the following criteria:

Tavalisse™ (Fosamatinib) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment; and
2. Member must be 18 years of age or older (Tavalisse™ is not recommended for use in patients younger than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies); and
3. Member must have a clinical diagnosis of persistent/chronic ITP for at least 3 months; and
4. Previous insufficient response with at least 2 of the following treatments:
    a. Corticosteroids; or
    b. Immunoglobulins; or
    c. Splenectomy; or
    d. Thrombopoietin receptor agonists; and
5. Degree of thrombocytopenia and clinical condition increase the risk for bleeding; and
6. Must be prescribed by, or in consultation with, a hematologist or oncologist;
7. Prescriber must verify the member's CBC, including platelet counts, will be monitored monthly until a stable platelet count (at least 50 X 10^9/L) is achieved and will be monitored regularly thereafter; and
8. Prescriber must verify liver function tests (LFTs) (e.g., ALT, AST, bilirubin) will be monitored monthly; and
9. Prescriber must verify member's blood pressure will be monitored every 2 weeks until establishment of a stable dose, then monthly thereafter; and
10. Female members must not be pregnant and must have a negative pregnancy test immediately prior to therapy initiation. Female members of reproductive potential must be willing to use effective contraception while on therapy and for at least 1 month after therapy completion; and
11. Prescriber must verify member is not breastfeeding; and
12. Member must not be taking strong CYP3A4 inducers (e.g., rifampicin) concurrently with Tavalisse™; and
13. Initial approvals will be for the duration of 12 weeks; and
14. Discontinuation criteria:
    a. Platelet count does not increase to a level sufficient to avoid clinically important bleeding after 12 weeks of therapy; and
15. A quantity limit of 2 tablets daily will apply.

Doptelet® (Avatrombopag) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure; and
2. A patient-specific, clinically significant reason why the member cannot use Mulpleta® (lusutrombopag); and
3. Date of procedure must be listed on the prior authorization request; and
4. Prescriber must verify the member will have the procedure within 5 to 8 days after the member receives the last dose of Doptelet®; and

5. Member must have a baseline platelet count <50 X 10^9/L; and
6. Must be prescribed by, or in consultation with, a hematologist, gastroenterologist, or hepatologist; and
7. Doptelet® must not be used in an attempt to normalize platelet counts; and
8. A quantity limit of 15 tablets per scheduled procedure will apply.

Mulpleta® (Lusutrombopag) Approval Criteria:

1. An FDA approved indication for the treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure; and
2. Date of procedure must be listed on the prior authorization request; and
3. Prescriber must verify member will have the procedure 2 to 8 days after member receives the last dose of Mulpleta®; and
4. Member must have a baseline platelet count <50 X 10^9/L; and
5. Must be prescribed by, or in consultation with, a hematologist, gastroenterologist, or hepatologist; and
6. Mulpleta® must not be used in an attempt to normalize platelet counts; and
7. A quantity limit of 7 tablets per scheduled procedure will apply.

Additionally, the College of Pharmacy recommends removing the prior authorization for Nplate® (romiplostim) and Promacta® (eltrombopag), based on net cost and appropriate utilization.

Utilization Details of Thrombocytopenia Medications: Fiscal Year 2018

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS*	TOTAL COST	COST/ CLAIM	COST/ DAY	% COST
PROMACTA TAB 50MG	63	15	$575,776.23	$9,139.31	$320.95	53.02%
PROMACTA TAB 25MG	33	8	$171,058.63	$5,183.59	$172.79	15.75%
PROMACTA TAB 75MG	23	7	$311,298.44	$13,534.71	$432.36	28.67%
PROMACTA TAB 12.5MG	4	2	$16,192.56	$4,048.14	$134.94	1.49%
NPLATE INJ 250MCG	2	1	$11,536.10	$5,768.05	$206.00	1.06%
	125	**23***	**$1,085,861.96**	**$8,686.90**	**$295.07**	**100%**

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

[1] U.S. Food and Drug Administration (FDA) Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm. Last revised 10/2018. Last accessed 11/20/2018.

[2] Rigel Pharmaceuticals, Inc. Rigel Announces FDA Approval of Tavalisse™ (fostamatinib disodium hexahydrate) for Chronic Immune Thrombocytopenia (ITP) in Adult Patients. *PR Newswire*. Available online at: https://www.prnewswire.com/news-releases/rigel-announces-fda-approval-of-tavalisse-fostamatinib-disodium-hexahydrate-for-chronic-immune-thrombocytopenia-itp-in-adult-patients-300631702.html. Issued 04/17/2018. Last accessed 11/20/2018.

[3] Dova Pharmaceuticals. Dova Pharmaceuticals Announces U.S. FDA Approval of Doptelet® (avatrombopag). *Globe Newswire*. Available online at: https://globenewswire.com/news-release/2018/05/21/1509548/0/en/Dova-Pharmaceuticals-Announces-U-S-FDA-Approval-of-DOPTELET-avatrombopag.html. Issued 05/21/2018. Last accessed 11/20/2018.

[4] Shionogi & Co. Shiongi Announces FDA Approval of Mulpleta® (Lusutrombopag). *Business Wire*. Available online at: https://www.businesswire.com/news/home/20180801005551/en/Shionogi-Announces-FDA-Approval-Mulpleta%C2%AE-Lusutrombopag. Issued 08/01/2018. Last accessed 11/20/2018.
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[6] Argenx. Argenx reports positive topline results from Phase 2 proof-of-concept trial of efgartigimod in primary immune thrombocytopenia. Available online at: https://www.argenx.com/en-GB/news-internal/argenx-reports-positive-topline-results-from-phase-2-proof-of-concept-trial-of-efgartigimod-in-primary-immune-thrombocytopenia/30200/. Issued 09/17/2018. Last accessed 11/21/2018.
[7] Tavalisse™ (fostamatinib) Prescribing Information. Rigel Pharmaceuticals, Inc. Available online at: https://tavalisse.com/downloads/pdf/Tavalisse-Full-Prescribing-Information.pdf. Last revised 04/2018. Last accessed 11/19/2018.
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[10] Mulpleta® (lusutrombopag) Prescribing Information. Shionogi & Co., Ltd. Available online at: https://www.shionogi.com/pdf/pi/wp-content/themes/pdfs/mulpleta.pdf. Last revised 07/2018. Last accessed 11/19/2018.

Appendix J

Fiscal Year 2018 Annual Review of Inhaled Anti-Infective Medications and 30-Day Notice to Prior Authorize Arikayce® (Amikacin Liposome Inhalation Suspension)

Oklahoma Health Care Authority
December 2018

Introduction[1,2,3,4]

Mycobacterium avium complex (MAC) is a type of nontuberculous mycobacteria (NTM) commonly found in water and soil that encompasses several species including *Mycobacterium avium (M. avium)*, *M. intracellulare*, and *M. chimaera*. MAC is transmitted via inhalation or ingestion of contaminated water or soil. MAC is primarily a pulmonary pathogen that affects individuals who are immunocompromised [e.g., from Human Immunodeficiency Virus (HIV), hairy cell leukemia, immunosuppressive chemotherapy]. MAC lung disease occurs rarely in immunocompetent hosts, and the estimated incidence of MAC is 1 per 100,000 persons per year. MAC is more commonly found in females, particularly post-menopausal women.

The American Thoracic Society and Infectious Disease Society of America's diagnostic criteria for nontuberculous mycobacterial pulmonary infections include both imaging studies consistent with pulmonary disease and recurrent isolation of mycobacteria from sputum or isolated from at least one bronchial wash in a symptomatic patient. Symptoms of MAC in immunocompromised patients can include sweating, weight loss, fatigue, diarrhea, dyspnea, osteomyelitis, tenosynovitis, synovitis, and disseminated disease involving the lymph nodes, the central nervous system (CNS), the liver, the spleen, and the bone marrow. Symptoms of MAC in immunocompetent patients are nonspecific and consist of persistent cough, fatigue, malaise, weakness, dyspnea, chest discomfort, and occasionally hemoptysis. Fever and weight loss can occur but are more common in disseminated MAC (DMAC) disease. Severe disability or death can result from respiratory failure.

The clinical course of pulmonary MAC infection in HIV-negative patients is usually indolent. Treatment success rates in HIV-negative patients have ranged from 20 to 90% in various studies. HIV-positive patients have a poorer prognosis; however, patients with non-disseminated disease receiving antiretroviral therapy and anti-MAC treatment have treatment results similar to non-HIV-infected patients.

Recommended treatment for MAC consists of a 3-drug regimen of a macrolide (e.g., azithromycin), a rifamycin (e.g., rifampin), and ethambutol for a minimum of 12 months. Sputum conversion often requires 3 to 6 months of treatment, resulting in a usual treatment duration of 15 to 18 months. Treatment failure is typically defined as failure to achieve culture conversion after 6 to 12 months of therapy. In September 2018, the U.S. Food and Drug Administration (FDA) approved Arikayce® (amikacin liposome inhalation suspension) for the treatment of lung disease caused by MAC. The approval was limited to patients with MAC who do not respond to conventional treatment (i.e., refractory disease).

Current Prior Authorization Criteria

Inhaled Tobramycin Products (Bethkis®, Tobi®, Tobi® Podhaler®, and Kitabis® Pak), Pulmozyme® (Dornase Alfa), and Cayston® (Aztreonam) Approval Criteria:

1. Use of inhaled tobramycin products, Pulmozyme® (dornase alfa), and Cayston® (aztreonam) is reserved for members who have a diagnosis of cystic fibrosis (CF).
   a. Authorization of Tobi® Podhaler® requires a trial of tobramycin nebulized solution or a patient-specific, clinically significant reason why tobramycin nebulized solution is not appropriate for the member.
   b. Tobramycin nebulized solution (including Bethkis®, Kitabis® Pak, and generic nebulized solution), dornase alfa, and aztreonam inhalation will not require a prior authorization and claims will pay at the point of sale if member has a reported diagnosis of CF within the past 12 months of claims history.
   c. If the member does not have a reported CF diagnosis, a manual prior authorization will be required for coverage consideration.
2. Use of inhaled tobramycin products and Cayston® (aztreonam) is restricted to 28 days of therapy per every 56 days to ensure cycles of 28 days on therapy followed by 28 days off therapy.
   a. Use outside of this recommended regimen may be considered for coverage via a manual prior authorization submission with a patient-specific, clinically significant reason why the member would need treatment outside of the FDA approved dosing.
   b. Pharmacies should process the prescription claim with a 56-day supply.

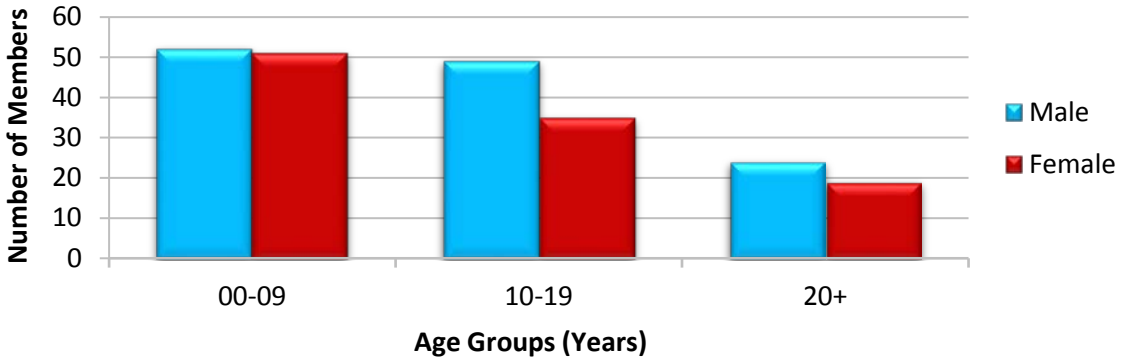
Utilization of Inhaled Anti-Infective Medications: Fiscal Year 2018

Comparison of Fiscal Years

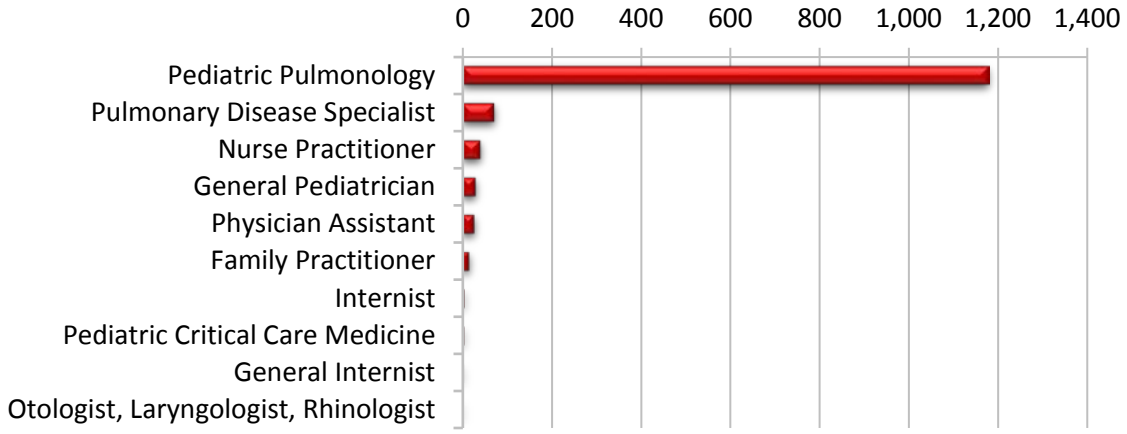
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	234	1,343	$5,087,066.64	$3,787.84	$100.27	169,406	50,734
2018	230	1,379	$4,941,872.58	$3,583.66	$93.27	177,467	52,983
% Change	**-1.70%**	**2.70%**	**-2.90%**	**-5.40%**	**-7.00%**	**4.80%**	**4.40%**
Change	**-4**	**36**	**-$145,194.06**	**-$204.18**	**-$7.00**	**8,061**	**2,249**

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

Demographics of Members Utilizing Inhaled Anti-Infective Medications



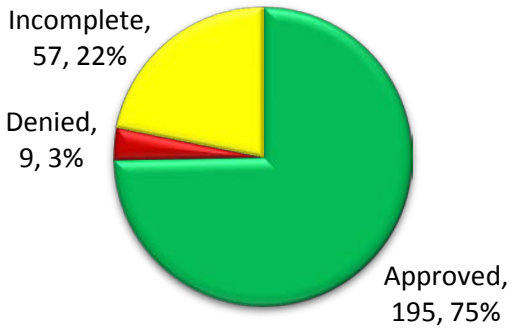
Top Prescriber Specialties of Inhaled Anti-Infective Medications by Number of Claims



Prior Authorization of Inhaled Anti-Infective Medications

There were 261 prior authorization requests submitted for inhaled anti-infective medications during fiscal year 2018. Computer edits are in place to detect a cystic fibrosis diagnosis in a member's recent diagnosis claims history and generate automated prior authorizations where possible. The following chart shows the status of the submitted petitions.

Status of Petitions



Market News and Updates[4,5,6]

Patent Expiration(s):

- Tobi® (tobramycin inhalation solution) and Kitabis® Pak (tobramycin inhalation solution): There are no unexpired patents for the nebulized solution formulation of Tobi® and Kitabis® Pak. Generic nebulized formulations of tobramycin are currently available.
- Cayston® (aztreonam inhalation solution): December 2021
- Bethkis® (tobramycin inhalation solution): September 2022
- Tobi® Podhaler® (tobramycin inhalation powder): October 2025
- Arikayce® (amikacin liposome inhalation suspension): May 2035

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

- **September 2018:** The FDA approved Arikayce® (amikacin liposome inhalation suspension) for the treatment of lung disease caused by MAC. The approval was limited to patients with MAC who do not respond to conventional treatment (i.e., refractory

disease). In a Phase 2 trial of patients with NMT, Arikayce® did not meet the primary endpoint of change in mycobacterial density on a 7-point scale; Arikayce® did reach statistical significance in 11 out of 44 patients for a secondary endpoint, negative cultures by day 84. After completion of the Phase 2 trial, 59 patients enrolled in an 84-day extension trial and results found that the majority of patients continued to have negative sputum cultures and showed improvements in a 6-minute walk test. Results of a subsequent Phase 3 trial are included in this report in the product summary of Arikayce®. Arikayce® is the first drug to be approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs, or LPAD pathway, established by Congress to advance development and approval of antibacterial and antifungal drugs to treat serious or life-threatening infections in a limited population of patients with unmet need. Approval under the LPAD pathway may be supported by a streamlined clinical development program. These programs may involve smaller, shorter, or fewer clinical trials. As required for drugs approved under the LPAD pathway, labeling for Arikayce® includes certain statements to convey that the drug has been shown to be safe and effective only for use in a limited population. Arikayce® also was approved under the Accelerated Approval pathway. Under this approach, the FDA may approve drugs for serious or life-threatening diseases or conditions where the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients. The approval of Arikayce® was based on achieving 3 consecutive negative monthly sputum cultures by month 6 of treatment. The manufacturer of Arikayce® will be required to conduct an additional, post-market study to describe the clinical benefits of Arikayce®. Arikayce® is currently being studied as a potential treatment for cystic fibrosis patients with chronic *Pseudomonas aeruginosa* infection.

Arikayce® (Amikacin Liposome Inhalation Suspension) Product Summary[7]

Indication(s): Arikayce® (amikacin liposome inhalation suspension) is an aminoglycoside antibacterial indicated in adults who have limited or no alternative treatment options, for the treatment of MAC lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for amikacin inhalation are currently available, amikacin inhalation should be reserved for use in adults who have limited or no alternative treatment options.

- Limitation of Use: Amikacin inhalation has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of amikacin inhalation is not recommended for patients with nonrefractory MAC lung disease.

Boxed Warning: Risk of Increased Respiratory Adverse Reactions

- Amikacin inhalation has been associated with an increased risk of respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalization in some cases.

Dosing:

- Arikayce® is supplied as a sterile, liposome suspension for oral inhalation in a unit-dose glass vial containing amikacin 590mg/8.4mL; Arikayce® is packaged as a 28-vial kit with a Lamira™ Nebulizer System.
- Amikacin inhalation vials should be refrigerated at 2°C to 8°C (36°F to 46°F), and can be stored at room temperature for up to 4 weeks (if the product is not used within 4 weeks after removal from refrigeration, the remaining medication should be discarded).
- Amikacin inhalation is for oral inhalation only and is only recommended to be used with the Lamira™ Nebulizer System.
- The recommended dose of amikacin inhalation is 590mg/8.4mL via inhalation once daily.
- Pre-treatment prior to amikacin inhalation administration with short-acting $beta_2$ agonists (SABAs) should be considered for patients with known hyperreactive airway disease, chronic obstructive pulmonary disease (COPD), asthma, or bronchospasm.

Contraindication(s):

- Patients with a known hypersensitivity to any aminoglycoside

Warnings and Precautions:

- Hypersensitivity Pneumonitis: Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, or allergic reaction to amikacin inhalation) was reported at a higher frequency in patients treated with amikacin inhalation plus a background regimen (3.1%) compared to patients treated with a background regimen alone (0%).
- Hemoptysis: Hemoptysis was reported at a higher frequency in patients treated with amikacin inhalation in clinical trials plus a background regimen (17.9%) compared to patients treated with a background regimen alone (12.5%).
- Bronchospasm: Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, or wheezing) was reported at a higher frequency in patients treated with amikacin inhalation plus a background regimen (28.7%) compared to patients treated with a background regimen alone (10.7%).
- Exacerbation of Underlying Pulmonary Disease: Exacerbations of underlying pulmonary disease (reported as COPD, infective exacerbation of COPD, or infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with amikacin inhalation plus a background regimen (14.8%) compared to patients treated with a background regimen alone (9.8%).
- Ototoxicity: Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) was reported with a higher frequency in patients treated with amikacin inhalation plus a background regimen (17%) compared to patients treated with a background regimen alone (9.8%). This was primarily driven by tinnitus (7.6% vs. 0.9%) and dizziness (6.3% vs. 2.7%).
- Nephrotoxicity: Nephrotoxicity was observed during the clinical trials of amikacin inhalation in patients with MAC lung disease but not at a higher frequency than the background regimen alone. Nephrotoxicity has been associated with aminoglycosides.

Close monitoring of patients with known or suspected renal dysfunction may be warranted.

- Neuromuscular Blockade: Patients with neuromuscular disorders were not enrolled in amikacin inhalation clinical trials. Patients with known or suspected neuromuscular disorders (e.g., myasthenia gravis) should be closely monitored since aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions.
- Embryo-Fetal Toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including amikacin inhalation, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed in utero.

Adverse Reactions: The most common adverse reactions (≥5% and more frequent than background regimen alone) experienced during clinical trials of amikacin inhalation included the following:

- Dysphonia
- Cough
- Bronchospasm
- Hemoptysis
- Ototoxicity
- Upper airway irritation
- Musculoskeletal pain
- Fatigue and asthenia
- Exacerbation of underlying pulmonary disease
- Diarrhea
- Nausea
- Pneumonia
- Headache
- Pyrexia
- Vomiting
- Rash
- Decreased weight
- Change in sputum
- Chest discomfort

Use in Specific Populations:

- Pregnancy: There are no data on amikacin inhalation use in pregnant women to evaluate any drug-associated risk. Although systemic absorption of amikacin following oral inhalation is expected to be low, systemic exposure to aminoglycoside antibacterial drugs, including amikacin inhalation, may be associated with total, irreversible, bilateral congenital deafness in a fetus when administered to pregnant women.
- Lactation: There is no information regarding the presence of amikacin inhalation in human milk, the effects on the breastfed infant, or the effects on milk production after administration of amikacin inhalation by inhalation.
- Pediatric Use: The safety and effectiveness of amikacin inhalation in pediatric patients younger than 18 years of age have not been established.
- Geriatric Use: In NTM clinical trials, 50.5% of patients who received amikacin inhalation were ≥65 years of age and 14.2% were ≥75 years of age. No overall differences in safety and effectiveness were observed between elderly subjects and younger subjects.
- Hepatic Impairment: Amikacin inhalation has not been studied in patients with hepatic impairment. No dose adjustments based on hepatic impairment are required since amikacin is not hepatically metabolized.
- Renal Impairment: Amikacin inhalation has not been studied in patients with renal impairment. Given the low systemic exposure to amikacin following administration of amikacin inhalation, clinically relevant accumulation of amikacin is unlikely to occur in patients with renal impairment. However, renal function should be monitored in

patients with known or suspected renal impairment, including elderly patients with potential age-related decreases in renal function.

Efficacy: The efficacy of amikacin inhalation was evaluated in an open-label, randomized (2:1), multi-center trial in 336 patients with refractory MAC lung disease as confirmed by ≥2 sputum cultures. Patients were considered to have refractory MAC lung disease if they did not achieve negative sputum cultures after a minimum duration of 6 consecutive months of background regimen therapy that was either ongoing or stopped no more than 12 months before the screening visit. Patients were randomized to either amikacin inhalation plus a background regimen or a background regimen alone. The surrogate endpoint for assessing efficacy was based on achieving culture conversion (3 consecutive monthly negative sputum cultures) by month 6. The date of conversion was defined as the date of the first of the 3 negative monthly cultures. A total of 336 patients were randomized (amikacin inhalation plus background regimen, N=224; background regimen alone, N=112) with a mean age of 64.7 years. At the time of enrollment, 302 (89.9%) were either on a guideline-based regimen for MAC or off guideline-based therapy for MAC for <3 months, while 34 (10.1%) were off treatment for 3 to 12 months prior to enrollment. At screening, patients were stratified by smoking status (current smoker or not) and by whether patients were on treatment or off treatment for at least 3 months. Most patients at screening were not current smokers (89.3%) and had underlying bronchiectasis (62.5%). At baseline, background regimens included a macrolide (91.9%), a rifamycin (85.7%), or ethambutol (80.3%). Overall, 54.9% of subjects were receiving a triple background regimen of a macrolide, a rifamycin, and ethambutol.

- The proportion of patients achieving culture conversion by month 6 was statistically significantly (P<0.0001) greater for amikacin inhalation plus a background regimen (65/224, 29.0%) compared to a background regimen alone (10/112, 8.9%).
- An analysis of sustained sputum culture conversion through month 6 (defined as consecutive negative sputum cultures with no positive culture on solid media or no more than 2 consecutive positive cultures in liquid media following achieving initial culture conversion) showed that 3 subjects in each treatment arm who initially achieved culture conversion did not have sustained sputum culture conversion through month 6. Thus, 27.7% (62/224) of amikacin inhalation plus background regimen patients and 6.3% (7/112) of background regimen alone patients had sustained sputum culture conversion through month 6.
- Additional endpoints to assess the clinical benefit of amikacin inhalation, for example, change from baseline in 6-minute walk test distance and the Saint George's Respiratory Questionnaire, did not demonstrate clinical benefit by month 6.

Cost: The Wholesale Acquisition Cost (WAC) per mL of Arikayce® is $363.00 resulting in a cost per dose of $3,049.20 and cost per 28-day supply of $85,377.60.

Recommendations

The College of Pharmacy recommends the prior authorization of Arikayce® (amikacin liposome inhalation suspension) with the following criteria:

Arikayce® (Amikacin Liposome Inhalation Suspension) Approval Criteria:

1. An FDA approved indication for the treatment of *Mycobacterium avium* complex (MAC) lung disease in adults who have limited or no alternative treatment options; and
2. Member must have had a minimum of 6 consecutive months of a multidrug background regimen therapy used compliantly and not achieved negative sputum cultures within the last 12 months. Dates of previous treatments and regimens must be listed on the prior authorization request; and
    a. If claims for a multidrug background regimen are not in the member's claim history, the pharmacy profile should be submitted or detailed information regarding dates and doses should be included along with the signature from the physician; and
3. Member must continue multidrug background regimen therapy while on Arikayce®, unless contraindicated, or provide reasoning why continuation of the multidrug background regimen is not appropriate for the member.
4. Arikayce® will not be approved for patients with non-refractory MAC lung disease; and
5. Arikayce® must be prescribed by or in consultation with a pulmonary disease or infectious disease specialist (or be an advanced care practitioner with a supervising physician who is a pulmonary disease or infectious disease specialist); and
6. Initial approvals will be for the duration of 6 months after which time the prescriber must document the member is responding to treatment for continued approval.
7. A quantity limit of 28 vials per 28 days will apply.

Utilization Details of Inhaled Anti-Infective Medications: Fiscal Year 2018

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	CLAIMS/ MEMBER	COST/ CLAIM
DORNASE ALFA PRODUCTS					
PULMOZYME SOL 1MG/ML	919	160	$3,054,487.66	5.74	$3,323.71
SUBTOTAL	**919**	**160**	**$3,054,487.66**	**5.74**	**$3,323.71**
TOBRAMYCIN NEBULIZED PRODUCTS					
TOBRAMYCIN NEB 300MG/5ML	312	114	$637,324.69	2.74	$2,042.71
BETHKIS NEB 300MG/4ML	16	8	$90,968.80	2	$5,685.55
SUBTOTAL	**328**	**119**	**$728,293.49**	**2.76**	**$2,220.41**
TOBRAMYCIN POWDER PRODUCTS					
TOBI PODHALR CAP 28MG	42	17	$412,968.65	2.47	$9,832.59
SUBTOTAL	**42**	**17**	**$412,968.65**	**2.47**	**$9,832.59**
AZTREONAM PRODUCTS					
CAYSTON INH 75MG	90	29	$746,122.78	3.1	$8,290.25
SUBTOTAL	**90**	**29**	**$746,122.78**	**3.1**	**$8,290.25**
TOTAL	**1,379**	**230***	**$4,941,872.58**	**6**	**$3,583.66**

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

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[5] FDA. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. Available online at: https://www.accessdata.fda.gov/scripts/cder/ob/. Last revised 10/2018. Last accessed 11/20/2018.

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Appendix K

Fiscal Year 2018 Annual Review of Anti-Emetic Medications and 30-Day Notice to Prior Authorize Akynzeo® IV (Fosnetupitant/ Palonosetron Injection for Intravenous Use)

Oklahoma Health Care Authority
December 2018

Current Prior Authorization Criteria

Akynzeo® (Netupitant/Palonosetron) Approval Criteria:

1. An FDA approved indication 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; and
4. A quantity limit of 1 capsule per chemotherapy cycle will apply; and
5. Akynzeo® will not require 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 6 months of claims history.
    a. Based on the current low net cost, Akynzeo® will not require 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.

Diclegis® and Bonjesta® (Doxylamine/Pyridoxine) Approval Criteria:

1. An FDA approved diagnosis of nausea and vomiting associated with pregnancy that is not responsive to conservative management; and
2. Trials with at least 2 non-pharmacological therapies that have failed to relieve nausea and vomiting; and
3. A patient-specific, clinically significant reason why member cannot use over-the-counter (OTC) doxylamine and OTC Vitamin B_6 (pyridoxine); and
4. Authorization of Bonjesta® requires a patient-specific, clinically significant reason why the member cannot use Diclegis®.

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 6 months) used for at least 3 days or 1 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 6 years and younger will apply. Members older than 6 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.

Marinol® and Syndros® (Dronabinol) and Cesamet® (Nabilone) Approval Criteria:

1. Approval can be granted for 6 months for the diagnosis of HIV-related loss of appetite; or
2. The diagnosis of chemotherapy-induced nausea and vomiting requires the following:
    a. A recent trial of ondansetron (within the past 6 months) used for at least 3 days or 1 cycle that resulted in inadequate response; and
3. Approval length will be based on duration of need; and
4. For Marinol® (dronabinol) and Cesamet® (nabilone), a quantity limit of 60 capsules per 30 days will apply; and
5. For Syndros® (dronabinol) oral solution, the quantity approved will be patient-specific depending on patient diagnosis, maximum recommended dosage, and manufacturer packaging; and
6. For Syndros® (dronabinol) oral solution, an age restriction of 6 years and younger will apply. Members older than 6 years of age will require a patient-specific, clinically significant reason why dronabinol oral capsules cannot be used.

Sustol® (Granisetron Subcutaneous Injection) Approval Criteria:

1. An FDA approved indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens; and
2. Chemotherapy regimen must be listed on the prior authorization request; and
3. A recent trial of ondansetron (within the past 6 months) used for at least 3 days or 1 cycle that resulted in an inadequate response is required for authorization in members receiving MEC; and
4. No ondansetron trial is required for authorization of granisetron in members receiving AC combination chemotherapy regimens; and
5. A patient-specific, clinically significant reason why the member cannot use Kytril® (granisetron hydrochloride injection for intravenous use); and
6. A quantity limit of 1 injection per chemotherapy cycle will apply.

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 oral aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why oral 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; and
5. A quantity limit of 2 tablets or 2 vials per chemotherapy cycle will apply.

Zuplenz® (Ondansetron Oral Soluble Film) Approval Criteria:

1. An FDA approved diagnosis; and
2. A patient-specific, clinically significant reason why the member cannot take all other available formulations of generic ondansetron.

Utilization of Anti-Emetic Medications: Fiscal Year 2018

Comparison of Fiscal Years: Pharmacy Claims

Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Cost/ Day	Total Units	Total Days
2017	68,611	92,955	$1,285,022.11	$13.82	$1.97	1,482,505	652,897
2018	71,626	97,295	$1,460,708.58	$15.01	$2.20	1,580,835	662,765
% Change	**4.40%**	**4.70%**	**13.70%**	**8.60%**	**11.70%**	**6.60%**	**1.50%**
Change	**3,015**	**4,340**	**$175,686.47**	**$1.19**	**$0.23**	**98,330**	**9,868**

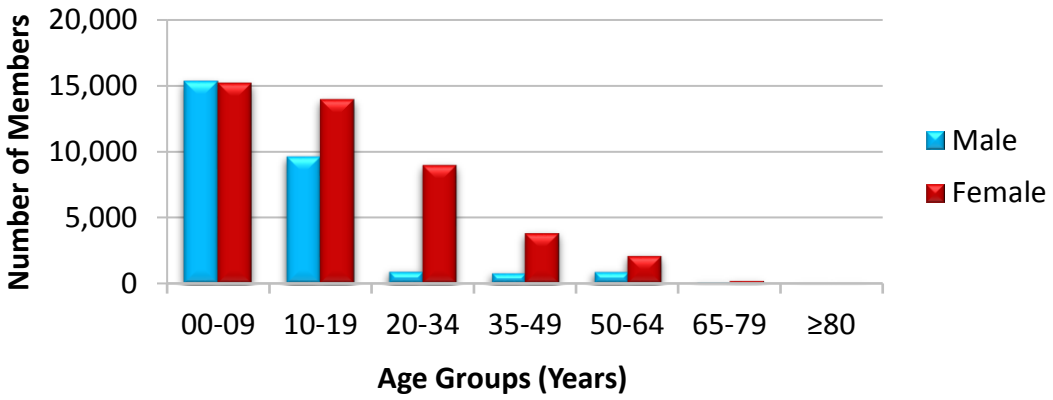
*Total number of unduplicated members.
Costs do not reflect rebated prices or net costs.

Comparison of Fiscal Years: Medical Claims

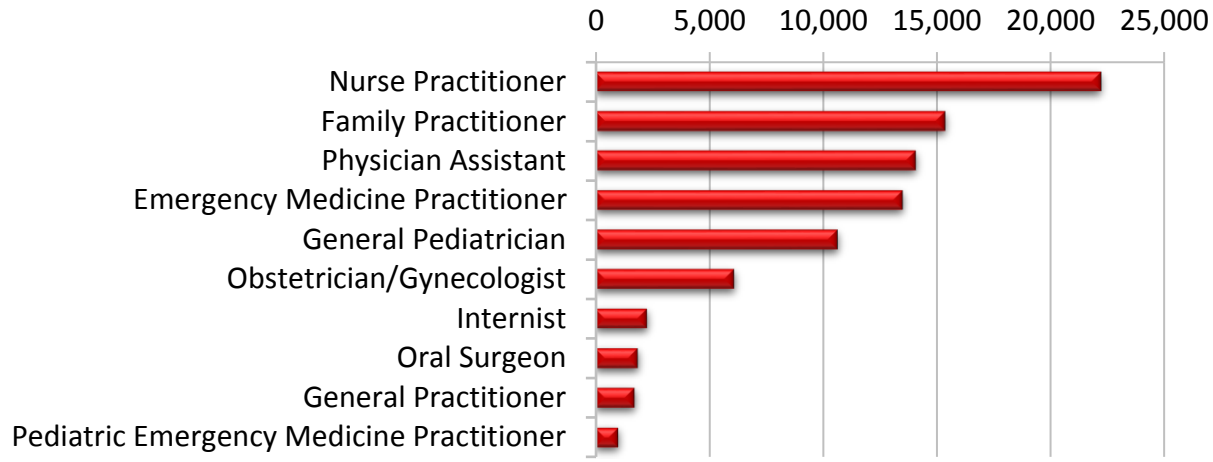
Fiscal Year	*Total Members	Total Claims	Total Cost	Cost/ Claim	Claims/ Member
2017	642	4,403	$950,252.56	$215.82	6.86
2018	605	4,266	$805,664.11	$188.86	7.05
% Change	**-5.76%**	**-3.11%**	**-15.22%**	**-12.49%**	**2.79%**
Change	**-37**	**-137**	**-$144,588.45**	**-$26.96**	**0.19**

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

Demographics of Members Utilizing Anti-Emetic Medications



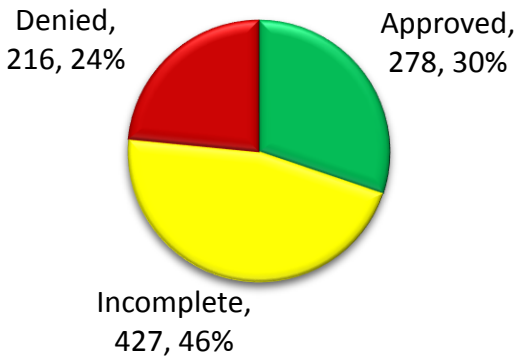
Top Prescriber Specialties of Anti-Emetic Medications by Number of Claims



Prior Authorization of Anti-Emetic Medications

There were 921 prior authorization requests submitted for anti-emetic medications during fiscal year 2018. The following chart shows the status of the submitted petitions for fiscal year 2018.

Status of Petitions



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

Anticipated Patent Expiration(s):

- Emend® [fosaprepitant for intravenous (IV) use]: September 2019
- Diclegis® [doxylamine/pyridoxine delayed-release (DR) tablet]: June 2021
- Sustol® [granisetron subcutaneous (sub-Q) injection]: September 2024
- Sancuso® (granisetron transdermal patch): January 2025
- Syndros® (dronabinol oral solution): August 2028
- Varubi® (rolapitant tablet): October 2029
- Zuplenz® (ondansetron oral soluble film): July 2030
- Akynzeo® IV (fosnetupitant/palonosetron for IV use): May 2032
- Bonjesta® [doxylamine/pyridoxine extended-release (ER) tablet]: February 2033
- Akynzeo® (netupitant/palonosetron capsule): September 2035
- Cinvanti® (aprepitant IV emulsion): September 2035

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

- **April 2018:** The FDA approved Akynzeo® IV (fosnetupitant/palonosetron IV) for use in combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC). Akynzeo® IV has not been studied for the prevention of nausea and vomiting associated with anthracycline plus cyclophosphamide (AC) chemotherapy. Akynzeo® (netupitant/palonosetron) oral capsules were first FDA approved in 2014 for use in combination with dexamethasone in adults for the prevention of nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC. Akynzeo® IV is a combination of palonosetron and fosnetupitant, a prodrug of netupitant. Palonosetron prevents nausea and vomiting during the acute phase, and fosnetupitant/netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy. Akynzeo® IV is supplied as a single-dose vial (SDV) containing lyophilized powder for reconstitution prior to IV infusion and should be infused over 30 minutes, starting 30 minutes before chemotherapy, or 1 Akynzeo® capsule should be taken by mouth, with or without food, 1 hour before chemotherapy. The Wholesale Acquisition Cost (WAC) of Akynzeo® IV is $510 per SDV.

News:

- **Varubi® IV (Rolapitant Injectable Emulsion):** Tesaro suspended the distribution of Varubi® IV beginning in March 2018, following updates to the *Contraindications, Warnings and Precautions,* and *Adverse Reactions* sections of the label made in collaboration with the FDA in January 2018. The FDA issued a safety alert for Varubi® IV in January 2018 regarding the risk of anaphylaxis and other serious hypersensitivity reactions. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have been reported in the post marketing setting, some requiring hospitalization. These reactions have occurred during or soon after infusion of Varubi® IV; most reactions have occurred within the first few minutes of administration. The FDA urges that health care professionals be vigilant for the signs of hypersensitivity or anaphylaxis in all patients receiving Varubi® IV, both during and following its administration. It is advised that health care professionals consult with patients to determine if the patient is hypersensitive to any component of the product (including soybean oil). Furthermore, as cross reactions to other allergens are possible, patients with known allergies to legumes or other related allergens should be monitored closely. Patients with a potential hypersensitivity should not be administered Varubi® IV. Appropriate treatment should be available for immediate use in the event of an anaphylactic reaction during treatment with Varubi® IV. If anaphylaxis or any other serious hypersensitivity/infusion reaction occurs, administration of Varubi® IV should be stopped immediately, appropriate medical management (e.g., epinephrine, antihistamines) should be initiated, and Varubi® IV should be permanently discontinued. The FDA website currently indicates that Varubi® IV has been discontinued.

Pipeline:

- **Barhemsys™ (Amisulpride):** Acacia Pharma submitted a New Drug Application (NDA) to the FDA in January 2018 for Barhemsys™ (formerly Baremsis™), an IV formulation of amisulpride, for the management of post-operative nausea and vomiting (PONV). Amisulpride, a selective dopamine antagonist, is not approved by the FDA for use in the United States, but is currently used in Europe and other countries to treat psychosis and schizophrenia. In October 2018, the FDA issued a Complete Response Letter (CRL) to Acacia regarding the NDA for Barhemsys™. The CRL identified deficiencies reported during a recent pre-approval FDA inspection of the contract manufacturer of amisulpride, but did not raise any concerns about any of the clinical or non-clinical data in the NDA or require any further clinical studies or data analyses. Acacia stressed that, working with its contract manufacturer, it prepared a corrective and preventative action (CAPA) plan to robustly address the outstanding deficiency at its facility. The CAPA was submitted to the FDA by the contract manufacturer, and Acacia resubmitted the NDA to the FDA for Barhemsys™ in November 2018. Acacia is continuing to prepare for an anticipated launch of Barhemsys™ in the first half of 2019.
- **APD403:** Acacia Pharma is currently developing APD403 for chemotherapy-induced nausea and vomiting (CINV). APD403 is based on the selective dopamine antagonist amisulpride, the same active ingredient as in Barhemsys™. APD403 is being developed as an IV injection for cancer patients to be administered immediately prior to chemotherapy to prevent acute CINV and as an oral tablet to prevent delayed CINV. APD403 has successfully completed 1 proof-of-concept and 1 Phase 2 dose-ranging clinical study demonstrating it is well tolerated and effective at preventing acute and delayed CINV. Acacia intends to advance APD403 into Phase 3 studies following completion of a further Phase 2 clinical study.
- **Bekinda® (Ondansetron ER):** RedHill Biopharma is currently developing Bekinda®, a proprietary, bimodal ER (24-hour) oral tablet formulation of ondansetron, for the treatment of acute gastroenteritis and gastritis and for the treatment of irritable bowel syndrome with diarrhea (IBS-D). A positive Phase 3 clinical study with Bekinda® for the treatment of acute gastroenteritis and gastritis (the GUARD study) successfully met its primary endpoint, and a positive Phase 2 clinical study with Bekinda® for the treatment of IBS-D also successfully met its primary endpoint. RedHill is currently in discussions with the FDA on the design of a confirmatory Phase 3 clinical study with Bekinda® for acute gastroenteritis and gastritis and is planning to finalize the design of 2 pivotal Phase 3 studies with Bekinda® for IBS-D.

Cost Comparison

The following table shows a cost comparison of various oral anti-emetic medications used for CINV. Dronabinol oral capsules are currently available generically from multiple pharmaceutical companies. Most SoonerCare prior authorization requests for dronabinol for CINV are for twice daily dosing and most members have previously failed ondansetron for CINV prior to requesting dronabinol.

Medication	Cost Per Capsule	Cost Per Month or Per Chemotherapy Cycle
dronabinol 2.5mg capsule	$1.69	$101.40[+]
dronabinol 5mg capsule	$3.52	$211.20[+]
dronabinol 10mg capsule	$5.41	$324.60[+]
aprepitant 125mg/80mg capsule dose pack[¥]	$161.25	$483.75[¥]
Cesamet® (nabilone) 1mg capsule[Ω]	$39.20	$705.60[Ω]

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 Costs (SMAC) if NADAC unavailable.
[+]Cost per month for dronabinol capsules is based on twice daily dosing (#60 capsules for a 30-day supply).
[¥]Aprepitant dose pack includes one 125mg capsule and two 80mg capsules; aprepitant recommended dosing for CINV is 125mg on day 1 of chemotherapy cycle (1 hour prior to chemotherapy) and 80mg on days 2 and 3. Cost per chemotherapy cycle is based on 3 days of therapy (#3 capsules for a 3-day supply).
[Ω]Nabilone recommended dosing for CINV is 1 to 2mg twice daily (first dose taken 1 to 3 hours prior to chemotherapy); may administer up to 3 times daily during the entire course of each cycle of chemotherapy and continue up to 48 hours after the last dose of chemotherapy (maximum of 6mg per day in 3 divided doses). Cost per chemotherapy cycle is based on 3 days of therapy at a dose of 6mg per day (#18 capsules for a 3-day supply).

Recommendations

The College of Pharmacy recommends the prior authorization of Akynzeo® IV (fosnetupitant/palonosetron IV) with the following criteria (changes noted in red):

Akynzeo® (Netupitant/Palonosetron) and Akynzeo® IV (Fosnetupitant/Palonosetron) Approval Criteria:

1. An FDA approved indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy; and
2. For Akynzeo® oral capsules, a previously failed trial of oral aprepitant (Emend®) that resulted in an inadequate response, or a patient-specific, clinically significant reason why oral aprepitant cannot be used must be provided; and
3. For Akynzeo® IV, 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. Akynzeo® IV will require a patient-specific, clinically significant reason why the oral capsule formulation cannot be used; and
5. Approval length will be based on duration of need; and
6. A quantity limit of 1 capsule or vial per chemotherapy cycle will apply; and
7. Akynzeo® oral capsules will not require 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 6 months of claims history.
    a. Based on the current low net cost, Akynzeo® oral capsules will not require prior authorization for members with cancer; however, Akynzeo® oral capsules will follow the original criteria and require a previously failed trial of oral aprepitant if the net cost increases compared to other available products.

Additionally, the College of Pharmacy recommends updating the approval criteria for Marinol® (dronabinol) based on generic availability and low net cost (changes noted in red):

Marinol® and Syndros® (Dronabinol) and Cesamet® (Nabilone) Approval Criteria:

~~1. Approval can be granted for 6 months for the diagnosis of HIV related loss of appetite; or~~

~~2. The diagnosis of chemotherapy induced nausea and vomiting requires the following:~~

~~a. A recent trial of ondansetron (within the past 6 months) used for at least 3 days or 1 cycle that resulted in inadequate response; and~~

3. An FDA approved diagnosis; and
4. Approval length will be based on duration of need.
5. For Marinol® (dronabinol) and Cesamet® (nabilone), a quantity limit of 60 capsules per 30 days will apply; and
6. Cesamet® (nabilone) will require a patient-specific, clinically significant reason why dronabinol oral capsules cannot be used; and
7. For Syndros® (dronabinol) oral solution, the quantity approved will be patient-specific depending on patient diagnosis, maximum recommended dosage, and manufacturer packaging; and
8. For Syndros® (dronabinol) oral solution, an age restriction of 6 years and younger will apply. Members older than 6 years of age will require a patient-specific, clinically significant reason why dronabinol oral capsules cannot be used.

Utilization Details of Anti-Emetic Medications: Fiscal Year 2018

Pharmacy Claims

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
ONDANSETRON PRODUCTS						
ONDANSETRON ODT 4MG	61,676	50,362	$842,562.20	$13.66	1.22	57.68%
ONDANSETRON TAB 4MG	12,536	9,051	$149,673.90	$11.94	1.39	10.25%
ONDANSETRON ODT 8MG	12,407	9,021	$195,438.01	$15.75	1.38	13.38%
ONDANSETRON SOL 4MG/5ML	6,097	5,455	$139,079.15	$22.81	1.12	9.52%
ONDANSETRON TAB 8MG	4,311	2,683	$58,266.82	$13.52	1.61	3.99%
ONDANSETRON INJ 40/20ML	8	3	$184.80	$23.10	2.67	0.01%
ONDANSETRON INJ 4MG/2ML	8	7	$185.66	$23.21	1.14	0.01%
SUBTOTAL	**97,043**	**71,590***	**$1,385,390.54**	**$14.28**	**1.36**	**94.84%**
DRONABINOL PRODUCTS						
DRONABINOL CAP 2.5MG	80	38	$12,469.00	$155.86	2.11	0.85%
DRONABINOL CAP 5MG	76	25	$22,224.79	$292.43	3.04	1.52%
DRONABINOL CAP 10MG	24	3	$9,524.33	$396.85	8	0.65%
SYNDROS SOL 5MG/ML	1	1	$3,202.87	$3,202.87	1	0.22%
MARINOL CAP 2.5MG	1	1	$665.67	$665.67	1	0.05%
SUBTOTAL	**182**	**60***	**$48,086.66**	**$264.21**	**3.03**	**3.29%**
APREPITANT PRODUCTS						
EMEND SUS 125MG/5ML	14	6	$4,617.94	$329.85	2.33	0.32%
APREPITANT PAK 80MG & 125MG	13	7	$6,963.66	$535.67	1.86	0.48%
APREPITANT CAP 80MG	3	2	$568.66	$189.55	1.5	0.04%
APREPITANT CAP 40MG	2	1	$167.60	$83.80	2	0.01%

PRODUCT UTILIZED	TOTAL CLAIMS	TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
SUBTOTAL	**32**	**15***	**$12,317.86**	**$384.93**	**2.13**	**0.84%**
GRANISETRON PRODUCTS						
GRANISETRON TAB 1MG	14	8	$899.81	$64.27	1.75	0.06%
SANCUSO DIS 3.1MG	6	4	$4,960.59	$826.77	1.5	0.34%
SUBTOTAL	**20**	**12***	**$5,860.40**	**$293.02**	**1.67**	**0.40%**
DOXYLAMINE/PYRIDOXINE PRODUCTS						
DICLEGIS TAB 10-10MG	16	9	$8,115.08	$507.19	1.78	0.56%
SUBTOTAL	**16**	**9***	**$8,115.08**	**$507.19**	**1.78**	**0.56%**
NETUPITANT/PALONOSETRON PRODUCTS						
AKYNZEO CAP 300-0.5MG	2	1	$938.04	$469.02	2	0.06%
SUBTOTAL	**2**	**1***	**$938.04**	**$469.02**	**2**	**0.06%**
TOTAL	**97,295**	**71,626***	**$1,460,708.58**	**$15.01**	**1.36**	**100%**

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

Medical Claims

PRODUCT UTILIZED	TOTAL CLAIMS	*TOTAL MEMBERS	TOTAL COST	COST/ CLAIM	CLAIMS/ MEMBER	% COST
PALONOSETRON INJ J2469	2,451	483	$498,584.95	$203.42	5.07	61.88%
FOSAPREPITANT INJ J1453	976	279	$294,516.00	$301.76	3.50	36.56%
GRANISETRON INJ J1626	791	105	$2,677.97	$3.39	7.53	0.33%
ROLAPITANT INJ J3490	40	22	$8,850.00	$221.25	1.82	1.10%
APREPITANT CAPS J8501	8	7	$1,035.19	$129.40	1.14	0.13%
TOTAL	**4,266**	**605**	**$805,664.11**	**$188.86**	**7.05**	**100%**

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

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Appendix L

30-Day Notice to Prior Authorize Carbaglu® (Carglumic Acid)

Oklahoma Health Care Authority
December 2018

Introduction[1,2]

N-acetylglutamate synthase (NAGS) deficiency is a rare genetic disorder characterized by complete or partial lack of the enzyme NAGS. NAGS deficiency is part of a group of disorders that affect the urea cycle. NAGS is one of 6 enzymes that play a role in the break down and removal of nitrogen from the body. The lack of NAGS enzyme results in excessive ammonia in the blood.

NAGS deficiency is an autosomal recessive genetic disorder caused by mutations in the *NAGS* gene. A diagnosis is made based on detailed patient/family history, identification of characteristic findings, and is confirmed through genetic testing that reveals a mutation of the *NAGS* gene. NAGS deficiency is a very rare disorder with only a few cases having been reported worldwide.

NAGS deficiency can be associated with a complete or partial absence of the NAGS enzyme. A complete lack of the NAGS enzyme results in a severe form of the disorder in which symptoms present shortly after birth. A partial lack of the NAGS enzyme results in a milder form of the disorder that occurs later during infancy or childhood. Symptoms of NAGS deficiency are caused by the accumulation of ammonia in the blood. Infants with severe NAGS deficiency may exhibit refusal to eat, progressive lethargy, recurrent vomiting, diarrhea, irritability, and hepatomegaly. More severe complications can include seizures, confusion, respiratory distress, and cerebral edema. Some patients may progress to coma and subsequent neurological abnormalities including developmental delays, learning disabilities, and intellectual disability. Patients with a partial lack of the NAGS enzyme may exhibit symptoms such as ataxia, lethargy, vomiting, and failure to grow or gain weight at the expected rate.

Treatment of NAGS deficiency is aimed at preventing excessive ammonia from being formed or removing excessive ammonia during hyperammonemic episodes. Dietary restrictions are aimed at limiting the amount of protein intake. Nitrogen scavengers like phenylacetate and sodium benzoate provide an option to remove excess nitrogen. Carbaglu® (carglumic acid) was approved by the U.S. Food and Drug Administration (FDA) in 2010 and is the only FDA approved medication for the chronic treatment of patients with NAGS deficiency to reduce blood ammonia levels.

Carbaglu® (Carglumic Acid) Product Summary[3,4]

Indication(s): Carbaglu® (carglumic acid) is a Carbamoyl Phosphate Synthetase 1 (CPS 1) activator indicated as adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of the hepatic enzyme NAGS, and maintenance therapy for the treatment of chronic hyperammonemia due to NAGS deficiency.

Dosing:

- Carbaglu® is supplied as a white, elongated 200mg scored tablet for oral suspension.
- The recommended dosage of carglumic acid for the acute treatment of hyperammonemia is 100 to 250mg/kg/day titrated based on plasma ammonia level and clinical symptoms.
- The recommended maintenance dose of carglumic acid for chronic hyperammonemia is 10 to 100mg/kg/day titrated to a normal plasma ammonia level for the patient's age.
- Total daily dosing should be divided into 2 to 4 doses.

Mechanism of Action: Carglumic acid is a synthetic structural analogue of N-acetylglutamate (NAG) which acts as an essential allosteric activator of CPS 1.

Contraindication(s): None

Adverse Reactions: The most common adverse reactions reported with carglumic acid (>10%) in clinical studies were abdominal pain, diarrhea, vomiting, anemia, decreased hemoglobin, headache, fever, and infections.

Use in Specific Populations:

- Pregnancy: There are no adequate studies or available human data with carglumic acid in pregnant women. Because untreated NAGS deficiency results in irreversible neurologic damage and death, women with NAGS deficiency must remain on treatment throughout pregnancy.
- Nursing Mothers: It is not known whether carglumic acid is excreted in human milk. Carglumic acid is excreted in rat milk, and because many drugs are excreted in human milk, breastfeeding is not recommended.
- Pediatric Use: The efficacy of carglumic acid was evaluated in patients with NAGS deficiency from birth to adulthood in a retrospective review. There are no apparent differences in clinical response between adults and pediatric patients with NAGS deficiency.
- Geriatric Use: Carglumic acid has not been studied in the geriatric population. Therefore, the safety and effectiveness in geriatric patients have not been established.

Efficacy: The efficacy of carglumic acid for the treatment of hyperammonemia due to NAGS deficiency was evaluated in a retrospective review of the clinical course of 23 patients with NAGS deficiency who received carglumic acid treatment for a median of 7.9 years (range 0.6 to 20.8 years). Treatment with carglumic acid was divided in 2 regimens: for acute treatment, patients received a total daily dose of 100 to 250mg/kg for the first few days of treatments; for maintenance treatment, the dosage was reduced over time based on biochemical and clinical response. A subset of 13 patients with well documented plasma ammonia levels prior to carglumic acid treatment, during acute treatment, and after long-term treatment with carglumic acid were selected for analysis. At baseline the mean plasma ammonia level was 271micromol/L. By day 3, the mean plasma ammonia level was 27micromol/L. Through the long-term part of the study, the mean ammonia level was 23micromol/L with a mean treatment duration of 8 years.

Cost Comparison:

Medication	Cost Per Tablet	Acute Treatment Cost Per 3 Days	Maintenance Treatment Cost Per 30 Days
Carbaglu® (carglumic acid) 200mg tablet	**$192.35**	**$4,616.40 - $10,963.95**	**$5,770.35 - $46,164.00**

Costs do not reflect rebated prices or net costs. Costs based on National Average Drug Acquisition Costs (NADAC), or Wholesale Acquisition Costs (WAC) if NADAC unavailable.
Dosing based on average weight of 4-year-old male (15kg).

Recommendations

The College of Pharmacy recommends the prior authorization of Carbaglu® (carglumic acid) with the following criteria:

Carbaglu® (Carglumic Acid) Approval Criteria:

1. An FDA approved diagnosis of N-acetylglutamate synthase (NAGS) deficiency; and
2. Carbaglu® must be prescribed by a geneticist or in consultation with a geneticist; and
3. Documentation of active management with a low protein diet; and
4. Initial approvals will be for the duration of 1 year. After that time, reauthorization will require the prescriber to verify the member is responding to therapy.

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Appendix M

Fiscal Year 2018 Annual Review of Muscular Dystrophy Medications

Oklahoma Health Care Authority
December 2018

Current Prior Authorization Criteria

Exondys 51™ (Eteplirsen) Approval Criteria:

1. An FDA approved diagnosis of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping; and
2. The member's recent weight must be provided on the prior authorization request in order to authorize the appropriate amount of drug required according to package labeling.

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. Member must have a minimum 6-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. Prescriber must verify 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
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.

Utilization of Muscular Dystrophy Medications: Fiscal Year 2018

There was no SoonerCare utilization of muscular dystrophy medications during fiscal year 2018.

Prior Authorization of Muscular Dystrophy Medications

There were no prior authorization requests submitted for muscular dystrophy medications during fiscal year 2018.

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

Anticipated Patent Expiration(s):

- Emflaza® (deflazacort): Emflaza® has no unexpired patents, but exclusivity expires in February 2022 for New Chemical Entity and in February 2024 for Orphan Drug exclusivity for the treatment of Duchenne muscular dystrophy (DMD) in patients 5 years of age and older.
- Exondys 51™ (eteplirsen): March 2034

News:

- **March 2018:** To address the emerging needs of patients, caregivers, and physicians of patients with DMD, the Centers for Disease Control and Prevention (CDC) revised guidelines to improve patient transitions into age 30 years and beyond. These revised guidelines were published as 3 separate articles in *The Lancet Neurology* as an update to the guidelines originally published in 2010. The revised guidelines include 11 topic areas, 3 of which are new topics. The 3 new topics include "primary care and emergency management," "endocrine management (growth, development and hormone deficiencies)," and "transitions of care across the lifespan." The report draws attention to new and emerging DMD treatments, like Exondys 51™ (eteplirsen) and Emflaza® (deflazacort). In the treatment recommendations, prednisone/prednisolone or deflazacort is recommended when initiating steroid treatment, and preference is not given to one over the other. Eteplirsen is acknowledged as the first mutation-specific therapy to be approved by the U.S. Food and Drug Administration (FDA) for DMD, but no treatment guidelines regarding its use are provided.
- **April 2018:** In a letter to the United States Department of Health and Human Services (HHS) Secretary Alex Azar, 6 advocacy groups called on the HHS to lower the price of eteplirsen, marketed by Sarepta Therapeutics under the brand name Exondys 51™. These groups, which included Patients for Affordable Drugs, Knowledge Ecology International, and Universities Allied for Essential Medicines, asked the federal government to take control of 5 patents on eteplirsen. These advocacy groups claim that after researchers looked into the drug's patents and the associated records of grant funding, it was discovered that Sarepta failed to disclose several National Institutes of Health (NIH) grants that helped fund the development of the drug. Under the Bayh-Dole Act, companies that have received government funding for an invention must declare this in the patent, provide the government with a worldwide royalty free right license, make the benefits "available to the public on reasonable terms", and manufacture products in the United States. According to the letter, failing to disclose funding renders recipients subject to possible sanctions by the funding agency, and the group suggests taking control of the patents and negotiating a lower price is a possible solution. Although the federal government has asked recipients of federal grants to correct failures to disclose funding in the past, it has never taken over patents for the purpose of changing drug prices. The groups acknowledged that they are asking HHS to "do something new."
- **June 2018:** The European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) recommended against approval of eteplirsen for the treatment DMD. This decision is at odds with the controversial accelerated approval by the FDA of eteplirsen in September 2016. The FDA's approval was against the recommendation of

their Peripheral and Central Nervous System Drugs Advisory Committee, which concluded that studies of eteplirsen failed to provide persuasive evidence that the drug is effective in DMD. A statement from the EMA notes "The CHMP was concerned that the main study, which involved just 12 patients, did not compare Exondys with placebo beyond 24 weeks, during which there was no meaningful difference between Exondys and placebo in the 6-minute walking distance." The CHMP indicated further data were needed to show that the amount of shortened dystrophin produced with eteplirsen treatment results in lasting patient benefits and concluded the balance of benefits and risks cannot be established at this time. Sarepta acknowledged it was expecting the decision and will appeal it. The Company will also request a Scientific Advisory Group (SAG) on DMD be called so that neuromuscular specialists can provide expert guidance and insight into the validity of the external controls used and the importance of certain functional endpoints.

- **June 2018:** Summit Therapeutics PLC announced that PhaseOut DMD has not met its primary or secondary endpoints after 48 weeks of treatment in patients with DMD. PhaseOut DMD is Summit's multi-center, open-label Phase 2 clinical trial of the utrophin modulator, ezutromid. Based on this outcome, Summit is discontinuing the development of ezutromid and as a result, will be implementing cost reduction measures. A total of 40 boys with DMD were enrolled in PhaseOut DMD, with 38 completing the 48-week clinical trial. The primary endpoint was the change from baseline in magnetic resonance parameters related to the leg muscles. Biopsy measures evaluating utrophin and muscle damage were included as secondary endpoints, with patients having 2 biopsies: 1 at baseline and their second after either 24 weeks or 48 weeks of ezutromid treatment. Summit plans to explore ways that information gathered as part of PhaseOut DMD can be made available to support other research activities in DMD for the benefit of the DMD community.
- **July 2018:** A post hoc analysis from the Ataluren Confirmatory Trial (ACT) was published in the journal *Muscle & Nerve* comparing the efficacy and safety of deflazacort and prednisone/prednisolone in the placebo arm of the trial. The ACT trial was a Phase 3, randomized, double-blind, placebo-controlled, 48-week trial that evaluated ataluren's treatment effect in stabilizing motor function and delaying disease progression in patients 7 to 16 years of age with nonsense mutation DMD (nmDMD). Efficacy assessments were conducted every 8 weeks at clinic visits. The primary endpoint assessed the ability of treatment to slow the progression of disease and was evaluated by the change from baseline to week 48 in 6-minute walk distance (6MWD). All patients enrolled in this study had been receiving corticosteroid therapy (deflazacort or prednisone/prednisolone) for ≥6 months at study entry, had no clinically significant change in dosage or dosing regimen for ≥3 months before study entry, and were expected to maintain a stable dose and regimen during the study. The placebo arm consisted of 114 patients in the intent-to-treat (ITT) population, 53 of whom received deflazacort and 61 of whom received prednisone/prednisolone at entry and throughout the study. Patients treated with deflazacort had notably less decline from baseline in 6MWD at week 48 than those treated with prednisone/prednisolone. The extrapolated time to loss of ambulation (LoA) when using a linear model was 8.58 years for deflazacort and 4.74 years with prednisone/prednisolone. The safety profiles for deflazacort and prednisone/prednisolone were generally comparable. Patients in the

placebo arm receiving deflazacort had numerically smaller increases in weight, height, and body mass index (BMI) during the study than patients receiving prednisone/ prednisolone. Similarly in 2015, an observational study of 340 patients in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS) demonstrated that deflazacort was associated with later LoA than prednisone (P=0.003). Deflazacort, however, showed higher frequencies of growth delay (P<0.001), cushingoid appearance (P=0.002), and cataracts (P<0.001), but not weight gain. Differences in standards of care and dosing complicate interpretation of this finding. In patients treated for ≥1 year while ambulatory and ≥1 year before LoA with either glucocorticoid [GC-treated (N=252)], a 3-year median delay in LoA (P<0.001) was shown when compared to those patients classified as untreated. Untreated patients were those who had been receiving GC regimens for <1 year while ambulatory.

Pipeline:

- **Golodirsen:** Golodirsen uses Sarepta Therapeutics' proprietary phosphorodiamidate morpholino oligomer (PMO) chemistry and exon-skipping technology to skip exon 53 of the DMD gene. Golodirsen is designed to bind to exon 53 of dystrophin pre-messenger RNA (mRNA), resulting in exclusion, or "skipping," of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon skipping is intended to allow for production of an internally truncated but functional dystrophin protein. A Phase 1/2 study to assess the safety, tolerability, pharmacokinetics, and efficacy of golodirsen in 25 boys with confirmed deletions of the DMD gene amenable to exon 53 skipping demonstrated statistically significant results in favor of golodirsen on all biological endpoints. The endpoints included properly exon-skipped RNA transcript using reverse transcription polymerase chain reaction, quantity of dystrophin expression using Western blot, and dystrophin intensity pursuant to immunohistochemistry. Based on the results of the study and the FDA's feedback advising Sarepta to seek guidance from the FDA's Division of Neurology Products on the development pathway of golodirsen, Sarepta intends to complete a rolling submission of a New Drug Application (NDA) by year-end 2018. On further guidance from the FDA, Sarepta is seeking accelerated approval of golodirsen based on an increase in dystrophin protein as a surrogate endpoint. The FDA's Division of Neurology Products reported that in light of the precedent of eteplirsen's approval, based on an increase in dystrophin protein as a surrogate endpoint reasonably likely to predict clinical benefit, a statistically significant increase in truncated dystrophin protein may serve as a basis for accelerated approval of golodirsen for the treatment of DMD.
- **rAAVrh74.MHCK7.micro-dystrophin:** An experimental gene therapy, which is being developed by Sarepta Therapeutics, dramatically improved the ability of a young boy with DMD to rise from the ground and climb stairs, repeating and improving on results seen in 3 previous patients who received the treatment. Douglas Ingram, Sarepta's president and chief executive states, "The cautionary note is this all has to be confirmed in a larger trial." This comes after The FDA lifted the clinical hold on the Phase 1/2 trial. The hold was placed after the FDA found trace amounts of plasmid DNA that is used in the raw material to make the therapy. Testing showed that these trace fragments were quickly cleared by the body and showed no safety concerns. Sarepta's gene therapy, called rAAVrh74.MHCK7.micro-dystrophin, uses a modified version of the adeno-associated virus (AAV) to insert a shortened version of the gene for dystrophin into a

patients' cells. In DMD, the gene for dystrophin is mutated leading to progressive muscle fiber destruction. Sarepta had previously announced that in 3 boys, this approach led to levels of the new dystrophin (called microdystrophin) that were 40% of normal based on the Western blot. In the previous results, levels of creatinine kinase, a marker for how quickly muscle is being destroyed, dropped 87%. Those results have largely held up; the average drop in creatinine kinase is now 78%. For the fourth patient, microdystrophin levels were 183% of normal, and creatinine kinase levels dropped 95%. Additionally, the time it took the boy to rise up from the ground dropped from 4.1 seconds to 2.3 seconds. The time to climb 4 stairs went from 4.8 seconds to 2.2 seconds. For the whole group of patients, time to rise improved 13% and time to climb 4 stairs improved 31%.

- **SGT-001:** Solid Biosciences, Inc.'s lead candidate, SGT-001, is a novel AAV vector-mediated gene transfer therapy being studied for its ability to address mutations in the dystrophin gene that result in the absence or near-absence of dystrophin protein in patients with DMD. SGT-001 is systemically administered and delivers a synthetic dystrophin transgene, called microdystrophin, to the body. In June 2018, Solid Biosciences announced that the FDA lifted the clinical hold on IGNITE DMD, the Company's Phase 1/2 clinical trial for SGT-001. The FDA placed a clinical hold on IGNITE DMD following the company's report of a serious adverse event (SAE) in the first patient dosed with SGT-001. The patient experienced a decrease in platelet count followed by a reduction in red blood cell count, transient renal impairment, and evidence of complement activation. The patient received standard medical care, remained clinically stable and generally asymptomatic throughout the event, and the event fully resolved. Solid Biosciences expects to report initial data from a pre-specified interim analysis of IGNITE DMD in the second half of 2019.
- **Translarna™:** Translarna™ (ataluren) is a protein restoration therapy designed to enable the formation of a functioning protein in patients with genetic disorders caused by a nonsense mutation, an alteration in the genetic code that prematurely halts the synthesis of an essential protein. In DMD, this protein is dystrophin. In 2016, the FDA issued a Refusal to File on grounds that the application for ataluren "was not sufficiently complete to permit a substantive review." Then in October 2017, the FDA turned down PTC Therapeutic, Inc.'s NDA for ataluren, issuing a Complete Response Letter (CRL) stating that it is unable to approve the application in its current form. The letter indicated that evidence of effectiveness from an additional adequate and well-controlled clinical trial(s) would be necessary at a minimum to provide substantial evidence of effectiveness. In February 2018, PTC announced that the FDA's Office of New Drugs reiterated the FDA's prior position and denied PTC's appeal of the CRL in relation to the NDA for ataluren. The FDA recommended a possible path forward for the ataluren NDA submission based on the accelerated approval pathway. This would involve a re-submission of an NDA containing the current data on effectiveness of ataluren with new data to be generated on dystrophin production in nmDMD patients' muscles, as quantified by procedures to be agreed upon between PTC and the FDA and using newer technologies. The letter adds that PTC's Study 041, which is currently enrolling, could serve as the confirmatory post-approval trial required in connection with the accelerated approval framework. In October 2018, PTC announced preliminary data from the first international drug registry for DMD patients receiving ataluren. The

data show that children and adolescents receiving ataluren in the real-world setting are continuing to walk years longer than untreated children, when compared with published natural history. A time-to-event analysis for LoA has shown that patients on ataluren had a median age of LoA of 16.5 years; this is up to 5 years later than seen with natural disease progression in untreated children. Ataluren has been given a conditional approval in the European Union.

Cost Changes

- Since the last annual review of this medication class, the Wholesale Acquisition Cost (WAC) for Emflaza® (deflazacort) has increased for all tablet strengths and the suspension. The current WAC for Emflaza® ranges from $47.67 to $265.60 per tablet, with the suspension costing $241.55 per milliliter. This results in an approximate annual cost range of $51,480.00 to $269,571.60 based on the recommended dosing of 0.9mg/kg daily (annual cost range includes both tablet and suspension formulations). By comparison, the National Average Drug Acquisition Cost (NADAC) for prednisone 20mg is $0.13 per tablet, resulting in an approximate annual cost of $46.80 to $140.40 based the recommended dosing of 0.75mg/kg daily.
- The WAC for Exondys 51™ has remained the same since the last annual review at $800 per milliliter. This results in an approximate annual cost of $460,800 to $1,766,400 based on the recommended dosing of 30mg/kg once weekly. The costs provided are based on the average weight for males 5 to 19 years of age.

Recommendations

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

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Appendix N

Industry News and Updates

Oklahoma Health Care Authority
December 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]

News:

- **Generic Drug Approvals:** The U.S. Food and Drug Administration (FDA) announced it approved and tentatively approved more generic drugs in fiscal year (FY) 2018 than any other prior year. In FY 2018, the FDA had 971 total approvals, including 781 final approvals and 190 tentative approvals, this is in comparison to FY 2017 which had 937 total approvals. In October 2018, the FDA approved 110 generic drugs and tentatively approved 18 generic drugs. The FDA Commissioner Scott Gottlieb, M.D., stated "Over the past two consecutive years, the agency approved record numbers of generic drugs. Now we're beginning the new fiscal year by breaking another record, this time with the highest number of approved or tentatively approved generics ever in a month." The FDA also issued a series of guidance documents in October 2018 that will advance the development of generic transdermal and topical delivery systems (TDS). The recommendations will give applicants seeking FDA approval of generic versions of these complex products a better understanding of how to successfully develop these products and to help prepare a more complete application. Promoting more generic competition to complex medicines is a key part of the FDA's Drug Competition Action Plan.
- **Genetic Tests:** The FDA issued an alert warning against the use of unapproved genetic tests intended to predict patient responses to medications. The FDA issued the warning in response to reports of DNA tests and software programs claiming they could predict the effectiveness or side effects of certain drugs, including antidepressants. The FDA stated that the claims are not based on any currently existing sufficient clinical evidence. The FDA said that there is no established relationship between DNA variations and the effectiveness of antidepressants and they expressed particular concern regarding reports that some prescribers have changed prescriptions based on genetic test results, which could put patients at risk.

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Appendix O

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

FDA NEWS RELEASE

For Immediate Release: November 26th, 2018

FDA approves an oncology drug that targets a key genetic driver of cancer, rather than a specific type of tumor

New drug Vitrakvi® targets specific receptor kinase that promotes tumors

The FDA granted accelerated approval to Vitrakvi® (larotrectinib), a treatment for adult and pediatric patients whose cancers have a specific genetic feature (biomarker). This is the second time the agency has approved a cancer treatment based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated. The approval marks a new paradigm in the development of cancer drugs that are "tissue agnostic." It follows the policies that the FDA developed in a guidance document released earlier this year.

Vitrakvi® is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment. Research has shown that the NTRK genes, which encode for TRK proteins, can become fused to other genes abnormally, resulting in growth signals that support the growth of tumors. NTRK fusions are rare but occur in cancers arising in many sites of the body. Prior to this approval, there had been no treatment for cancers that frequently express this mutation, like mammary analogue secretory carcinoma, cellular or mixed congenital mesoblastic nephroma and infantile fibrosarcoma.

The efficacy of larotrectinib was studied in three clinical trials that included 55 pediatric and adult patients with solid tumors that had an identified NTRK gene fusion without a resistance mutation and were metastatic or where surgical resection was likely to result in severe morbidity. These patients had no satisfactory alternative treatments or had cancer that progressed following treatment. Larotrectinib demonstrated a 75% overall response rate across different types of solid tumors. These responses were durable, with 73% of responses lasting at least 6 months, and 39% lasting a year or more at the time results were analyzed. Examples of tumor types with an NTRK fusion that responded to larotrectinib include soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, and lung cancer.

Vitrakvi® received an accelerated approval, which enables the FDA to approve drugs for serious conditions to fill an unmet medical need using clinical trial data that is thought to predict a clinical benefit to patients. Further clinical trials are required to confirm Vitrakvi®'s clinical benefit and the sponsor is conducting or plans to conduct these studies.

Common side effects reported by patients receiving Vitrakvi in clinical trials include fatigue, nausea, cough, constipation, diarrhea, dizziness, vomiting, and increased AST and ALT enzyme blood levels in the liver. Health care providers are advised to monitor patient ALT and AST liver tests every 2 weeks during the first month of treatment, then monthly and as clinically indicated. Women who are pregnant or breastfeeding should not take Vitrakvi® because it may cause harm to a developing fetus or newborn baby. Patients should report signs of neurologic reactions such as dizziness.

The FDA granted this application Priority Review and Breakthrough Therapy designation. Vitrakvi® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.

The FDA granted the approval of Vitrakvi® to Loxo Oncology.

FDA NEWS RELEASE

For Immediate Release: November 28th, 2018

FDA approves treatment for adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a certain genetic mutation

The FDA approved Xospata® (gilteritinib) tablets for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test. The FDA also approved an

expanded indication for a companion diagnostic, to include use with Xospata®. The LeukoStrat CDx FLT3 Mutation Assay, developed by Invivoscribe Technologies, Inc., is used to detect the FLT3 mutation in patients with AML.
AML is a rapidly progressing cancer that crowds out normal cells in the bone marrow and bloodstream, resulting in low numbers of normal blood cells and a continuous need for transfusions. The National Cancer Institute estimates that approximately 19,520 people will be diagnosed with AML this year; approximately 10,670 patients with AML will die of the disease in 2018.
The efficiency of Xospata® was studied in a clinical trial of 138 patients with relapsed or refractory AML having a confirmed FLT3 mutation. A total of 21% of patients achieved complete remission or complete remission with partial hematologic recovery with treatment. Of the 106 patients who required red blood cell or platelet transfusions at the start of treatment with Xospata®, 31% became transfusion-free for at least 56 days.
Common side effects reported by patients in clinical trials were muscle and joint pain (myalgia/arthralgia), fatigue, and elevated liver enzymes (liver transaminase). Health care providers are advised to monitor patients for posterior reversible encephalopathy syndrome (a syndrome characterized by headache, confusion, seizures, and visual loss), prolonged QT interval (a heart rhythm condition that can potentially cause fast, chaotic heartbeats), and pancreatitis. Rare cases of differentiation syndrome (symptoms of which may include fever, cough, trouble breathing, fluid around the lungs or heart, rapid weight gain, swelling, and renal or hepatic dysfunction) have been seen in patients taking Xospata®. Women who are pregnant or breastfeeding should not take Xospata® because it may cause harm to a developing fetus or newborn baby.
The FDA granted this application Fast Track and Priority Review designation. Xospata® also received Orphan Drug designation, which provides incentives to assist and encourage the development of drugs for rare diseases.
The FDA granted the approval of Xospata® to Astellas Pharma.

Safety Announcements

FDA alerts consumers of Kadesh Incorporation's voluntary nationwide recall of Puriton™ Eye Relief Drops due to non-sterile production conditions

[11/08/2018] The FDA is alerting consumers about a voluntary recall of all lots of Puriton™ Eye Relief Drops, 0.5 oz. (15 mL) bottle. These products are labeled as a homeopathic and are being recalled due to non-sterile production conditions at the manufacturing facility. Consumers should stop using this product and contact their physician or health care provider if they experience any problems that may be related to using this product.
Puriton™ Eye Relief Drops are over-the-counter homeopathic eye drops marketed for the temporary relief of burning and irritation due to eye dryness and eye discomfort due to minor irritations or to exposure to wind or sun. Kadesh, Inc., is voluntarily recalling all non-expired lots of Puriton™ Eye Relief Drops. The company distributed the product nationwide via its own online stores and retailers.
Use of a non-sterile eye drop product is potentially vision-threatening due to the risk of an eye infection. Additionally, the pH of this product is relatively high and can cause direct destruction of tissues in the cornea, anterior chamber and deeper structures of the eye, which can lead to scarring, glaucoma or vision loss.
The FDA is not aware of any adverse event reports associated with Puriton™ Eye Relief Drops.

Safety Announcements

FDA warns about severe worsening of multiple sclerosis (MS) after stopping the medicine Gilenya® (fingolimod)

[11-20-2018] The FDA is warning that when the MS medicine Gilenya® (fingolimod) is stopped, the disease can become much worse than before the medicine was started or while it was being taken. This MS worsening is rare but can result in permanent disability. As a result, the FDA has added a new warning about this risk to the prescribing information of the Gilenya® drug label and patient Medication Guide.
Gilenya® is one of several medicines approved to treat relapsing MS, which are periods of time when MS symptoms get worse. The medicine was approved in the United States in 2010.
Health care professionals should inform patients before starting treatment about the potential risk of severe increase in disability after stopping Gilenya®. When Gilenya® is stopped, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately. Patients should be advised to seek immediate medical attention if they experience new or worsened symptoms of MS after Gilenya® is stopped.

Patients should contact their health care professional immediately if they experience new or worsened symptoms of MS after Gilenya® treatment is stopped. These symptoms vary and include new or worsened weakness, increased trouble using arms or legs, or changes in thinking, eyesight, or balance. Gilenya® treatment may have to be stopped for reasons such as adverse drug reactions, planned or unplanned pregnancy, or because the medicine is not working. However, patients should not stop taking it without first talking to their prescribers, as stopping treatment can lead to worsening MS symptoms.
In the 8 years since Gilenya® was approved in September 2010, the FDA identified 35 cases of severely increased disability accompanied by the presence of multiple new lesions on magnetic resonance imaging (MRI) that occurred 2 to 24 weeks after Gilenya® was stopped. Most patients experienced this worsening in the first 12 weeks after stopping. The FDA's analyses include only reports submitted to FDA and those found in the medical literature, so there may be additional cases about which the FDA is unaware. The severe increase in disability in these patients was more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state. Several patients who were able to walk without assistance prior to discontinuing Gilenya® progressed to needing wheelchairs or becoming totally bedbound. In patients experiencing worsening of disability after stopping Gilenya®, recovery varied. A total of 17 patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during Gilenya® treatment.
The FDA previously communicated safety information about Gilenya® in August 2015 and August 2013 (rare brain infection), May 2012 (revised cardiovascular monitoring recommendations), and December 2011 (safety review of reported death).
To help FDA track safety issues with medicines, they urge health care professionals and patients to report side effects involving Gilenya® and other medicines to the FDA MedWatch program.

Safety Announcements

FDA warns that symptoms of a serious condition affecting the blood cells are not being recognized with the leukemia medicine Idhifa® (enasidenib)

[11/29/2018] The FDA is warning that signs and symptoms of a life-threatening side effect called differentiation syndrome are not being recognized in patients receiving the acute myeloid leukemia (AML) medicine Idhifa® (enasidenib). The Idhifa® prescribing information and patient Medication Guide already contain a warning about differentiation syndrome. However, the FDA has become aware of cases of differentiation syndrome not being recognized and patients not receiving the necessary treatment.
As a result, the FDA is alerting health care professionals and patients about the need for early recognition and aggressive management of differentiation syndrome to lessen the likelihood of serious illness and death. The FDA is continuing to monitor this safety concern.
Health care professionals should describe to patients the symptoms of differentiation syndrome listed in the Medication Guide when starting Idhifa® and at follow-up visits, and inform them to call their health care professional if such symptoms occur. Differentiation syndrome has occurred as early as 10 days and up to 5 months after starting the medicine. If patients experience unexplained respiratory distress or other symptoms, consider a diagnosis of differentiation syndrome and treat promptly with oral or intravenous corticosteroids.
Patients should contact their health care professional or go to the nearest hospital emergency room right away if they develop any of the following symptoms of differentiation syndrome while they are taking Idhifa®:

- Fever
- Cough
- Shortness of breath
- Swelling of arms and legs
- Swelling around the neck, groin, or underarm area
- Fast weight gain of more than 10 pounds within a week
- Bone pain
- Dizziness or feeling lightheaded

Idhifa® was approved in August 2017 to treat patients with AML with a specific genetic mutation called isocitrate dehydrogenase (IDH)-2 whose disease has come back or has not improved after treatment with other chemotherapy medicines. AML is a rapidly progressing cancer that forms in the bone marrow and results in an increased number of abnormal white blood cells. Idhifa® works by blocking several enzymes that promote this abnormal blood cell growth.

In the clinical trial conducted for Idhifa®'s approval, at least 14% of patients experienced differentiation syndrome. The manufacturer's safety report, which included the period of May 1, 2018 to July 31, 2018, reported 5 cases of death associated with differentiation syndrome in patients taking Idhifa®. Until Idhifa® was approved, differentiation syndrome had been associated only with induction chemotherapy in patients with a rare form of cancer called acute promyelocytic leukemia. Health care professionals and patients may not recognize the signs and symptoms of differentiation syndrome associated with Idhifa®. Another recently approved drug for AML with a specific genetic mutation called isocitrate dehydrogenase (IDH)-1, Tibsovo® (ivosidenib), also carries a risk of differentiation syndrome. Health care professionals should also be vigilant in monitoring for differentiation syndrome when prescribing Tibsovo® and patients should alert their health care professional of any symptoms.

Safety Announcements

FDA warns about rare but serious risks of stroke and blood vessel wall tears with multiple sclerosis (MS) drug Lemtrada® (alemtuzumab)

[11/29/2018] The FDA is warning that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with MS shortly after they received Lemtrada® (alemtuzumab). These problems can lead to permanent disability and even death. As a result, the FDA has added a new warning about these risks to the prescribing information in the drug label and to the patient Medication Guide. The FDA has also added the risk of stroke to the existing *Boxed Warning*, the FDA's most prominent warning. Alemtuzumab is also approved under the brand name Campath®, which was approved in May 2001 to treat a type of cancer called B-cell chronic lymphocytic leukemia (B-CLL). The Campath® drug label will also be updated to include these risks in the *Adverse Reactions* section under *Postmarketing Experience*.
Patients or their caregivers should seek emergency treatment as soon as possible if the patient experiences signs or symptoms of a stroke or tears in the lining of the head and neck arteries, called arterial dissection, which can include:

- Sudden numbness or weakness in the face, arms, or legs, especially if it occurs on only one side of the body
- Sudden confusion, trouble speaking, or difficulty understanding speech
- Sudden trouble seeing in one or both eyes
- Sudden trouble with walking, dizziness, or loss of balance or coordination
- Sudden severe headache or neck pain

Most patients taking Lemtrada® who developed stroke or tears in the artery linings, developed symptoms within 1 day of receiving Lemtrada. One patient reported symptoms that occurred 3 days after treatment.
Health care professionals should advise patients at every Lemtrada® infusion to seek immediate emergency medical attention if they experience symptoms of ischemic or hemorrhagic stroke or cervicocephalic arterial dissection. The diagnosis is often complicated because early symptoms such as headache and neck pain are not specific. Patients who complain of symptoms consistent with these conditions should be promptly evaluated.
In the nearly 5 years since the FDA approved Lemtrada® in 2014 to treat relapsing forms of MS, the FDA identified 13 worldwide cases of ischemic and hemorrhagic stroke or arterial dissection that occurred shortly after the patient received Lemtrada®. This number includes only reports submitted to FDA, so additional cases the FDA is unaware of may have occurred. Twelve of these cases reported symptoms within 1 day of receiving Lemtrada®. As a result, the FDA has added a new warning about this risk in the *Warnings and Precautions* section of the prescribing information in the drug label. The FDA has also added the risk of stroke to the existing *Boxed Warning*, the FDA's most prominent warning.

Current Drug Shortages Index (as of Dec 3rd, 2018):

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

Abciximab (ReoPro) Injection	***Currently in Shortage***
Amino Acids	***Currently in Shortage***
Aminophylline Injection, USP	***Currently in Shortage***
Asparaginase Erwinia Chrysanthemi (Erwinaze)	***Currently in Shortage***
Atenolol Tablets	***Currently in Shortage***

Atropine Sulfate Injection	***Currently in Shortage***
Azithromycin (Azasite) Ophthalmic Solution 1%	***Currently in Shortage***
Belatacept (Nulojix) Lyophilized Powder for Injection	***Currently in Shortage***
Belladonna and Opium Suppository	***Currently in Shortage***
Bisoprolol Fumarate Tablets	***Currently in Shortage***
Bumetanide Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride and Epinephrine Injection, USP	***Currently in Shortage***
Bupivacaine Hydrochloride Injection, USP	***Currently in Shortage***
Buspirone HCl Tablets	***Currently in Shortage***
Calcium Chloride Injection, USP	***Currently in Shortage***
Calcium Gluconate Injection	***Currently in Shortage***
Carbidopa and Levodopa Extended Release Tablets	***Currently in Shortage***
Cefazolin Injection	***Currently in Shortage***
Cefepime Injection	***Currently in Shortage***
Cefotaxime Sodium (Claforan) Injection	***Currently in Shortage***
Cefotetan Disodium Injection	***Currently in Shortage***
Deferoxamine Mesylate for Injection, USP	***Currently in Shortage***
Dexrazoxane Injection	***Currently in Shortage***
Dextrose 5% Injection Bags	***Currently in Shortage***
Dextrose 50% Injection	***Currently in Shortage***
Diazepam Injection, USP	***Currently in Shortage***
Diltiazem Hydrochloride	***Currently in Shortage***
Diltiazem Hydrochloride ER (Twice-a-Day) Capsules	***Currently in Shortage***
Diphenhydramine Injection	***Currently in Shortage***
Disopyramide Phosphate (Norpace) Capsules	***Currently in Shortage***
Dobutamine Hydrochloride Injection	***Currently in Shortage***
Dopamine Hydrochloride Injection	***Currently in Shortage***
Dorzolamide Hydrochloride and Timolol Maleate (Cosopt) Ophthalmic Solution	***Currently in Shortage***
Dorzolamide Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Eflornithine Hydrochloride (Vaniqa) Cream	***Currently in Shortage***
Epinephrine Injection, 0.1 mg/mL	***Currently in Shortage***
Epinephrine Injection, Auto-Injector	***Currently in Shortage***
Erythromycin Lactobionate for Injection, USP	***Currently in Shortage***
Ethiodized Oil (Lipiodol) Injection	***Currently in Shortage***
Etoposide Injection	***Currently in Shortage***
Etoposide Phosphate (Etopophos) Injection	***Currently in Shortage***
Fentanyl Citrate (Sublimaze) Injection	***Currently in Shortage***
Fluorescein Injection	***Currently in Shortage***
Fluorescein Sodium and Benoxinate Hydrochloride Ophthalmic Solution	***Currently in Shortage***
Fluorescein Strips	***Currently in Shortage***
Gemifloxacin Mesylate (Factive) Tablets	***Currently in Shortage***
Guanfacine Hydrochloride Tablets	***Currently in Shortage***
Haloperidol Tablets	***Currently in Shortage***
Heparin Sodium and Sodium Chloride 0.9% Injection	***Currently in Shortage***
Hydromorphone Hydrochloride Injection, USP	***Currently in Shortage***
Imipenem and Cilastatin for Injection, USP	***Currently in Shortage***

Isocarboxazid Tablets	***Currently in Shortage***
Ketamine Injection	***Currently in Shortage***
Ketoprofen Capsules	***Currently in Shortage***
Ketorolac Tromethamine Injection	***Currently in Shortage***
L-Cysteine Hydrochloride Injection	***Currently in Shortage***
Labetalol Hydrochloride Injection	***Currently in Shortage***
Letermovir (Prevymis) Injection	***Currently in Shortage***
Leucovorin Calcium Lyophilized Powder for Injection	***Currently in Shortage***
Leuprolide Acetate Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) and Dextrose Injection Solution-Premix Bags	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection	***Currently in Shortage***
Lidocaine Hydrochloride (Xylocaine) Injection with Epinephrine	***Currently in Shortage***
Liotrix (Thyrolar) Tablets	***Currently in Shortage***
Lorazepam Injection, USP	***Currently in Shortage***
Magnesium Sulfate Injection	***Currently in Shortage***
Methadone Hydrochloride Injection	***Currently in Shortage***
Methocarbamol Tablets	***Currently in Shortage***
Methotrexate Sodium Injection	***Currently in Shortage***
Methyldopa Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLICHEW ER) Extended-Release Chewable Tablets	***Currently in Shortage***
Methylphenidate Hydrochloride (QUILLIVANT XR) for Extended-Release Oral Suspension	***Currently in Shortage***
Metoclopramide Injection, USP	***Currently in Shortage***
Metronidazole Injection, USP	***Currently in Shortage***
Molindone Hydrochloride Tablets	***Currently in Shortage***
Morphine Sulfate Injection, USP	***Currently in Shortage***
Multi-Vitamin Infusion (Adult and Pediatric)	***Currently in Shortage***
Mupirocin Calcium Nasal Ointment	***Currently in Shortage***
Nelarabine (Arranon) Injection	***Currently in Shortage***
Ondansetron Hydrochloride Injection	***Currently in Shortage***
Penicillamine (Depen) Titratable Tablets	***Currently in Shortage***
Penicillin G Procaine Injection	***Currently in Shortage***
Peritoneal Dialysis Solutions	***Currently in Shortage***
Phenytoin Sodium Injection, USP	***Currently in Shortage***
Phosphate Injection Products	***Currently in Shortage***
Piperacillin and Tazobactam (Zosyn) Injection	***Currently in Shortage***
Potassium Chloride Injection	***Currently in Shortage***
Potassium Phosphate Injection	***Currently in Shortage***
Procainamide Hydrochloride Injection, USP	***Currently in Shortage***
Progesterone Injection, USP	***Currently in Shortage***
Promethazine (Phenergan) Injection	***Currently in Shortage***
Ranitidine Injection, USP	***Currently in Shortage***
Remifentanil (Ultiva) Lyophilized Powder for Solution Injection	***Currently in Shortage***
Ropivacaine Hydrochloride Injection	***Currently in Shortage***
Sacrosidase (Sucraid) Oral Solution	***Currently in Shortage***

Sclerosol Intrapleural Aerosol	***Currently in Shortage***
Scopolamine Transdermal System	***Currently in Shortage***
Sincalide (Kinevac) Lyophilized Powder for Injection	***Currently in Shortage***
Sodium Acetate Injection, USP	***Currently in Shortage***
Sodium Bicarbonate Injection, USP	***Currently in Shortage***
Sodium Chloride 0.9% Injection Bags	***Currently in Shortage***
Sodium Chloride 23.4% Injection	***Currently in Shortage***
Sodium Chloride Injection USP, 0.9% Vials and Syringes	***Currently in Shortage***
Sodium Phosphate Injection	***Currently in Shortage***
Sterile Talc Powder	***Currently in Shortage***
Sterile Water	***Currently in Shortage***
Technetium Tc99m Succimer Injection (DMSA)	***Currently in Shortage***
Thioridazine Hydrochloride Tablets	***Currently in Shortage***
Thiothixene Capsules	***Currently in Shortage***
Trifluoperazine Hydrochloride Tablets	***Currently in Shortage***
Valsartan Tablets	***Currently in Shortage***